DECLARATION OF JUNE ANN MUNFORD

1. My name is June Ann Munford. I am over the age of 18, have personal knowledge of the facts set forth herein, and am competent to testify to the same.

2. I earned a Master of Library and Information Science (MLIS) from the University of Wisconsin-Milwaukee in 2009. I have over ten years of experience in the library/information science field. Beginning in 2004, I have served in various positions in the public library sector including Assistant Librarian, Youth Services Librarian and Library Director. I have attached my Curriculum Vitae as Appendix CV.

3. During my career in the library profession, I have been responsible for materials acquisition for multiple libraries. In that position, I have cataloged, purchased and processed incoming library works. That includes purchasing materials directly from vendors, recording publishing data from the material in question, creating detailed material records for library catalogs and physically preparing that material for circulation. In addition to my experience in acquisitions, I was also responsible for analyzing large collections of library materials, tailoring library records for optimal catalog

search performance and creating lending agreements between libraries during my time as a Library Director.

4. I am also familiar with the Internet Archive, a digital online library accessible and available to the general public. The Internet Archive, a 501(c)(3) non-profit and founded in 1996, is a publicly available digital library of Internet sites and other cultural artifacts that can be searched and accessed in digital form. Its mission is to provide universal access to all knowledge including books, films, magazines, websites, videos, software programs, audio recordings, and television. Like a physical library, it provides free access to everyone. The Internet Archive is available here: https://archive.org/.

5. The Internet Archive created a resource known as the "Wayback Machine" (https://web.archive.org/). The Wayback Machine makes it possible to search and browse more than 450 billion publicly available web pages stored in the Internet Archive's web archive. Visitors to the Wayback Machine can search the Archive by keyword or a website URL. If archived records for a URL or the keywords are available, the visitor will be presented with a display of available dates. The visitor may select one of those dates and be

taken to the collection of web captures associated with the specific web crawl and point in time the capture came from.

6. This archived data made viewable by the Wayback Machine is obtained using web archiving software that automatically stores copies of files available via the Internet, each file preserved as it existed at a particular point in time.

7. The Internet Archive assigns a URL to all archived files within the Wayback Machine in the following format: http://web.archive.org/web/[Year in yyyy][Month in mm][Day in dd][Time code in hh:mm:ss]/[Archived URL]. This is known as an "extended URL" format.

8. For example, the Internet Archive extended URL http://web.archive.org/web/19970126045828/http://www.archive.org/ denotes the URL for the record of the Internet Archive home page archived on January 26, 1997 at 4:58 a.m. and 28 seconds (1997/01/26 at 04:58:28).

9. I have reviewed Exhibit 1008: *Center for Drug Evaluation and Research, "Clinical Pharmacology and Biopharmaceutics Review(s)" App. No. 125387Orig1s000 (2011) ("2011 Eylea® Clinical Review")*.

10. Attached hereto as Appendix FDA01 is a screen capture of the Internet Archive Wayback Machine entry for http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/125387Orig1s000ClinPharmR.pdf. I secured these screen captures myself from https://web.archive.org/web/20170118195247/http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/125387Orig1s000ClinPharmR.pdf. This record was captured as of January 18, 2017.

11. Appendix FDA01 is an Internet Archive capture of *Center for Drug Evaluation and Research, "Clinical Pharmacology and Biopharmaceutics Review(s)" App. No. 125387Orig1s000 (2011) ("2011 Eylea® Clinical Review")* as hosted on the FDA website. In comparing Appendix FDA01 to Exhibit 1008, it is my determination that Exhibit 1008 is a true and correct copy of *Center for Drug Evaluation and Research, "Clinical Pharmacology and Biopharmaceutics Review(s)" App. No. 125387Orig1s000 (2011) ("2011 Eylea® Clinical Review")* as hosted on the FDA website. As the Internet Archive captured this file as of January 18, 2017, it is my determination that *Center for Drug Evaluation and Research, "Clinical Pharmacology and Biopharmaceutics Review(s)" App. No. 125387Orig1s000 (2011) ("2011 Eylea® Clinical Review")* was publicly available at least by January 18, 2017 via the Internet Archive.

12. I have reviewed Exhibit 1009: *Product Information EYLEA® aflibercept (rch), ("AU Eylea® Label")*.

13. Attached hereto as Appendix BAYER01 is a screen capture of the Internet Archive Wayback Machine entry for http:/www.bayerresources.com.au/resources/uploads/PI/file10294.pdf. I secured these screen captures myself from https://web.archive.org/web/20170308065657/http:/www.bayerresources.com.au/resources/uploads/PI/file10294.pdf. This record was captured as of March 8, 2017.

14. Appendix BAYER01 is an Internet Archive capture of *Product Information EYLEA® aflibercept (rch), ("AU Eylea® Label")* as hosted on the Bayer Resources website. In comparing Appendix BAYER01 to Exhibit 1009, it is my determination that Exhibit 1009 is a true and correct copy of *Product Information EYLEA® aflibercept (rch), ("AU Eylea® Label")* as hosted on the Bayer Resources website. As the Internet Archive captured this file as of March 8, 2017, it is my determination that *Product Information EYLEA® aflibercept (rch), ("AU Eylea® Label")* was publicly available at least by March 8, 2017 via the Internet Archive.

15. I have reviewed Exhibit 1030: *Lehman Brothers Presentation, 9th Annual Global Healthcare Conference, Mar. 2006*.

16. Attached hereto as Appendix REGENERON01 is a screen capture of the Internet Archive Wayback Machine entry for http:/www.regeneron.com/investor/Regn_LM_Mar06.pdf. I secured these screen captures myself from https://web.archive.org/web/20060316092055/http:/www.regeneron.com/investor/Regn_LM_Mar06.pdf. This record was captured as of March 16, 2006.

17. Appendix REGENERON01 is an Internet Archive capture of *Lehman Brothers Presentation, 9th Annual Global Healthcare Conference, Mar. 2006* as hosted on the Regeneron website. In comparing Appendix REGENERON01 to Exhibit 1030, it is my determination that Exhibit 1030 is a true and correct copy of *Lehman Brothers Presentation, 9th Annual Global Healthcare Conference, Mar. 2006* as hosted on the Regeneron website. As the Internet Archive captured this file as of March 16, 2006, it is my determination that *Lehman Brothers Presentation, 9th Annual Global Healthcare Conference, Mar. 2006* was publicly available at least as of March 16, 2006 via the Internet Archive.

18. I have reviewed Exhibit 1048: *Macugen® 2011 Label*.

19. Attached hereto as Appendix FDA02 is a screen capture of the Internet Archive Wayback Machine entry for https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021756s018lbl.pdf. I secured these screen captures myself from https://web.archive.org/web/20150117045738/https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021756s018lbl.pdf. This record was captured as of January 17, 2015.

20. Appendix FDA02 is an Internet Archive capture of *Macugen® 2011 Label* as hosted on the FDA website. In comparing Appendix FDA02 to Exhibit 1048, it is my determination that Exhibit 1048 is a true and correct copy of *Macugen® 2011 Label* as hosted on the FDA website. As the Internet Archive captured this file as of January 17, 2015, it is my determination that *Macugen® 2011 Label* was publicly available at least as of January 17, 2015 via the Internet Archive.

21. I have reviewed Exhibit 1049: *Beovu® 2019 Label.*

22. Attached hereto as Appendix FDA03 is a screen capture of the Internet Archive Wayback Machine entry for https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761125s000lbl.pdf. I secured these screen captures myself from https://web.archive.org/web/20191117202243/https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761125s000lbl.pdf. This record was captured as of November 17, 2019.

23. Appendix FDA03 is an Internet Archive capture of *Beovu® 2019 Label* as hosted on the FDA website. In comparing Appendix FDA03 to Exhibit 1049, it is my determination that Exhibit 1049 is a true and correct copy of *Beovu® 2019 Label* as hosted on the FDA website. As the Internet Archive captured this file as of November 17, 2019, it is my determination that *Beovu® 2019 Label* was publicly available at least as of November 17, 2019 via the Internet Archive.

24. I have reviewed Exhibit 1050: *Eylea® 2011 Label*.

25. Attached hereto as Appendix FDA04 is a screen capture of the Internet Archive Wayback Machine entry for http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/125387lbl.pdf. I

secured these screen captures myself from https://web.archive.org/web/20140430031100/http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/125387lbl.pdf. This record was captured as of April 30, 2014.

26. Appendix FDA04 is an Internet Archive capture of *Eylea® 2011 Label* as hosted on the FDA website. In comparing Appendix FDA03 to Exhibit 1050, it is my determination that Exhibit 1050 is a true and correct copy of *Eylea® 2011 Label* as hosted on the FDA website. As the Internet Archive captured this file as of April 30, 2014, it is my determination that *Eylea® 2011 Label* publicly available at least as of April 30, 2014 via the Internet Archive.

27. I have reviewed Exhibit 1051: *Eylea® 2012 Label*.

28. Attached hereto as Appendix FDA05 is a screen capture of the Internet Archive Wayback Machine entry for http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/125387s004lbl.pdf. I secured these screen captures myself from https://web.archive.org/web/20170120063346/http://www.accessdata.fda.go

v/drugsatfda_docs/label/2012/125387s004lbl.pdf. This record was captured as of January 20, 2017.

29. Appendix FDA05 is an Internet Archive capture of *Eylea® 2012 Label* as hosted on the FDA website. In comparing Appendix FDA05 to Exhibit 1051, it is my determination that Exhibit 1051 is a true and correct copy of *Eylea® 2012 Label* as hosted on the FDA website. As the Internet Archive captured this file as of January 20, 2017, it is my determination that *Eylea® 2012 Label* was publicly available at least as of January 20, 2017.

30. I have reviewed Exhibit 1052: *Eylea® 2014 Label*.

31. Attached hereto as Appendix FDA06 is a screen capture of the Internet Archive Wayback Machine entry for http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/125387s043lbl.pdf. I secured these screen captures myself from https://web.archive.org/web/20170216202634/http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/125387s043lbl.pdf. This record was captured as of February 16, 2017.

32. Appendix FDA06 is an Internet Archive capture of *Eylea® 2014 Label* as hosted on the FDA website. In comparing Appendix FDA06 to Exhibit

1052, it is my determination that Exhibit 1052 is a true and correct copy of *Eylea® 2014 Label* as hosted on the FDA website. As the Internet Archive captured this file as of February 16, 2017, it is my determination that *Eylea® 2014 Label* was publicly available at least as of February 16, 2017 via the Internet Archive.

33. I have reviewed Exhibit 1053: *Eylea® 2016 Label*.

34. Attached hereto as Appendix FDA07 is a screen capture of the Internet Archive Wayback Machine entry for http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/125387s052lbl.pdf. I secured these screen captures myself from https://web.archive.org/web/20170228032713/http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/125387s052lbl.pdf. This record was captured as of February 28, 2017.

35. Appendix FDA07 is an Internet Archive capture of *Eylea® 2016 Label* as hosted on the FDA website. In comparing Appendix FDA07 to Exhibit 1053, it is my determination that Exhibit 1053 is a true and correct copy of *Eylea® 2016 Label* as hosted on the FDA website. As the Internet Archive captured this file as of February 28, 2017, it is my determination that *Eylea®*

2016 Label was publicly available at least as of February 28, 2017 via the Internet Archive.

36. I have reviewed Exhibit 1054: *Eylea® HD 2024 Label*.

37. Attached hereto as Appendix REGENERON02 is a screen capture of the Internet Archive Wayback Machine entry for https://www.regeneron.com/downloads/eyleahd_fpi.pdf. I secured these screen captures myself from https://web.archive.org/web/20250820153626/https://www.regeneron.com/downloads/eyleahd_fpi.pdf. This record was captured as of August 20, 2025.

38. Appendix REGENRON02 is an Internet Archive capture of *Eylea® HD 2024 Label* as hosted on the FDA website. In comparing Appendix REGENERON02 to Exhibit 1054, it is my determination that Exhibit 1054 is a true and correct copy of *Eylea® HD 2024 Label* as hosted on the FDA website. As the Internet Archive captured this file as of August 20, 2025, it is my determination that *Eylea® HD 2024 Label* was publicly available at least as of August 20, 2025 via the Internet Archive.

39. I have reviewed Exhibit 1055: *Lucentis® 2017 Label*.

40. Attached hereto as Appendix GENE01 is a screen capture of the Internet Archive Wayback Machine entry for https://www.gene.com/download/pdf/lucentis_prescribing.pdf. I secured these screen captures myself from https://web.archive.org/web/20170408234317/https://www.gene.com/download/pdf/lucentis_prescribing.pdf. This record was captured as of April 8, 2017.

41. Appendix GENE01 is an Internet Archive capture of *Lucentis® 2017 Label* as hosted on the Gene.com website. In comparing Appendix GENE01 to Exhibit 1055, it is my determination that Exhibit 1055 is a true and correct copy of *Lucentis® 2017 Label* as hosted on the Gene.com website. As the Internet Archive captured this file as of April 8, 2017, it is my determination that *Lucentis® 2017 Label* was publicly available at least as of April 8, 2017 via the Internet Archive.

42. I have reviewed Exhibit 1057: *Vabysmo® 2022 Label*.

43. Attached hereto as Appendix FDA09 is a screen capture of the Internet Archive Wayback Machine entry for https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761235s000lbl.pdf. I secured these screen captures myself from

https://web.archive.org/web/20220216194214/https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761235s000lbl.pdf. This record was captured as of February 16, 2022.

44. Appendix FDA09 is an Internet Archive capture of *Vabysmo® 2022 Label* as hosted on the FDA website. In comparing Appendix FDA09 to Exhibit 1057, it is my determination that Exhibit 1057 is a true and correct copy of *Vabysmo® 2022 Label* as hosted on the FDA website. As the Internet Archive captured this file as of February 16, 2022, it is my determination that *Vabysmo® 2022 Label* was publicly available at least as of February 16, 2022 via the Internet Archive.

45. I have reviewed Exhibit 1058: *Assessment Report, Eylea aflibercept, Committee for Medicinal Products for Human Use (CHMP), European Medicines Agency Science Medicines Health, Sept. 2012*.

46. Attached hereto as Appendix EMA01 is a screen capture of the Internet Archive Wayback Machine entry for http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002392/WC500135744.pdf. I secured these screen captures myself from

https://web.archive.org/web/20151026043159/http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002392/WC500135744.pdf. This record was captured as of October 26, 2015.

47. Appendix EMA01 is an Internet Archive capture of *Assessment Report, Eylea aflibercept, Committee for Medicinal Products for Human Use (CHMP), European Medicines Agency Science Medicines Health, Sept. 2012* as hosted on the EMA website. In comparing Appendix EMA01 to Exhibit 1058, it is my determination that Exhibit 1058 is a true and correct copy of *Assessment Report, Eylea aflibercept, Committee for Medicinal Products for Human Use (CHMP), European Medicines Agency Science Medicines Health, Sept. 2012* as hosted on the EMA website. As the Internet Archive captured this file as of October 26, 2015, it is my determination that *Assessment Report, Eylea aflibercept, Committee for Medicinal Products for Human Use (CHMP), European Medicines Agency Science Medicines Health, Sept. 2012* was publicly available at least as of October 26, 2015 via the Internet Archive.

48. I have reviewed Exhibit 1059: *Center for Drug Evaluation and Research, "Pharmacology Review(s)" App. No. 125387Orig1s000 (2011) ("Eylea Pharmacology Review")*.

49. Attached hereto as Appendix FDA10 is a screen capture of the Internet Archive Wayback Machine entry for http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/125387Orig1s000PharmR.pdf. I secured these screen captures myself from https://web.archive.org/web/20170118195257/http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/125387Orig1s000PharmR.pdf. This record was captured as of January 18, 2017.

50. Appendix FDA10 is an Internet Archive capture of *Center for Drug Evaluation and Research, "Pharmacology Review(s)" App. No. 125387Orig1s000 (2011) ("Eylea Pharmacology Review")*. In comparing Appendix FDA10 to Exhibit 1059, it is my determination that Exhibit 1059 is a true and correct copy of *Center for Drug Evaluation and Research, "Pharmacology Review(s)" App. No. 125387Orig1s000 (2011) ("Eylea Pharmacology Review")* as hosted on the FDA website. As the Internet Archive captured this file as of January 18, 2017, it is my determination that *Center for Drug Evaluation and Research, "Pharmacology Review(s)" App.*

No. 125387Orig1s000 (2011) ("Eylea Pharmacology Review") was publicly available at least as of January 18, 2017 via the Internet Archive.

51. I have reviewed Exhibit 1060: *EMA Annex*.

52. Attached hereto as Appendix EMA02 is a screen capture of the Internet Archive Wayback Machine entry for http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002392/WC500135815.pdf. I secured these screen captures myself from https://web.archive.org/web/20160611010852/http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002392/WC500135815.pdf. This record was captured as of June 11, 2016.

53. Appendix EMA02 is an Internet Archive capture of *EMA Annex* as hosted on the EMA website. In comparing Appendix EMA02 to Exhibit 1060, it is my determination that Exhibit 1060 is a true and correct copy of *EMA Annex* as hosted on the EMA website. As the Internet Archive first captured this file as of June 11, 2016, it is my determination that *EMA Annex* was first

made available to the public at least as of June 11, 2016 via the Internet Archive and likely earlier via the original EMA website.

54. I have been retained on behalf of the Petitioner to provide assistance in the above-illustrated matter in establishing the authenticity and public availability of the documents discussed in this declaration. I am being compensated for my services in this matter at the rate of $200.00 per hour plus reasonable expenses. My statements are objective, and my compensation does not depend on the outcome of this matter.

55. I declare under penalty of perjury that the foregoing is true and correct. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Dated: 9/17/2025



June Ann Munford

APPENDIX CV

June A. Munford
Curriculum Vitae

Education

University of Wisconsin-Milwaukee - MS, Library & Information Science, 2009
Milwaukee, WI

- Coursework included cataloging, metadata, data analysis, library systems, management strategies and collection development.
- Specialized in library advocacy, cataloging and public administration.

Grand Valley State University - BA, English Language & Literature, 2008
Allendale, MI

- Coursework included linguistics, documentation and literary analysis.
- Minor in political science with a focus in local-level economics and government.

Professional Experience

Researcher / Expert Witness, October 2017 – present
Freelance ● Pittsburgh, Pennsylvania & Grand Rapids, Michigan

- Material authentication and public accessibility determination. Declarations of authenticity and/or public accessibility provided upon research completion. Experienced with appeals and deposition process.

- Research provided on topics of public library operations, material publication history, digital database services and legacy web resources.

- Past clients include Alston & Bird, Arnold & Porter, Baker Botts, Fish & Richardson, Erise IP, Irell & Manella, O'Melveny & Myers, Perkins-Coie, Pillsbury Winthrop Shaw Pittman and Slayden Grubert Beard.

Library Director, February 2013 - March 2015
Dowagiac District Library ● Dowagiac, Michigan

- Executive administrator of the Dowagiac District Library. Located in Southwest Michigan, this library has a service area of 13,000, an annual operating budget of over $400,000 and total assets of approximately $1,300,000.

● Developed careful budgeting guidelines to produce a 15% surplus during the 2013-2014 & 2014-2015 fiscal years while being audited.

● Using this budget surplus, oversaw significant library investments including the purchase of property for a future building site, demolition of existing buildings and building renovation projects on the current facility.

● Led the organization and digitization of the library's archival records.

● Served as the public representative for the library, developing business relationships with local school, museum and tribal government entities.

● Developed an objective-based analysis system for measuring library services - including a full collection analysis of the library's 50,000+ circulating items and their records.

November 2010 - January 2013
Librarian & Branch Manager, Anchorage Public Library ● Anchorage, Alaska

● Headed the 2013 Anchorage Reads community reading campaign including event planning, staging public performances and creating marketing materials for mass distribution.

● Co-led the social media department of the library's marketing team, drafting social media guidelines, creating original content and instituting long-term planning via content calendars.

● Developed business relationships with The Boys & Girls Club, Anchorage School District and the US Army to establish summer reading programs for children.

June 2004 - September 2005, September 2006 - October 2013
Library Assistant, Hart Area Public Library
Hart, MI

● Responsible for verifying imported MARC records and original MARC cataloging for the local-level collection as well as the Michigan Electronic Library.

● Handled OCLC Worldcat interlibrary loan requests & fulfillment via ongoing communication with lending libraries.

Professional Involvement

Alaska Library Association - Anchorage Chapter

- Treasurer, 2012

Library Of Michigan
- Level VII Certification, 2008
- Level II Certification, 2013

Michigan Library Association Annual Conference 2014
- New Directors Conference Panel Member

Southwest Michigan Library Cooperative
- Represented the Dowagiac District Library, 2013-2015

Professional Development

Library Of Michigan Beginning Workshop, May 2008
Petoskey, MI
- Received training in cataloging, local history, collection management, children's literacy and reference service.

Public Library Association Intensive Library Management Training, October 2011
Nashville, TN
- Attended a five-day workshop focused on strategic planning, staff management, statistical analysis, collections and cataloging theory.

Alaska Library Association Annual Conference 2012 - Fairbanks, February 2012
Fairbanks, AK
- Attended seminars on EBSCO advanced search methods, budgeting, cataloging, database usage and marketing.

Depositions

2019 ● Fish & Richardson

Apple v. Qualcomm (Case No. IPR2018-001281, 39521-00421IP, IPR2018-01282 and 39521-00421IP2)

2019 ● Erise IP

Implicit, LLC v. Netscout Systems, Inc (Case No. 2:18-cv-53-JRG)

2019 ● Perkins-Coie

Adobe Inc. v. RAH Color Technologies LLC (Case No. IPR2019-00627, IPR2019-00628, IPR2019-00629 and IPR2019-00646)

2020 ● O'Melveny & Myers

Maxell, Ltd. v. Apple Inc. (Case No. 5:19-cv-00036-RWS)

2021 ● Pillsbury Winthrop Shaw Pittman LLP

Intel v. SRC (Case No. IPR2020-1449)

2022 ● Perkins-Coie

Realtek v. Future Link (Case No. IPR2021-01182)

2023 ● Fish & Richardson

Neuroderm Ltd. v. Abbvie, Inc (Case No. PGR2022-00040)

2023 ● Fish & Richardson

Nearmap US Inc. v. Pictometry International Corp. (Case No. IPR2022-00735)

2023 ● Fish & Richardson

Samsung Electronics v. MemoryWeb LLC (Case No. 39843-0136PS1)

2023 ● Pillsbury Winthrop Shaw Whitman LLP

Gravel Rating Systems v. Costco Wholesale Corp. (Case No. 4:21-cv-149-ALM)

2024 ● Willkie-Farr

Netflix, Inc. v. VideoLabs. Inc. (Case No. IPR2023-00628)

2024 ● Quinn Emanuel Urquhart & Sullivan

Purdue University v. Wolfspeed (Case No. 1:21-CV-840)

2024 ● Fish & Richardson

Dish Network v. Entropic Communications (Case No. IPR2024-00393)

2025 ● Perkins Coie

Amazon.com, Inc. v. Nokia Technologies Oy (Case No. IPR2024-00572)

2025 ● Fish & Richardson

Dish Network v. Entropic Communications (Case No. IPR2024-00373)

Limited Case and Clientele History

Alston & Bird

- Ericsson

  v. Collision Communications (Case No. IPR2022-01233)

- Nokia

  v. Neptune Subsea, Xtera (Case No. 1:17-cv-01876)

- Universal Electronics Inc

  v. Roku Inc (Case No. IPR2022-00818)

Alavi & Anaipakos PLLC

- Stingray Group Inc. and Stingray Music USA, Inc.

  v. Edwin A. Hernandez-Mondragon and Egla Corp. (Case No. 1:24-cv-21226-RAR)

Arnold & Porter

- Ivantis

  v. Glaukos (Case No. 8:18-cv-00620)

- Samsung

  v. Jawbone (Case No. 2:21-cv-00186)

Benesch Friedlander Coplan & Aronoff

- Voyis

  v. Cathx (Case No. 5:21-cv-00077-RWS)

Buchanan, Ingersoll & Rooney PC

- Google LLC, AT&T Service Inc., T Mobile USA Inc., Cellco Partnership, Ericsson Inc. & Nokia of America Corp.

  v. KT Corp & Pegasus Wireless Innovation LLC (Case No. IPR2025-00293)

Deschert LLP

- Smaxtec Animal Care

  v. ST Reproductive Technologies, LLC (Case No. IPR2024-00885)

Duane Morris

- Kangxi Communication Technologies

  v. Skyworks Solutions Inc. (Case No. IPR2025-00373)

- Microsoft

  v. Edge Networking Systems LLC (Case No. 1:24-cv-00215)

Erise I.P.

- Apple

  v. Ericsson Inc. (Case No. IPR2022-00715)

  v. Future Link Systems (Case No. IPRs 6317804, 6622108, 6807505, and 7917680)

  v. INVT (Case No. 20-1881)

  v. Navblazer LLC (Case No. IPR2020-01253)

  v. Qualcomm (Case No. IPR2018-001281, 39521-00421IP, IPR2018-01282, 39521-00421IP2)

v. Quest Nettech Corp (Case No. 2:19-cv-00118-JRG)

v. Telefonaktiebolaget LM Ericsson (Case No. IPR2022-00275)

v. Theta IP, LLC (Case No. IPR2024-00818)

v. THL Holding Company LLC (Case No. 1:23-cv-00548)

- Fanduel

v. CGT (Case No. 19-1393)

- Garmin

v. Phillips North America LLC (Case No. 2:19-cv-6301-AB-KS)

- Netscout

v. Longhorn HD LLC (Case No. 2:20-cv-00349)

v. Implicit, LLC (Case No. 2:18-cv-53-JRG)

- Sony Interactive Entertainment LLC

v. Bot M8 LLC (Case No. IPR2020-01288)

v. Infernal Technology LLC (Case No. 2:19-CV-00248-JRG)

- Tesla

v. Charge Fusion Technologies LLC (Case No. IPR2025-00032)

- Unified Patents

v. GE Video Compression (Case No. 2:19-cv-248)

Fish & Richardson

- Apple

v. AliveCor (Case No. 3:21-cv-03958)

v. LBS Innovations (Case No. 2:19-cv-00119-JRG-RSP)

v. Koss Corporation (Case No. IPR2021-00305)

v. Masimo (Case No. IPR 50095-0012IP1, 50095-0012IP2, 50095-0013IP1, 50095-0013IP2, 50095-0006IP1, 50095-0135IP1)

v. Neonode (Case No. 21-cv-08872-EMC)

v. Qualcomm (Case No. IPR2018-001281, 39521-00421IP, IPR2018-01282, 39521-00421IP2)

v. Resonant Sys. (Case No. 7:23-cv-00077-ADA)

- AsusTek Computer Inc.
  v. Videolabs, Inc. (Case No. 22-CV-00720-ADA)

- Dell
  v. Neo Wireless (Case No. IPR2022-00616)

- Dish Network

  v. Entropic Communications, LLC (Case No. 2:2023-CV-01043)

  v. Entropic Communications LLC (Case No. IPR2024-00393)

  v. Realtime Adaptive Streaming (Case No. 1:17-CV-02097-RBJ)

  v. TQ Delta LLC (Case No. 18-1798)

- Evapco Dry Cooling

  v. SPG Dry Cooling (Case No. IPR2021-00688)

- Genetec

  v. Sensormatic Electronics (Case No. 1:20-CV-00760)

- Huawei

  v. Bell Northern Research LLC (Case No. IPR2019-01174)

- Kianxis

  v. Blue Yonder (Case No. 3:20-cv-03636)

- LG Electronics

  v. Bell Northern Research LLC (Case No. 3:18-cv-2864-CAB-BLM)

- MediaTek

  v. MOSAID (Case No. IPR2024-00718)

- Metaswitch

  v. Sonus Networks (Case No. IPR2018-01719)

- Microsoft

  v. Throughputer Inc (Case No. IPR2022-00757)

- Mom Enterprises

  v. Ddrops Company (Case No. 1:22-cv-00332)

- MLC Intellectual Property

  v. MicronTech (Case No. 3:14-cv-03657-SI)

- Nearmap Inc

  v. EagleView Technologies (Case No. IPR2022-01009)

- Neuroderm Ltd.

  v. Abbvie, Inc (Case No. PGR2022-00040)

- Posco Co Ltd.

  v. Pascal Drillet et al. (Case No. IPR2025-00370)

- Realtek Semiconductor

  v. Future Link (Case No. IPR2021-01182)

- Quectel
  - v. Koninklijke Philips (Case No. 1:20-cv-01710)

- Samsung
  - v. Aire Technology (Case No. IPR2022-00877)
  - v. Bell Northern Research (Case No. 2:19-cv-00286-JRG)
  - v. Communication Technologies Inc (Case No. IPR2022-01221)
  - v. Jawbone Innovations (Case No. IPR2022-00865)
  - v. MemoryWeb LLC (Case No. IPR2022-00885)
  - v. Dodots Licensing Solutions (Case No. IPR2023-00701)
  - v. Telefonaktiebolaget LM Ericsson (Case No. IPR2021-00615)

- Texas Instruments
  - v. Vantage Micro LLC (Case No. IPR2020-01261)

- Xilinx
  - v. Sentient Sensors LCC (Case No. 1:22-cv-00173)

Goodwin Proctor

- Intel
  - v. Proxense, LLC (Case No. 6:24-cv-00283)

- Samsung Electronics
  - v. Mobile Data Technologies (Case No. 2:24-cv-00435)

- Taiwan Semiconductor Manufacturing Company Ltd.
  - v. Advanced Integrated Circuit Process LLC (Case No. 2:24-cv-00623)

Groombridge Wu

- Nearmap

  v. Eagle View Technologies Inc. and Pictometry International Corp. (Case No. 2:21-cv-00283-TS-DAO)

Irell & Manella

- Curium

Latham & Watkins LLP

- Apple

  v. Advanced Coding Research LLC

Leydig, Voit & Mayer, Ltd.

- Public Availability Consultancy

O'Melveny & Myers

- Apple

  v. Maxell (Case No. 5:19-cv-00036-RWS)

- Disney Media & Entertainment Distribution LLC

  v. Digital Media Technology Holdings, LLC (Case No. 2:22-cv-01642)

- Micron Technology Inc.

  v. Besang Inc (Case No. IPR2023-00900)

- Samsung

  v. Daedalus Prime LLC (1335 Investigation)

Perkins-Coie

- Amazon
  - v. Nokia (Case No. IPR2024-00847 and IPR2024-00848)
  - v. Nokia Technologies Oy (Case No. IPR2024-00572)
- Heru Industries
  - v. The UAB Research Foundation (Case No. IPR2022-01148)
- Intel Corporation
  - v. BeSang Inc. (Case No. IPR2023-00991)
  - v. BitMICRO (Case No. 5:23-cv-00625)
  - v. Telefonaktiebolaget L M Ericsson (Case No. IPR2024-00610)
- Realtek Semiconductor
  - v. Future Link (Case No. IPR2021-01182)
- r-pac
  - v. Adasa, Inc. (Case No. 1:2024cv06102)
- Twitter Inc
  - v. VOIP-Pal.com (Case No. 3:20-cv-02397-JD)
- TCL Industries
  - v. Koninklijke Philips NV (Case No. IPR2021-00495, IPR2021-00496 and IPR2021-00497)
- VusionGroup
  - v. Hanshow (Case No. IPR2024-00857)

Pillsbury Winthrop Shaw Pittman

- Intel

  v. FG SRC LLC (Case No. 6:20-cv-00315)

- Gravel Rating Systems

  v. Costco (Case No. 4:21-cv-149)
  v. Lowe's Home Centers (Case No. 4:21-cv-150)
  v. T-Mobile USA (Case No. 4:21-cv-152)
  v. Kohl's Inc. (Case No. 4:21-cv-258)
  v. Under Armor (Case No. 4:21-cv-356)

Quinn Emanuel

- Exact Sciences Corporation

  v. Geneoscopy, Inc. (Case No. IPR2024-00459 and IPR2024-1330)

- ServiceNow, Inc.

  v. InQuisient, Inc. (Case No. 22-900-CJB)

- Wolfspeed

  v. The Trustees of Purdue University (Case No. 1:2021-cv-00840)

Sheppard, Mullin, Richter & Hampton LLP

- Advanced Micro Devices, Inc and Pensando Systems, Inc.

  v. Concurrent Ventures LLC and Xtreamedge, Inc. (Case No. IPR2025-00478)

- Cadence Design Systems Inc.

  v. Semiconductor Design Technologies (Case No. 3:23-cv-01001)

Shook, Hardy & Bacon LLP

- HP Inc.

  v. Universal Connectivity Technologies (Case No. 1:23-cv-01177)

Stern, Kessler, Goldstein & Fox

- Preliminary Research

Wilmer, Cutler, Pickering, Hale and Dorr

- Apple

  v. Shunock (Case No. 1:23-cv-08598)

- Quest Diagnostics Inc., Haystack Oncology Inc. and Haystack Oncology GmbH

  v. Natera, Inc. (Case No. 1:23-cv-08598)

- Roche Diabetes, Inc.

  v. Trividia Health, Inc. (Case No. 1:24-cv-00668)

Willkie, Farr & Gallagher LLP

- Lenovo, Dell, HP

  v. Universal Connectivity Technologies Inc. (Case No. 2:2023cv00449)

- Neurent

  v. The Foundry, LLC (Case No. IPR2024-00669)

- Netflix, Inc.

  v. VideoLabs, Inc. (Case No. IPR2023-00628)

APPENDIX FDA01

https://web.archive.org/web/20171201000000*/http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/125387Orig1s000ClinPharmR.pdf September 13, 2025

INTERNET ARCHIVE WEB TEXTS VIDEO AUDIO SOFTWARE IMAGES SIGN UP | LOG IN UPLOAD Search

ABOUT BLOG PROJECTS HELP DONATE CONTACT JOBS VOLUNTEER PEOPLE

DONATE

INTERNET ARCHIVE WayBackMachine

Explore more than 946 billion web pages saved over time

http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/12538

Calendar · Collections · Changes · Summary · Site Map · URLs

Saved **15 times** between January 18, 2017 and August 25, 2025.

002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 **2017** 2018 2019 2020 2021 2022 2023 2024 2025

JAN

1	2	3	4	5	6	7
8	9	10	11	12	13	14
15	16	17	18	19	20	21
22	23	24	25	26	27	28
29	30	31				

FEB

			1	2	3	4
5	6	7	8	9	10	11
12	13	14	15	16	17	18
19	20	21	22	23	24	25
26	27	28				

MAR

			1	2	3	4
5	6	7	8	9	10	11
12	13	14	15	16	17	18
19	20	21	22	23	24	25
26	27	28	29	30	31	

APR

						1
2	3	4	5	6	7	8
9	10	11	12	13	14	15
16	17	18	19	20	21	22
23	24	25	26	27	28	29
30						

MAY

	1	2	3	4	5	6
7	8	9	10	11	12	13
14	15	16	17	18	19	20
21	22	23	24	25	26	27
28	29	30	31			

JUN

				1	2	3
4	5	6	7	8	9	10
11	12	13	14	15	16	17
18	19	20	21	22	23	24
25	26	27	28	29	30	

JUL

						1
2	3	4	5	6	7	8
9	10	11	12	13	14	15
16	17	18	19	20	21	22
23	24	25	26	27	28	29
30	31					

AUG

		1	2	3	4	5
6	7	8	9	10	11	12
13	14	15	16	17	18	19
20	21	22	23	24	25	26
27	28	29	30	31		

SEP

				1	2	
3	4	5	6	7	8	9
10	11	12	13	14	15	16
17	18	19	20	21	22	23
24	25	26	27	28	29	30

OCT

1	2	3	4	5	6	7
8	9	10	11	12	13	14
15	16	17	18	19	20	21
22	23	24	25	26	27	28
29	30	31				

NOV

			1	2	3	4
5	6	7	8	9	10	11
12	13	14	15	16	17	18
19	20	21	22	23	24	25
26	27	28	29	30		

DEC

					1	2
3	4	5	6	7	8	9
10	11	12	13	14	15	16
17	18	19	20	21	22	23
24	25	26	27	28	29	30
31						

Note

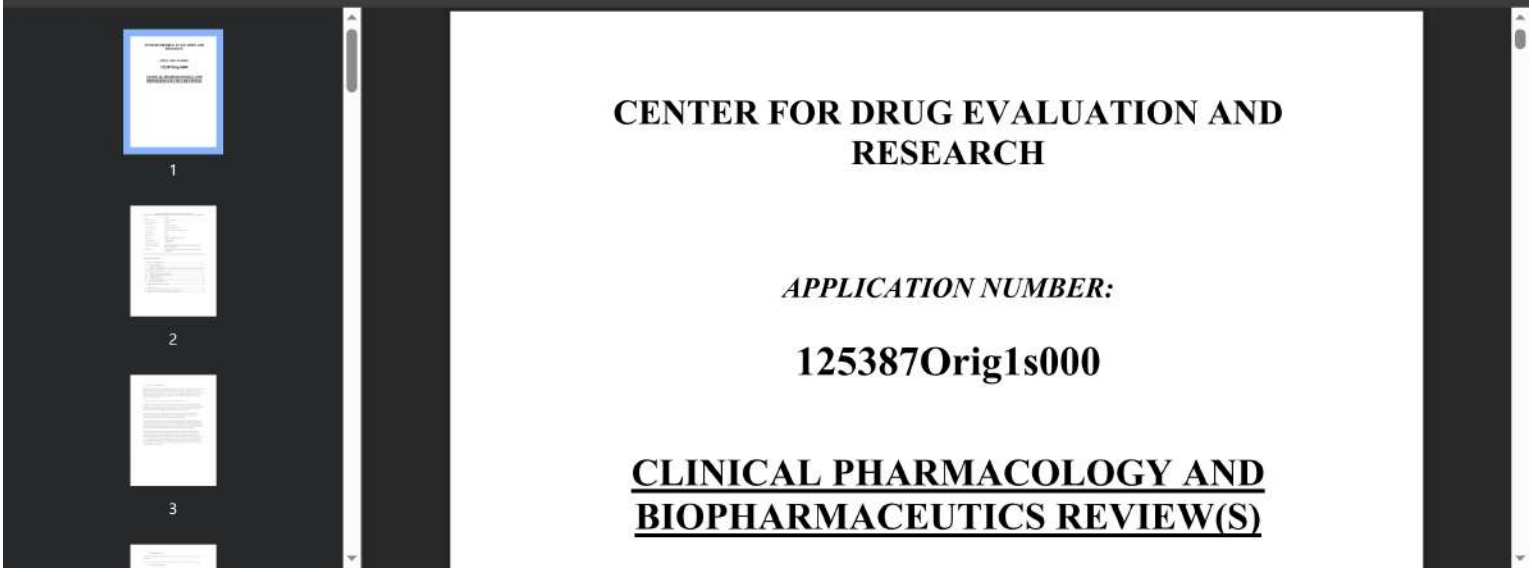
This calendar view maps the number of times **http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/125387Orig1s000ClinPharmR.pdf** was crawled by the Wayback Machine, *not* how many times the site was actually updated. More info in the FAQ.

FAQ | Contact Us | Terms of Service (Dec 31, 2014)

The Wayback Machine is an initiative of the Internet Archive, a 501(c)(3) non-profit, building a digital library of Internet sites and other cultural artifacts in digital form. Other projects include Open Library & archive-it.org.

Your use of the Wayback Machine is subject to the Internet Archive's Terms of Use.

https://web.archive.org/web/20170118195247/http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/125387Orig1s000ClinPharmR.pdf September 13, 2025
INTERNET ARCHIVE Wayback Machine http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/125387Orig1s000ClinPharmR.pdf Go DEC JAN MAR
15 captures 18 Jan 2017 - 25 Aug 2025 2016 18 2017 2020 About this capture



1

2

3

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125387Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125387Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

PGR2026-00039
Biocon Ex.1065
Page 38 of 595

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

BLA:	125-387
Submission Date(s):	February 17, 2011
Proposed Brand Name	EYLEA™
Generic Name	Aflibercept Injection
Primary Reviewer	Yongheng Zhang, Ph.D.
Team Leader	Philip M. Colangelo, Pharm.D., Ph.D.
OCP Division	DCP4
OND Division	DTOP
Applicant	Regeneron Pharmaceuticals, Inc.
Relevant IND(s)	12462, (b) (4)
Submission Type; Code	1P (NME)
Formulation; Strength(s)	Aflibercept Ophthalmic Solution for Intravitreal Injection; 40 mg/mL (2 mg/50 μL)
Indication	For the treatment of neovascular (wet) age-related macular degeneration

TABLE OF CONTENTS

1. EXECUTIVE SUMMARY 2
   1.1. RECOMMENDATION 3
   1.2. PHASE IV COMMITMENTS 3
   1.3. SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS 3
2. QUESTION BASED REVIEW 5
   2.1. GENERAL ATTRIBUTES OF THE DRUG 5
   2.2. GENERAL CLINICAL PHARMACOLOGY 8
   2.3. INTRINSIC FACTORS 15
   2.4. EXTRINSIC FACTORS 15
   2.5. GENERAL BIOPHARMACEUTICS 17
   2.6. ANALYTICAL SECTION 17
3. LABELING RECOMMENDATIONS 22
4. APPENDICES 23
   4.1. PROPOSED PACKAGE INSERT (ORIGINAL AND ANNOTATED) 23
   4.2. INDIVIDUAL STUDY REVIEW AVAILABLE UPON REQUEST 42

PGR2026-00039
Biocon Ex.1065
Page 39 of 595

1. EXECUTIVE SUMMARY

Aflibercept injection (Vascular Endothelial Growth Factor [VEGF] Trap-Eye) is a new chemical entity drug product developed for the treatment of neovascular (wet) age-related macular degeneration (AMD) administered as an intravitreal (IVT) injection. Aflibercept is a fully human, water-soluble recombinant decoy VEGF receptor. It is biologically engineered to contain key extracellular VEGF-binding domains of VEGF receptor-1 and VEGF receptor-2 fused to the constant Fc region of IgG1.

In support of the BLA, the Applicant submitted 10 clinical studies.

Among the six Phase 1 studies, four were following intravenous (IV) administration and two following IVT administration. Four studies following IV administration were conducted in either healthy volunteers (Studies PDY6655 & PDY6656), or in patients with AMD or choroidal neovascularization (CNV) (Studies VGFT-OD-0305 & VGFT-OD-0306).

The pharmacokinetic (PK) and pharmacodynamic (PD) information generated from IVT-administered aflibercept was derived from two Phase I clinical studies in patients with neovascular AMD (Studies VGFT-OD-0502 and VGFT-OD-0603).

Two Phase II studies were conducted in AMD patients receiving IVT injections of aflibercept (Studies VGFT-OD-0508 and VGFT-OD-0702). PK information was obtained in all patients in VGFT-OD-0508 and in a subset of patients in VGFT-OD-0702 (VGFT-OD-0702.PK sub-study). PD information including central retina/lesion thickness (CR/LT), choroidal neovascularization (CNV) area, and blood pressure (BP) measurements were obtained in both studies.

Two Phase III studies are being conducted in AMD patients receiving IVT-administered aflibercept [Studies VGFT-OD-0605 (VIEW 1) and 311523 (VIEW 2)]. These studies are randomized, double-masked, active-controlled (*vs.* Lucentis®), repeat-dose studies that are evaluating the efficacy, safety, and tolerability of aflibercept. Patients were randomly assigned in a 1:1:1:1 ratio to either of three aflibercept arms (0.5 mg q4w, 2 mg q4w, 2mg q8w following three loading doses at 2 mg q4w) or a ranibizumab arm (0.5 mg q4w). These studies are still ongoing with the total duration of 2 years. The reports submitted in the application contain the first-year data from the studies.

PGR2026-00039
Biocon Ex.1065
Page 40 of 595

1.1. Recommendation

The Clinical Pharmacology information provided by the Applicant in the BLA submission is acceptable.

The reviewer's proposed label changes in Appendix 4.1 should be forwarded to the sponsor.

1.2. Phase IV Commitments

None.

1.3. Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

In patients with neovascular AMD, following intravitreal administration of aflibercept ophthalmic solution, a fraction of the administered dose is expected to bind with endogenous VEGF in the eye to form an inactive aflibercept:VEGF complex. Once absorbed into the systemic circulation, aflibercept presents in the plasma as free aflibercept (unbound to VEGF) and a more predominant stable inactive form with circulating endogenous VEGF (i.e., aflibercept:VEGF complex).

Absorption/Distribution
Following intravitreal administration of 2 mg per eye of aflibercept ophthalmic solution (Study VGFT-OD-0702.PK) to patients with AMD, the mean plasma Cmax of free aflibercept was 0.02 mcg/mL (range: 0 to 0.054 mcg/mL) and was attained in 1 to 3 days. The free aflibercept plasma concentrations were undetectable two weeks post-dosing in all patients. Aflibercept did not accumulate in plasma when administered as repeat doses intravitreally every 4 weeks.

The volume of distribution of free aflibercept following intravenous (I.V.) administration of aflibercept has been determined to be approximately 6 L.

The aflibercept: VEGF complex plasma concentrations reach C_{max} in 14 to 28 days following a 2-mg intravitreal administration with a mean plasma C_{max} of approximately 0.186 mcg/mL (range from 0.100 to 0.286 mcg/mL).

Metabolism/Elimination
Aflibercept is a therapeutic protein and no drug metabolism studies have been conducted. Aflibercept is expected to undergo elimination through both target-mediated disposition via binding to free endogenous VEGF and metabolism via proteolysis. The terminal elimination half-life (t1/2) of free aflibercept in plasma was approximately 5 to 6 days after I.V. administration of doses of 2 to 4 mg/kg aflibercept.

The exploratory subgroup analyses in Phase 3 study VIEW2 did not reveal any clinically relevant influence of the covariants including age, sex, BMI, renal function (determined as creatinine clearance), or geographic region (Europe *vs.* Japan) on the plasma concentrations of free aflibercept or aflibercept :VEGF complex.

PGR2026-00039
Biocon Ex.1065
Page 41 of 595

Yongheng Zhang 06/July 2011

Yongheng Zhang, Ph.D.
Division of Clinical Pharmacology 4
Office of Clinical Pharmacology

Concurrence:

Philip M. Colangelo 7/6/11

Philip Colangelo, Pharm.D., Ph. D.
Team Leader
Division of Clinical Pharmacology 4
Office of Clinical Pharmacology

cc:
Division File: BLA 125387
HFD-520 (CSO/Puglisi)
HFD-520 (MO/Boyd)
HFD-520 (Chambers)
HFD-880 (Lazor)

PGR2026-00039
Biocon Ex.1065
Page 42 of 595

2. QUESTION BASED REVIEW

2.1. General Attributes of the Drug

2.1.1. What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Aflibercept is a recombinant protein consisting of sequences derived from human vascular endothelial growth factor (VEGF) receptor extracellular domains fused to the Fc portion of human immunoglobulin G1 (IgG1). The extracellular domain sequences come from two different VEGF receptors, VEGFR1 and VEGFR2. The amino acid sequence structure of a single aflibercept subunit chain comprises Ig domain 2 from VEGFR1, fused to Ig domain 3 from VEGFR2, which is in turn fused to an Fc domain fragment of IgG1. The presumptive Ig domain structure of aflibercept is provided in **Figure 2.1.1-1**. Aflibercept is a dimeric glycoprotein with a molecular weight (mw) of 96.9 kDa. It contains approximately 15 % glycosylation to give a total mw of 115 kDa. Its molecular formula (without glycosylation) is $C_{4318}H_{6788}N_{1164}O_{1304}S_{32}$. Recombinant aflibercept protein is expressed in CHO K1 cells, and then purified (b) (4) (b) (4) This formulation of aflibercept, which is specially purified and specifically formulated for IVT injection, is called aflibercept injection (VEGF Trap-Eye).

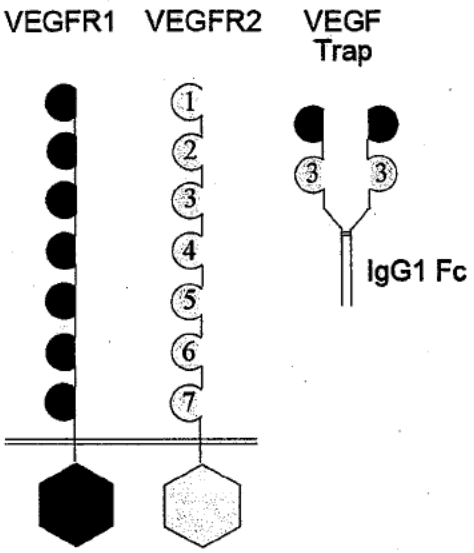


Figure 2.1.1-1: Secondary and tertiary structure of aflibercept, i.e. VEGF Trap

The physicochemical and biochemical properties of aflibercept are provided in **Table 2.1.1-1**. The aqueous solubility of aflibercept in water containing 10 mM sodium phosphate at pH 6.2 is >100 mg/mL at either 5°C or 25° C.

PGR2026-00039
Biocon Ex.1065
Page 43 of 595

Table 2.1.1-1: Physicochemical and biochemical properties of aflibercept

Characteristic	Data
Description	Aflibercept is a recombinant homodimeric glycoprotein with a molecular weight of approximately 115,000 Daltons.
Quaternary structure	Covalent (disulfide linked) dimer
[redacted]	[redacted]

Drug Product:

Aflibercept drug product (DP) is a sterile, clear, and colorless to pale yellow aqueous solution with a nominal pH of 6.2. It is approximately iso-osmotic and available in [redacted] 2 mg, corresponding to the concentration of [redacted] 40 mg/mL, [redacted] The product is intended for ophthalmic use and delivered by intravitreal injection (**Table 2.1.1-2**).

The sponsor submitted [redacted] aflibercept injection for approval (**Table 2.1.1-3**). [redacted]

- [redacted]
- [redacted]
- [redacted] Vials (10 mg/mL and 40 mg/mL)
- [redacted]

[redacted]

PGR2026-00039
Biocon Ex.1065
Page 44 of 595

During aflibercept clinical development, drug product was supplied primarily in vials filled at [redacted] In 2010, drug product in vials was also supplied by [redacted] The drug product manufactured at [redacted] is supplied in the same vials as those used during clinical development.

Table 2.1.1-2: Nominal Composition of Aflibercept Injection, [redacted] 40 mg/mL Formulation

Ingredient	Function	Reference to Quality Standard	Drug Product Concentration (mg/mL)	Quantity per Unit (0.278 mL/Vial) (mg)
VEGF Trap-Eye	Active Ingredient	Regeneron	40	11.120
Sodium phosphate, [redacted]	[redacted]	USP, BP	[redacted]	[redacted]
Sodium phosphate, [redacted]		USP		
Sodium chloride		USP, Ph. Eur., JP		
Sucrose		NF, Ph. Eur., JP		
Polysorbate 20		NF, Ph. Eur., JPE		
[redacted]		USP, Ph. Eur.		

USP = United States Pharmacopeia, BP = British Pharmacopeia, Ph. Eur. = European Pharmacopeia, JP = Japanese Pharmacopeia, JPE = Japanese Pharmaceutical Excipients, NF = National Formulary.

Table 2.1.1-3: Forms of Aflibercept Drug Product Described in BLA 125387

Primary container	Strength (mg/mL)	Dose (mg)	DP filling contractor	DP secondary packaging contractor	DP package sterilization method
[redacted]					
vial	[redacted] 40	[redacted] 2	[redacted]	[redacted]	[redacted]
vial	40	2	[redacted]	[redacted]	[redacted]

PGR2026-00039
Biocon Ex.1065
Page 45 of 595

2.1.2. What is the proposed mechanism of drug action and therapeutic indication?

VEGF-A and placental growth factor (PlGF) are members of the VEGF family of angiogenic factors that can act as potent mitogenic, chemotactic, and vascular permeability factors for endothelial cells. VEGF acts via two receptor tyrosine kinases, VEGFR-1 and VEGFR-2, present on the surface of endothelial cells. PlGF binds only to VEGFR-1, which is also present on the surface of leucocytes. Excessive activation of these receptors by VEGF-A can result in pathological neovascularization and excessive vascular permeability. PlGF can synergize with VEGF-A in these processes, and is also known to promote leukocyte infiltration and vascular inflammation. A variety of ocular diseases, including wet AMD, are associated with pathologic neovascularization and vascular leakage, and can result in thickening and edema of the retina, which is thought to contribute to vision loss.

Aflibercept acts as a soluble decoy receptor that binds VEGF-A and PlGF with higher affinity than their natural receptors, and thereby can inhibit the binding and activation of these cognate VEGF receptors. The equilibrium dissociation constant (K_D) for aflibercept binding to human VEGF-A_{165} is 0.5 pM and to human VEGF-A_{121} is 0.36 pM. The K_D for binding to human PlGF-2 is 39 pM.

Aflibercept ophthalmic solution is indicated for the treatment of patients with Neovascular (Wet) Age-Related Macular Degeneration (AMD).

2.1.3. What are the proposed dosage(s) and route(s) of administration?

The recommended dose regimen for aflibercept injection is 3 initial monthly intravitreal (IVT) injections of 2 mg (50 microliters), followewd by 2 mg (50 microliters) administered by IVT injection once every 2 months.

2.2. General Clinical Pharmacology

2.2.1. What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The PK and/or PD information generated following IV or IVT administration of aflibercept was derived from six Phase I studies.

Four **Phase I** studies following IV administration were conducted in either healthy volunteers, or in patients with AMD or choroidal neovascularization (CNV):

1. Study PDY6655: an open-label (OL), single dose, crossover study with both the IV and SC formulations in healthy male volunteers.
2. Study PDY6656: a randomized, double-blind, placebo-controlled, sequential ascending dose study with the IV formulation in healthy male volunteers.
3. Study VGFT-OD-0305: a double masked, placebo-controlled, sequential-group, dose-escalating study with the IV formulation in patients with neovascular AMD.
4. Study VGFT-OD-0306: an open-label, long-term study with the IV formulation in patients with neovascular AMD.

PGR2026-00039
Biocon Ex.1065
Page 46 of 595

The PK and PD information generated from IVT administered aflibercept were derived from two Phase I clinical studies in patients with neovascular AMD (VGFT-OD-0502 and VGFT-OD-0603).

1. VGFT-OD-0502: an OL dose-escalation study;
2. VGFT-OD-0603: a double-masked, randomized study that compared aflibercept formulated in either the ITV-1 or ITV-2 formulations.

Two **Phase II** studies were conducted in AMD patients receiving IVT injections of aflibercept (VGFT-OD-0508 and VGFT-OD-0702):

1. Study VGFT-OD-0508: a double-masked, prospective, randomized, multiple-dose study;
2. Study VGFT-OD-0702: a randomized, single-masked, long-term extension study in patients who had previously participated in either VGFT-OD-0502, VGFT-OD-0508, or VGFT-OD-0603.

Pharmacokinetics information was obtained in all patients in VGFT-OD-0508 and in a subset of patients in VGFT-OD-0702 (VGFT-OD-0702.PK). Pharmacodynamic information including central retina/lesion thickness (CR/LT), choroidal neovascularization (CNV) area, and blood pressure (BP) measurements were obtained in both studies.

Two **Phase III** studies are being conducted in AMD patients receiving IVT-administered aflibercept [VGFT-OD-0605 (VIEW 1) and 311523 (VIEW 2)]. These studies are randomized, double-masked, active controlled repeat-dose studies that evaluated the efficacy, safety, and tolerability of aflibercept. Patients were randomly assigned in a 1:1:1:1 ratio to either of three aflibercept arms (0.5 mg q4w, 2 mg q4w, 2mg q8w following three loading doses at 2 mg q4w) or a ranibizumab arm (0.5 mg q4w). The first year (through the primary endpoint) of these studies has been completed and the reports were submitted in this application.

Pharmacokinetic information was obtained only in Study 311523 (VIEW 2). Pharmacodynamics information (central retinal thickness [CRT] and change in CNV area) and blood pressure (BP) measurements were obtained in both studies.

2.2.2. What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics [PD]) and how are they measured in clinical pharmacology and clinical studies?

Optical coherence tomography (OCT) was used to measure retinal and subretinal fluid accumulation and thickness of AMD lesions. Central retinal/lesion thickness (CR/LT) is known to be a fast reacting variable that shows PD response to anti-VEGF treatments in a reproducible way. This makes CR/LT an accepted response marker even though it is known to not always correlate on an individual patient basis with the main efficacy variable, best corrected visual acuity (BCVA). In addition, measurements of choroidal neovascularization (CNV) area by fluorescein angiography (FA) were carried out providing additional morphological insight into the PD effects at the target site.

2.2.3. Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes, free aflibercept (active) and bound aflibercept (inactive) plasma concentrations were measured using validated enzyme-linked immunosorbent assay (ELISA) methods (*Refer to Section 2.6*).

PGR2026-00039
Biocon Ex.1065
Page 47 of 595

2.2.4. Exposure-response

2.2.4.1. What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy? If relevant, indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.

The dose-PD response in the eye was studied with respect to dose, in StudyVGFT-OD-0502, and to dosing regimen, in Study VGFT-OD-0508. The PD parameters used to assess the dose-response relationship in the eye include CR/LT and CNV area. Following IVT administration of aflibercept, a dose-dependent reduction in CR/LT was observed in AMD patients, with clear effects seen at 0.5 mg/eye, and the maximum improvement being achieved at a dose of 2 mg/eye. There was little further improvement observed at 4 mg/eye. These data suggest that the maximal decrease in CR/LT is achieved between 0.5 mg/eye and 2 mg/eye and that higher doses of aflibercept beyond 2 mg/eye are not warranted. Data obtained from the Phase-2 studies suggest that a dosing interval of Q12 weeks (0.5 mg, 2 mg or 4 mg) did not provide a sustained PD improvement over the entire dosing interval, indicating that the optimal dosing interval would be less than every 12 weeks. However, specific dosing intervals between every 4 weeks and every 12 weeks were not evaluated in these trials.

2.2.4.2. *What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety? If relevant, indicate the time to the onset and offset of the undesirable pharmacological response or clinical endpoint.*

The increases in both diastolic BP (DBP) and systolic BP (SBP) seen with systemic administration of drugs that inhibit or interfere with the VEGF signaling pathway are attributed to the reduction of free systemic VEGF. There is a dose-dependent correlation between plasma free aflibercept concentrations (systemic administration) and the appearance of systemic PD effects (BP change, *refer to Section 4.2.6*). When administered via the IVT route, aflibercept was not observed to cause increases in DBP (**Figure 2.2.4.2-1**) or SBP. This is further illustrated by the comparison between the systemic exposure (C_{max}) of free and bound aflibercept following IV and IVT administration of aflibercept (**Figure 2.2.4.2-2**), and the dose-response (BP change) relationship over time following IV and IVT administration of aflibercept (**Figure 2.2.4.2-3**).

Free aflibercept plasma concentrations following IVT administration of doses of up to 4 mg/eye (approximately 0.057 mg/kg, based on a 70 kg body weight) were approximately 1/1000th to 1/100th of the free aflibercept plasma concentrations observed following I.V. administration of doses $\geq$ 1 mg/kg (**Figure 2.2.4.2-2**). Concentrations of bound aflibercept in plasma following IVT administration of doses of up to 4 mg/eye were approximately 1/20th of the plasma bound aflibercept concentrations determined following IV administration of doses of 1 to 4 mg/kg. Considering that IV doses $\geq$ 1 mg/kg are required to completely bind the endogenous systemic VEGF present at the time of dosing as well as VEGF that is synthesized in the weeks thereafter, the IVT doses investigated in the application were far from saturating the endogenous systemic VEGF. This conclusion is further supported by the observation that the peak concentrations of bound aflibercept continue to increase in a dose-dependent manner with increasing IVT doses (*Refer to Section 4.2.2: Study VGFT-OD-0502*). Moreover, the absence of systemic PD findings following IVT administration (**Figure 2.2.4.2-1 & 3**) support the observation that these IVT doses and the resulting low systemic exposures are unable to reduce systemic free endogenous

PGR2026-00039
Biocon Ex.1065
Page 48 of 595

VEGF concentrations to a level sufficient to cause inhibition of systemic VEGF activity throughout the dosing interval.

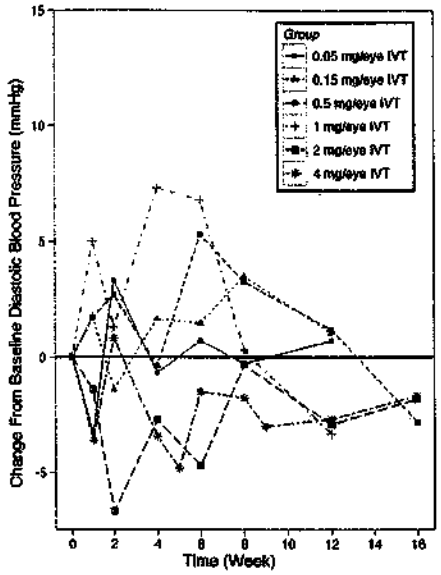
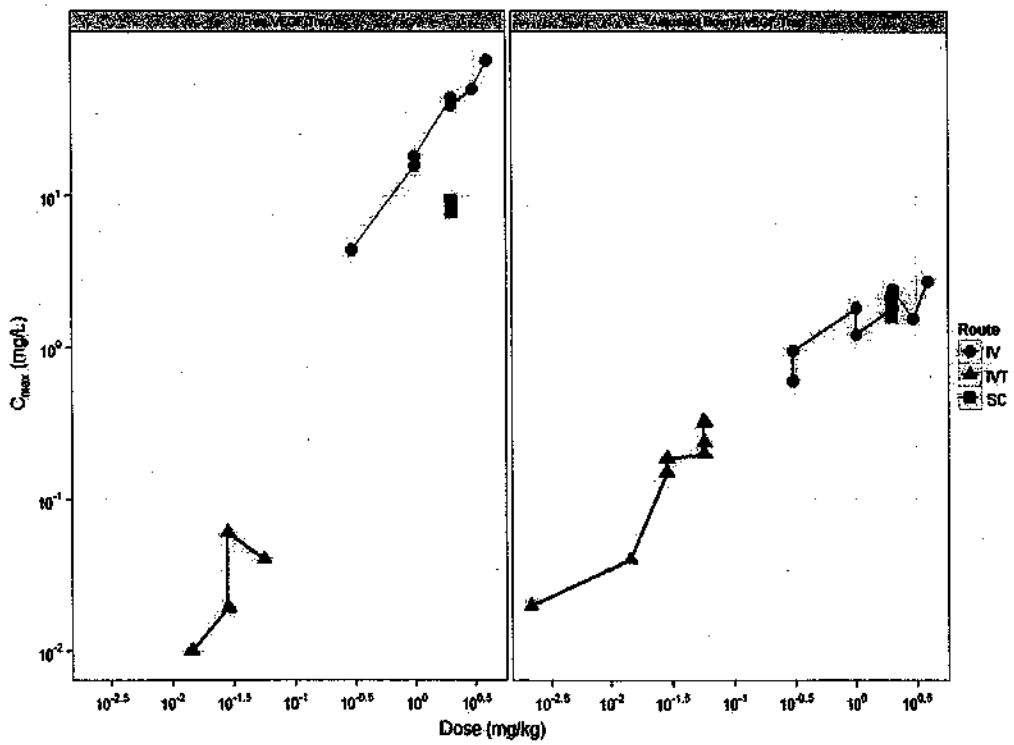


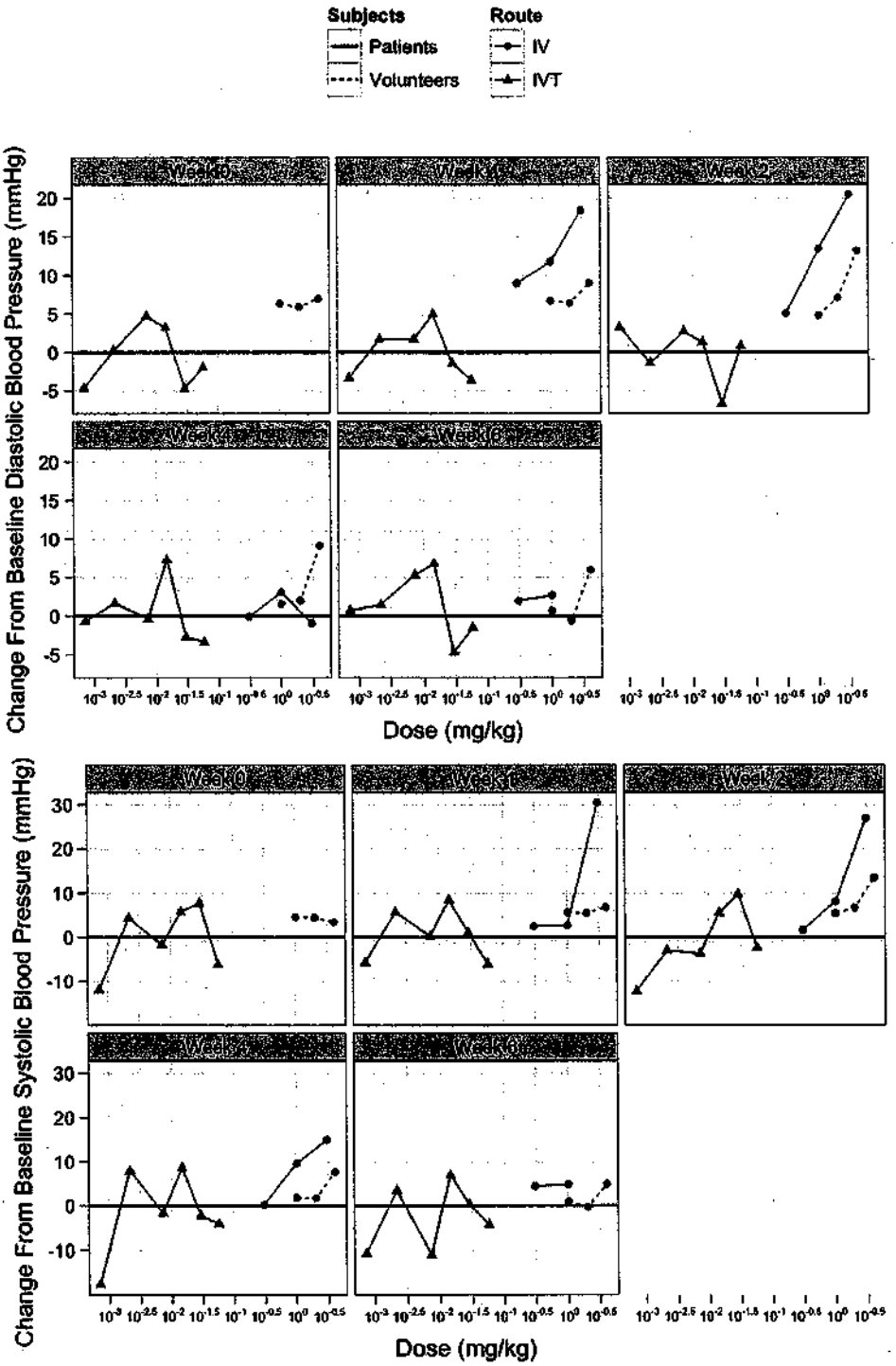
Figure 2.2.4.2-1: Mean Change from Baseline in Diastolic Blood Pressure by Dose (Phase I and II Studies including VGFT-OD-0502, -0603, and -0508)



Note: The IVT doses were converted to an approximate mg/kg value by assuming a patient weight of 70 kg.
Data source: VGFT-OD-0603, VGFT-OD-0502, VGFT-OD-0702.PK, PDY6656, and *VGFT-OD-0305/306,, PDY6655 (not reviewed).*

Figure 2.2.4.2-1: Mean or Median Cmax of Free and Adjusted Bound aflibercept After IVT, IV, or *SC (not reviewed)* Administration versus Weight-Normalized Dose of Aflibercept

PGR2026-00039
Biocon Ex.1065
Page 49 of 595



Note: The IVT doses were converted to an approximate mg/kg value by assuming a patient weight of 70 kg.

Data source: VGFT-OD-0603, VGFT-OD-0502, VGFT-OD-0508, PDY6656, and *VGFT-OD-0305, VGFT-OD-0307, PDY6655 (not reviewed).*

Figure 2.2.4.2-3: Comparison of Mean Change from Baseline Diastolic and Systolic Blood Pressures Following IV and IVT Administration of Aflibercept (Phase I and Phase II Studies)

PGR2026-00039
Biocon Ex.1065
Page 50 of 595

2.2.4.3. Does this drug prolong the QT or QTc interval? (You must answer this question, unless this is addressed in the question above.)

No, aflibercept did not prolong the QT or QTc interval following IVT administration in the clinical trials population. A thorough QT study was not conducted.

2.2.4.4. Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

The dosing rationale for both Phase 3 pivotal trials was based on the dose-response relationship derived from Phase 1 and 2 studies (Refer to *Section 2.2.4.1*). Both Phase 3 studies compared three aflibercept regimens (0.5 mg and 2 mg dosed monthly, and 2 mg dosed every two months) to ranibizumab 0.5 mg dosed monthly.

The 0.5-mg dose was chosen as the lowest dose for which efficacy could be expected. In particular, during the prn part of the Phase-2 study VGFT-OD-0508, the 0.5-mg dose did not perform as well as the 2 mg dose. No dose higher than 2 mg was selected for the Phase-3 program because the highest dose administered during Phase-2, i.e. 4 mg, was not associated with improvements in the efficacy parameters beyond those achieved with a dose of 2 mg. The rationale for including a prolonged dosing interval of two months for 2 mg aflibercept was based on the observation from VGFT-OD-0508 that, at Week 8, improvements in visual acuity after a single 2-mg dose were similar to those obtained with 2 mg dosed monthly, suggesting that a longer and less burdensome dosing interval (i.e. every 8 weeks) may be possible without compromising efficacy.

There is no unresolved dosing or administration issues.

2.2.5. What are the PK characteristics of the drug?

2.2.5.1. What are the single dose and multiple dose PK parameters?

For the single dose Study VGFT-OD-0502, systemic exposure (C_{max} and AUC) to free aflibercept following IVT administrations of aflibercept is summarized in **Table 2.2.5.1-1**. PK parameters including C_{max} and AUC for free aflibercept were highly variable (CV>69%).

Systemic PK parameters obtained from Study VGFT-OD-702.PK (repeated IVT doses) were not considered significantly different from that reported in the 2 mg single IVT dose group of Study VGFT-OD-0502, given the wide inter-subject variability and range of AUC and Cmax:

- Mean C_{max} of free aflibercept: 0.0193 mg/L (Study # -0702, range from 0 to 0.054 mg/L) vs. 0.0636±0.0404 mg/L (Study # -0502).
- Mean $AUC_{0\text{-}last}$ of free aflibercept: 0.153 day*mg/L (Study #-0702, range from 0 to 0.586 day*mg/L) vs. 0.302±0.215 day*mg/L (Study # -0502).

PGR2026-00039
Biocon Ex.1065
Page 51 of 595

Table 2.2.5.1-1: Summary of PK Parameters of Free Aflibercept by Dose (Single IVT dose)
Source: VGFT-OD-0502 PK report

Dose (mg) / Parameter		N	Mean	SE	CV%	Min	Median	Max
Cmax (mg/L)	**0.05**	3	0	0	N/A	0	0	0
	0.15	17	0	0	N/A	0	0	0
	0.5	3	0	0	N/A	0	0	0
	1	6	0.00796	0.00507	156.	0	0	0.0263
	2	4	0.0636	0.0404	127.	0	0.0430	0.168
	4	16	0.0411	0.00715	69.5	0	0.0341	0.110
AUCall (day*mg/L)	**0.05**	3	0	0	N/A	0	0	0
	0.15	17	0	0	N/A	0	0	0
	0.5	3	0	0	N/A	0	0	0
	1	6	0.0302	0.0196	158.	0	0	0.107
	2	4	0.302	0.215	143.	0	0.147	0.913
	4	16	0.407	0.0739	72.6	0	0.362	0.954

Notes: Winnonlin NCA Model 200. In the noncompartmental model, dose was expressed in mg.

$AUC_{all} = AUC_{0\text{-last}}$

2.2.5.2. How does the PK of the drug in healthy volunteers compare to that in patients?

The systemic exposure to free aflibercept following IVT administration was only evaluated in patients.

2.2.5.3. What are the characteristics of drug absorption?

The free aflibercept plasma concentration reached the maximal concentration (C_{max}) in 1 to 3 days following a 2-mg intravitreal administration (Study VGFT-OD-0702.PK) with a mean C_{max} of approximately 0.02 µg/mL (range from 0 to 0.054 µg/mL), and were undetectable two weeks post-dosing in all patients. Free aflibercept did not accumulate in the plasma when administered intravitreally every 4 weeks.

2.2.5.4. What are the characteristics of drug distribution?

In patients with neovascular AMD, following IVT administration of aflebercept, a fraction of administered dose is expected to bind with endogenous VEGF in the eye to form an inactive aflibercept: VEGF complex. Once absorbed into systemic circulation, aflibercept presents as free aflibercept and a more predominant inactive form with circulating endogenous VEFG, i.e., the aflibercept: VEFG complex. The terminal elimination half-life (t1/2) and volume of distribution of free aflibercept following IV administration has been determined to be approximately 5 to 6 days and 6 L, respectively (Study PDY6656).

2.2.5.5. Does the mass balance study suggest renal or hepatic as the major route of elimination? (This may include table with results of mass balance study.)

A mass balance study was not performed.

2.2.5.6. What are the characteristics of drug metabolism?

PGR2026-00039
Biocon Ex.1065
Page 52 of 595

No drug metabolism studies were conducted.

2.2.5.7. What are the characteristics of drug excretion?

Free aflibercept is eliminated both through binding to VEGF, as well as through a slower non-saturable clearance (e.g. protein catabolism by proteolysis) mechanism. Free aflibercept is not expected to be eliminated by the kidney due to its relatively large molecular size (115 KDa).

2.2.5.8. Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

As shown in **Table 2.2.5.1-1**(Study VGFT-OD-0502), C_{max} and AUC values of free aflibercept were highly variable (CV% >69%) and generally increase as the dose increases.

2.2.5.9. How do the PK parameters change with time following chronic dosing?

Refer to *Section 2.2.5.1.*

2.2.5.10. What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

The systemic exposure to free aflibercept following IVT administration was only evaluated in patients. As shown in **Table 2.2.5.1-1**(Study VGFT-OD-0502), C_{max} and AUC values of free aflibercept were highly variable (CV% >69%). This level of inter-subject variability in systemic exposure is not considered unexpected following IVT administration, particularly when considering that drug absorption to systemic circulation may vary due to the potential permeability differences in the retina-blood barrier among AMD patients.

2.3. Intrinsic Factors

2.3.1. What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

The exploratory subgroup analyses in Phase 3 study VIEW2 did not reveal any clinically relevant influence of the covariants including age, sex, BMI, renal function determined as creatinine clearance, or geographic region (Europe vs. Japan) on the plasma concentrations of free aflibercept or bound aflibercept. For example, pharmacokinetic analysis of a subgroup of patients (n=496) in one Phase 3 study, of which 41% had renal impairment (mild N=118, moderate N=72, and severe N=15), revealed no differences with respect to plasma concentrations of free aflibercept after intravitreal administration every 4 or 8 weeks. As a therapeutic protein of 115 KDa, aflibercept is not expected to be eliminated by the kidney. It is expected to undergo elimination through both target-mediated disposition via binding to endogenous VEGF and metabolism via proteolysis. Therefore from a PK perspective, there is no mechanistic basis for dose adjustment based on renal or hepatic impairment status following IVT administration of aflibercept.

2.4. Extrinsic Factors

PGR2026-00039
Biocon Ex.1065
Page 53 of 595

2.4.1. What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?
Based upon what is known about exposure-response relationships and their variability, what dosage regimen adjustments, if any, do you recommend for each of these factors? If dosage regimen adjustments across factors are not based on the exposure-response relationships, describe the basis for the recommendation.

No extrinsic factors have been shown to influence aflibercept exposure-response. Therefore, no dosage adjustments for extrinsic factors are recommended.

2.4.2. Drug-drug interactions

2.4.2.1. Is there an in vitro basis to suspect in vivo drug-drug interactions?

There is no in vitro basis to suspect in vivo drug-drug interactions with aflibercept.

2.4.2.2. Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

As a fusion protein, aflibercept is expected to be degraded into small peptides and individual amino acids. Therefore, it is not expected to be a substrate of CYP enzymes nor have metabolism influenced by genetics.

2.4.2.3. Is the drug an inhibitor and/or an inducer of CYP enzymes?

As a fusion protein, aflibercept is not expected to be an inhibitor and/or an inducer of CYP enzymes.

2.4.2.4. Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

As a fusion protein, aflibercept is not expected to be an inhibitor and/or substrate of P-glycoprotein transport process.

2.4.2.5. Are there other metabolic/transporter pathways that may be important?

Since aflibercept is a fusion protein, other metabolic/transporter pathways are not expected to be of importance.

2.4.2.6. Does the label specify co-administration of another drug and, if so, has the interaction potential between these drugs been evaluated?

No, the label does not specify co-administration of another drug.

2.4.2.7. What other co-medications are likely to be administered to the target patient population?

No co-administered drugs can be specified.

PGR2026-00039
Biocon Ex.1065
Page 54 of 595

2.4.2.8. Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

In vivo drug-drug interactions studies have not been conducted and are not needed.

2.4.2.9. Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?

There is no known mechanistic basis for PD drug-drug interaction.

2.4.2.10. Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding?

There are no unresolved questions related to metabolism, active metabolites, metabolic drug interaction, or protein binding.

2.4.3. What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions?

No issues related to dose, dosing regimens, or administration remain unresolved.

2.5. General Biopharmaceutics

Not applicable. Aflibercept is formulated as an ophthalmic solution for intravitreal administration.

2.6. Analytical Section

This section summarizes the bioanalytical methods (**Table 2.6-1**) utilized to assess therapeutic protein concentrations and the formation of the anti-product antibodies. Details for the bioanalytical methodology used to determine free and bound aflibercept plasma concentrations and anti-drug antibody are presented in the individual study review in *Section 4.2*.

Table 2.6-1: Summary of Bioanalytical Methods Used in Clinical Studies

Methods Report (Report Location)	Matrix (Anticoagulant)	Analytes	Calibration Range (ng/mL)	LLOQ[a] (Sensitivity)	Intra-Assay Precision (%CV)[b]	Intra-Assay Accuracy (AR%)[c]	Inter-Assay Precision (%CV)	Inter-Assay Accuracy (AR%)
VGFT-AS-01026-SA-01V2	Plasma (CTAD)	Free VEGF Trap	3.13 – 100	31.3 ng/mL	3.3 to 3.8	103 to 112	2.4 to 10.5	91 to 106
VGFT-AV-01026-PV01-01V2			1.56 – 100	15.6 ng/mL	9.6 to 13.7	106 to 110	1.1 to 16.2	92 to 103
VGFT-AS-02016-SA-01V2		Bound VEGF Trap	8.78 – 100	43.9 ng/mL[d]	2.0 to 4.4	79 to 84	1.6 to 10.0	80 to 110
VGFT-AV-02016-PV01-01V2					1.1 to 1.6	116 to 123	0.4 – 16.2	94 to 110
VGFT-AS-03019/03036-SA-01V6	Serum	ADA[e]	11.92-200	238.4 ng/mL	2.3 to 6.5	96 to 107	1.0 to 10.0	93 to 106
VGFT-AV-08035-SA-01V1			Non quantitative assay	(5.4 ng/mL)	NA[f]			
VGFT-AV-07023-SA-01V1		NAb[g]		(940 ng/mL)				

[a] LLOQ: Lower limit of quantitation; LLOQ differs from calibration range due to dilution of samples for analysis
[b] %CV: Percent coefficient of variance
[c] AR%: Analyte recovery expressed as a percentage
[d] LLOQ of 43.9 ng/mL is for the bound VEGF Trap; the LLOQ for the adjusted bound VEGF Trap is 31.5 ng/mL, see Section 1.5.3
[e] Anti-drug antibodies
[f] Accuracy and precision not applicable for non-quantitative assays
[g] Neutralizing antibodies

PGR2026-00039
Biocon Ex.1065
Page 55 of 595

2.6.1. How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

Free aflibercept (active, aflibercept) plasma concentrations were measured using a validated enzyme-linked immunosorbent assay (ELISA) method.

2.6.2. Which metabolites have been selected for analysis and why?

The bound aflibercept (inactive) concentrations in the plasma were analyzed by a validated ELISA method.

In addition, as a fusion protein administered into the body, aflibercept has the potential to induce an immune response resulting in the development of anti-drug antibodies (ADA). The potential immunogenicity of aflibercept in subjects participating in clinical studies was evaluated using one of two different ADA assays.

2.6.3. For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

Not applicable as aflibercept is a fusion protein.

2.6.4. What bioanalytical methods are used to assess concentrations?

Assay for free aflibercept:
Plasma concentrations of free aflibercept were determined using a validated ELISA performed in 10% human CTAD (buffered citrate, theophylline, adenosine and dipyridamole) plasma in a microplate coated with human $VEGF_{165}$ to capture free aflibercept in the sample matrix (*Validation report VGFT-AV-01026-PV01-SA-01V3*). A mouse monoclonal antibody, specific to an epitope on aflibercept, was used as the primary detection reagent in the assay. An enzyme-linked antibody (peroxidase-conjugated Affinipure goat anti-mouse IgG Fc-γ) was then used as a secondary antibody to detect the captured aflibercept. To determine free aflibercept, a luminol-based substrate specific for peroxidase was used to achieve a signal intensity that is directly proportional to the concentration of free aflibercept.

Assay for bound aflibercept:
Plasma concentrations of bound aflibercept were determined using a validated ELISA (*Validation report VGFT-AS-02016-PV01-SA-01V2*). The assay did not detect the free form of aflibercept in human plasma samples. The bound aflibercept assay used a microplate coated with goat anti-VEGF polyclonal antibody to capture bound aflibercept. This antibody only captured aflibercept that is bound to VEGF. A mouse monoclonal antibody specific to an epitope on aflibercept was used to detect bound aflibercept that has been captured by the goat anti-VEGF polyclonal antibody. An enzyme-linked antibody (peroxidase-conjugated Affinipure goat anti-mouse IgG Fc-γ) is used as a secondary detection reagent to detect the captured aflibercept. To determine bound aflibercept, a luminol-based substrate specific for peroxidase was used to achieve a signal intensity that is directly proportional to the concentration of bound aflibercept.

Assay for anti-aflibercept antibody:
Two assays for anti-drug antibody response (ADA) were developed: an original, quasi-quantitative, ELISA-based assay used in the Phase I/II studies with a sensitivity of ~ 240 ng/mL, and a more sensitive, titer-based, non-quantitative, bridging immunoassay used in the Phase III

PGR2026-00039
Biocon Ex.1065
Page 56 of 595

studies (VIEW 1 and VIEW 2) with a sensitivity of ~ 5.4 ng/mL. Samples that were positive in the anti-drug antibody (ADA) assays (VIEW 1 and VIEW 2 trials) were further characterized by a neutralizing antibody (NAb) assay (*Not reviewed*).

2.6.4.1. What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

Assay for free aflibercept:
This assay was calibrated using a standard curve generated from seven free aflibercept standards (100, 50, 25, 12.5, 6.25, 3.13 and 1.56 ng/mL).

The Relative Light Unit (RLU) readings of the standards are calibrated against their respective nominal concentrations using a 4-parameter logistic curve fit (see equation below), from which all other measurements (samples and QCs) are subsequently computed.

$$y = ((A-D) / (1 + (x / C)^B)) + D$$

A is the y-value corresponding to the bottom asymptote, D is the y-value corresponding to the top asymptote, C is x-value at the inflection point of the sigmoidal curve and B is the slope. The curve parameters are automatically computed for each equation using the Levenberg-Marquardt curve-fitting algorithm. The y-axis represents the RLU values and the x-axis represents the nominal aflibercept concentrations. The RLU response from each sample is then back-calculated from the respective calibration equation. The triplicate back-calculated dose-response (ng/mL) of each sample is then averaged and the relative standard deviation is described in term of the percent coefficient of variance (%CV). The mean back-calculated concentration from each sample is finally corrected for dilutions to estimate aflibercept levels.

The range of the standard curve is adequate for purposes of determining plasma concentrations of free aflibercept in the clinical studies.

Assay for bound aflibercept:
This assay was calibrated using a standard curve generated from seven bound aflibercept standards (100, 66.67, 44.44, 29.63, 19.75, 13.17 and 8.78 ng/mL).

The Relative Light Unit (RLU) readings of the Standards are calibrated against their respective nominal concentrations using a Log-Log curve fit (see equation below) from which all other measurements (samples and QCs) are subsequently computed.

$$\text{Log10}(y) = A + B(\text{Log10}(x))$$

Where A is the log10 y-intercept (when log10 x = 0), B is the slope of the line, x = dose or back calculated concentration of bound aflibercept and y is the corresponding RLU. Based on this equation, the RLU readings of the QCs and plasma samples were used to calculate their bound aflibercept concentration.

The range of the standard curve is adequate for purposes of determining plasma concentrations of bound aflibercept in the clinical studies.

Assay for anti-aflibercept antibody:
ELISA assay - This assay was calibrated using a standard curve generated from seven standards prepared using the anti-R1 monoclonal antibody at concentrations of 200, 125, 78.13, 48.83,

PGR2026-00039
Biocon Ex.1065
Page 57 of 595

30.52, 19.07 and 11.92 ng/mL. The absorbance of the calibration standards was plotted against the nominal concentrations of anti-aflibercept antibody and fitted with a four-parameter logistic (4PL) curve fit and the results reported in terms of mass equivalent antibody unit per volume (ng/mL). The ranges of standard curve are adequate for purposes of determining serum concentrations of ADA in the clinical studies.

2.6.4.2. What are the lower and upper limits of quantification (LLOQ/ULOQ)?

Assay for free aflibercept:
The assay was performed in a 10% human (CTAD) plasma matrix. The LLOQ and ULOQ are 15.6 ng/mL and 1000 ng/mL in the undiluted plasma sample, respectively.

Assay for bound aflibercept:
The assay was performed in a 20% human (CTAD) plasma matrix. The LLOQ and ULOQ are 43.9 ng/mL and 500 ng/mL in the undiluted plasma sample, respectively.

Assay for anti-aflibercept antibody:
ELISA assay - The assay was performed in a 5% human serum matrix. The LLOQ and ULOQ are 238.4 ng/mL and 4 µg/mL in the undiluted serum sample, respectively.

Non-quantitative bridging immunoassay- The sensitivity of the bridging immunoassay is approximately 5.4 ng/mL in the absence of aflibercept and about 25.2 ng/mL in the presence of **20 µg/mL of** aflibercept.

2.6.4.3. What are the accuracy, precision, and selectivity at these limits?

Assay for free aflibercept:
The assay accuracy and precision were determined from the assay standards and QCs. The accuracy values ranged from 92.2% to 109.9%. The precision values ranged from 1.05% to 16.18%. Assay selectivity was confirmed by analyzing 10 naïve human plasma samples and none yielded above BLQ results.

Assay for bound aflibercept:
The assay accuracy and precision were determined from the assay standards and QCs. The accuracy values ranged from 93.38% to 123.34%. The precision values ranged from 0.38% to 16.17%. Assay selectivity was not evaluated.

Assay for anti-aflibercept antibody:
ELISA assay- The assay accuracy and precision were determined from the assay standards and positive QCs. The accuracy values ranged from 94.53% to 103.76%. The precision values ranged from 0.14% to 6.44%. Assay selectivity was confirmed by analyzing 10 naïve human plasma samples and none yielded above BLQ results.

2.6.4.4. What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler)?

Assay for free aflibercept:
Free aflibercept was stable when stored at ~ -80°C up to 15 months, in human plasma after 9 freeze-thaw cycles, stored at room temperature for 4 hours, and stored overnight at 2°C to 8°C.

Assay for bound aflibercept:

PGR2026-00039
Biocon Ex.1065
Page 58 of 595

Samples were stable when stored at ~ -80°C up to 24 months and after 10 freeze-thaw cycles.

Assay for anti-aflibercept antibody:
ELISA assay- The positive QCs for the assay (the mouse monoclonal) in human serum was shown to be stable after 3 freeze-thaw cycles, storage at room temperature for 4 hours and storage overnight at 2°C to 8°C. Long-term stability of the mouse monoclonal in human serum was demonstrated for up to 12 months at -80°C.

Non-quantitative bridging immunoassay- The positive QCs were shown to be stable after 10 freeze-thaw cycles, storage at room temperature for 5 hours, storage overnight at 2°C to 8°C and after long-term storage at -80°C for up to 24 months.

2.6.4.5. What is the QC sample plan?

Assay for free aflibercept:
Three QCs prepared in plasma at a concentration of 700, 350 and 40 ng/mL of free aflibercept were diluted to 10% plasma (final concentrations of 70, 35 and 4 ng/mL) and included in each analysis.

Assay for bound aflibercept:
Three QCs prepared in plasma at a concentration of 400, 200 and 125 ng/mL of VEGF: aflibercept were diluted to 20% plasma (final concentrations of 80, 40 and 25 ng/mL) and included in each analysis.

Assay for anti-aflibercept antibody:
ELISA assay- The positive QCs were prepared in serum at a concentration of 3200, 1280 and 512 ng/mL of anti-R1 monoclonal antibody and then diluted to 5% serum (final concentrations of 160, 64 and 25.6 ng/mL) and included in each analysis.

Non-quantitative bridging immunoassay- Three positive QC samples, prepared with the mouse anti-aflibercept monoclonal antibody were included in each assay run: a high QC (6000 ng/mL), a mid QC (600 ng/mL), and a low QC (30 ng/mL) sample.

21 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

PGR2026-00039
Biocon Ex.1065
Page 59 of 595

APPENDIX BAYER01

https://web.archive.org/web/20170815000000*/http://www.bayerresources.com.au/resources/uploads/PI/file10294.pdf September 17, 2025

INTERNET ARCHIVE WEB TEXTS VIDEO AUDIO SOFTWARE IMAGES SIGN UP | LOG IN UPLOAD Search

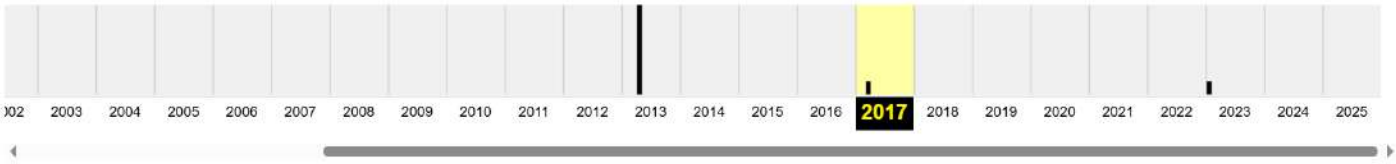
ABOUT BLOG PROJECTS HELP DONATE CONTACT JOBS VOLUNTEER PEOPLE

DONATE INTERNET ARCHIVE WayBackMachine Explore more than 946 billion web pages saved over time

http://www.bayerresources.com.au/resources/uploads/PI/file102

Calendar · Collections · Changes · Summary · Site Map · URLs

Saved **9 times** between April 22, 2013 and January 16, 2023.



JAN

1	2	3	4	5	6	7
8	9	10	11	12	13	14
15	16	17	18	19	20	21
22	23	24	25	26	27	28
29	30	31				

FEB

			1	2	3	4
5	6	7	8	9	10	11
12	13	14	15	16	17	18
19	20	21	22	23	24	25
26	27	28				

MAR

			1	2	3	4
5	6	7	8	9	10	11
12	13	14	15	16	17	18
19	20	21	22	23	24	25
26	27	28	29	30	31	

APR

						1
2	3	4	5	6	7	8
9	10	11	12	13	14	15
16	17	18	19	20	21	22
23	24	25	26	27	28	29
30						

MAY

	1	2	3	4	5	6
7	8	9	10	11	12	13
14	15	16	17	18	19	20
21	22	23	24	25	26	27
28	29	30	31			

JUN

				1	2	3
4	5	6	7	8	9	10
11	12	13	14	15	16	17
18	19	20	21	22	23	24
25	26	27	28	29	30	

JUL

						1
2	3	4	5	6	7	8
9	10	11	12	13	14	15
16	17	18	19	20	21	22
23	24	25	26	27	28	29
30	31					

AUG

		1	2	3	4	5
6	7	8	9	10	11	12
13	14	15	16	17	18	19
20	21	22	23	24	25	26
27	28	29	30	31		

SEP

				1	2	
3	4	5	6	7	8	9
10	11	12	13	14	15	16
17	18	19	20	21	22	23
24	25	26	27	28	29	30

OCT

1	2	3	4	5	6	7
8	9	10	11	12	13	14
15	16	17	18	19	20	21
22	23	24	25	26	27	28
29	30	31				

NOV

			1	2	3	4
5	6	7	8	9	10	11
12	13	14	15	16	17	18
19	20	21	22	23	24	25
26	27	28	29	30		

DEC

					1	2
3	4	5	6	7	8	9
10	11	12	13	14	15	16
17	18	19	20	21	22	23
24	25	26	27	28	29	30
31						

Note

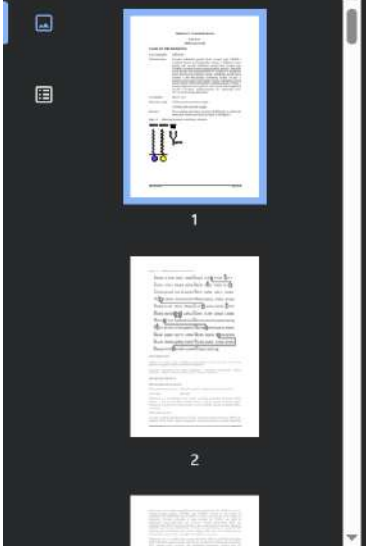
This calendar view maps the number of times **http://www.bayerresources.com.au/resources/uploads/PI/file10294.pdf** was crawled by the Wayback Machine, *not* how many times the site was actually updated. More info in the FAQ.

FAQ | Contact Us | Terms of Service (Dec 31, 2014)

The Wayback Machine is an initiative of the Internet Archive, a 501(c)(3) non-profit, building a digital library of Internet sites and other cultural artifacts in digital form. Other projects include Open Library & archive-it.org.

Your use of the Wayback Machine is subject to the Internet Archive's Terms of Use.

https://web.archive.org/web/20170308065657/http:/www.bayerresources.com.au/resources/uploads/PI/file10294.pdf September 17, 2025
INTERNET ARCHIVE WayBack Machine http://www.bayerresources.com.au/resources/uploads/PI/file10294.pdf Go APR MAR JAN
9 captures 22 Apr 2013 - 16 Jan 2023 2013 08 2017 2023 About this capture



PRODUCT INFORMATION

EYLEA®
aflibercept (rch)

NAME OF THE MEDICINE

Active ingredient:	Aflibercept
Chemical names:	Vascular endothelial growth factor receptor type VEGFR-1 (synthetic human immunoglobulin domain 2 fragment) fusion protein with vascular endothelial growth factor receptor type VEGFR-2 (synthetic human immunoglobulin domain 3 fragment) fusion protein with immunoglobulin G1 (synthetic Fc fragment), dimer des-432-lysine-[human vascular endothelial growth factor receptor 1-(103-204)-peptide (containing Ig-like C2-type 2 domain) fusion protein with human vascular endothelial growth factor receptor 2-(206-308)-peptide (containing Ig-like C2-type 3 domain fragment) fusion protein with human immunoglobulin G1-(227 C-terminal residues)-peptide (Fc fragment)], (211-211':214-214')-bisdisulfide dimer
CAS number:	862111-32-8
Molecular weight:	97 kDa (protein molecular weight)

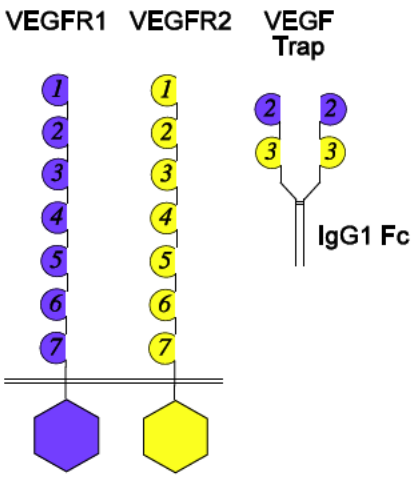
PRODUCT INFORMATION

EYLEA®
aflibercept (rch)

NAME OF THE MEDICINE

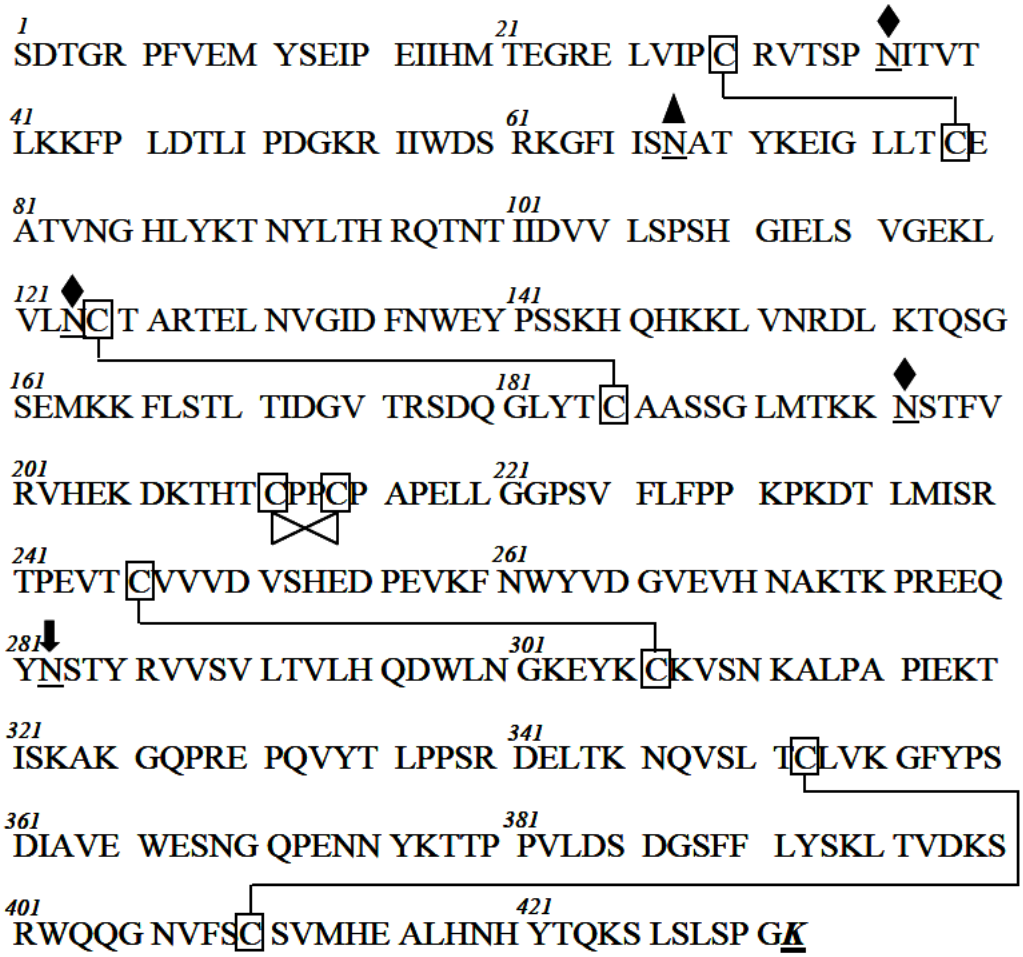
Active ingredient:	Aflibercept
Chemical names:	Vascular endothelial growth factor receptor type VEGFR-1 (synthetic human immunoglobulin domain 2 fragment) fusion protein with vascular endothelial growth factor receptor type VEGFR-2 (synthetic human immunoglobulin domain 3 fragment) fusion protein with immunoglobulin G1 (synthetic Fc fragment), dimer des-432-lysine-[human vascular endothelial growth factor receptor 1-(103-204)-peptide (containing Ig-like C2-type 2 domain) fusion protein with human vascular endothelial growth factor receptor 2-(206-308)-peptide (containing Ig-like C2-type 3 domain fragment) fusion protein with human immunoglobulin G1-(227 C-terminal residues)-peptide (Fc fragment)], (211-211':214-214')-bisdisulfide dimer
CAS number:	862111-32-8
Molecular weight:	97 kDa (protein molecular weight) 115 kDa (total molecular weight)
Structure:	The secondary and tertiary structures of aflibercept as well as the amino acid structure are shown in Figure 1 and Figure 2.

Figure 1: Aflibercept secondary and tertiary structures



PGR2026-00039
Biocon Ex.1065
Page 63 of 595

Figure 2: Aflibercept amino acid structure



DESCRIPTION

EYLEA is a sterile, clear, colourless to pale yellow, preservative-free, iso-osmotic aqueous 40 mg/mL solution for intravitreal injection.

Excipients: Polysorbate 20, sodium phosphate - monobasic monohydrate, sodium phosphate - dibasic, sodium chloride, sucrose, water for injections.

PHARMACOLOGY

Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmologicals / Antineovascularisation agents

ATC Code: S01LA05

Aflibercept is a recombinant fusion protein consisting of portions of human VEGF receptor 1 and 2 extracellular domains fused to the Fc portion of human IgG1. Aflibercept is produced in Chinese hamster ovary (CHO) K1 cells by recombinant DNA technology.

Mechanism of action

Vascular endothelial growth factor-A (VEGF-A) and placental growth factor (PlGF) are members of the VEGF family of angiogenic factors that can act as potent mitogenic,

PGR2026-00039
Biocon Ex.1065
Page 64 of 595

chemotactic, and vascular permeability factors for endothelial cells. VEGF acts via two receptor tyrosine kinases, VEGFR-1 and VEGFR-2, present on the surface of endothelial cells. PlGF binds only to VEGFR-1, which is also present on the surface of leukocytes. Excessive activation of these receptors by VEGF-A can result in pathological neovascularisation and excessive vascular permeability. PlGF can synergise with VEGF-A in these processes, and is also known to promote leukocyte infiltration and vascular inflammation. A variety of ocular diseases is associated with pathologic neovascularisation and vascular leakage, and/or can result in thickening and oedema of the retina, which is thought to contribute to vision loss.

Aflibercept acts as a soluble decoy receptor that binds VEGF-A and PlGF with higher affinity than their natural receptors, and thereby can inhibit the binding and activation of these cognate VEGF receptors. The equilibrium dissociation constant (K_D) for aflibercept binding to human VEGF-A_{165} is 0.5 pM and to human VEGF-A_{121} is 0.36 pM. The K_D for binding to human PlGF-2 is 39 pM.

Pharmacodynamic effects

<u>Neovascular (wet) age-related macular degeneration (wet AMD)</u>

Wet AMD is characterised by pathological choroidal neovascularisation (CNV). Leakage of blood and fluid from CNV may cause retinal oedema and/or sub-/intra-retinal haemorrhage, resulting in loss of visual acuity.

In patients treated with EYLEA (one injection per month for three consecutive months, followed by one injection every 2 months), retinal thickness decreased soon after treatment initiation, and the mean CNV lesion size was reduced, consistent with the results seen with ranibizumab 0.5 mg every month.

In pivotal phase III clinical studies, VIEW 1 and VIEW 2, there were mean decreases in retinal thickness on optical coherence tomography (OCT) at week 52: -130 and -129 microns for the EYLEA 2 mg every two months and ranibizumab 0.5 mg every month study groups, respectively, in VIEW 1; -149 and -139 microns for the EYLEA 2 mg every two months, and ranibizumab 0.5 mg every month study groups, respectively, in VIEW 2.

The reduction of CNV size and reduction in retinal thickness were generally maintained in the second year of the studies.

<u>Macular oedema following central retinal vein occlusion (CRVO)</u>

In CRVO, retinal ischaemia occurs and signals the release of VEGF which in turn destabilises the tight junctions and promotes endothelial cell proliferation. Up-regulation of VEGF is associated with the breakdown of the blood retina barrier and this increased vascular permeability results in retinal oedema, stimulation of endothelial cell growth and neovascularisation.

In patients treated with EYLEA (one injection every month for six months), there was consistent, rapid and robust response in morphology (central retinal thickness [CRT] as assessed by OCT). Improvements in mean CRT were maintained through week 24.

Retinal thickness on OCT at week 24 compared to baseline was a secondary efficacy endpoint in both the COPERNICUS and GALILEO studies. In both studies, the mean change in CRT from baseline to week 24 statistically significantly favoured EYLEA.

PGR2026-00039
Biocon Ex.1065
Page 65 of 595

Table 1: Pharmacodynamic parameter at week 24, week 52 and week 76/100 (Full Analysis Set with Last Observation Carried Forward (LOCF)) in COPERNICUS and GALILEO studies

Efficacy Outcomes	**COPERNICUS**						**GALILEO**					
	24 Weeks		**52 Weeks**		**100 Weeks**		**24 Weeks**		**52 Weeks**		**76 Weeks**	
	Control (N = 73)	**EYLEA 2 mg Q4 (N = 114)**	**Control** [c)] **(N = 73)**	**EYLEA 2 mg (N = 114)**	**Control** [c, d)] **(N = 73)**	**EYLEA** [d)] **2 mg (N = 114)**	**Control (N = 68)**	**EYLEA 2 mg Q4 (N = 103)**	**Control (N = 68)**	**EYLEA 2 mg (N = 103)**	**Control** [e)] **(N = 68)**	**EYLEA** [e)] **2 mg (N = 103)**
Mean change in retinal thickness from baseline	-145	-457	-382	-413	-343	-390	-169	-449	-219	-424	-306	-389
Difference in LS mean [a,b,c)] (95% CI)		-312 (-389, -234)		-28 (-121, 64)		-45 (-142, 53)		-239 (-286, -193)		-167 (-217, -118)		-44 (-99, 10)
p-value		p < 0.0001		p = 0.5460		p = 0.3661		p < 0.0001		p < 0.0001		p = 0.1122

a) Difference is EYLEA 2 mg Q4 minus control

b) LS: Least square mean difference and confidence interval (CI) based on an ANCOVA model with baseline value as covariate and factors treatment group, region (America vs. rest of the world for COPERNICUS and Europe vs. Asia/Pacific for GALILEO) and baseline BCVA category (> 20/200 and ≤ 20/200)

c) In COPERNICUS study, control group patients could receive EYLEA on an as-needed basis as frequently as every 4 weeks during week 24 to week 52; patients had visits every 4 weeks

d) In COPERNICUS study, both control group and EYLEA 2 mg patients received EYLEA 2 mg on an as-needed basis as frequently as every 4 weeks starting from Week 52 to Week 96; patients had mandatory quarterly visits but may have been seen as frequently as every 4 weeks if necessary

e) In GALILEO study, both control group and EYLEA 2 mg patients received EYLEA 2 mg on an as-needed basis every 8 weeks starting from Week 52 to Week 68; patients had mandatory visits every 8 weeks

PGR2026-00039
Biocon Ex.1065
Page 66 of 595

Macular oedema following branch retinal vein occlusion (BRVO)

In BRVO, retinal ischaemia occurs and signals the release of VEGF, which in turn destabilises the tight junctions and promotes endothelial cell proliferation. Up-regulation of VEGF is associated with the breakdown of the blood retina barrier and this increased vascular permeability results in retinal oedema, stimulation of endothelial cell growth and neovascularisation.

In patients treated with EYLEA (one injection every month for six months) in the VIBRANT study, there was consistent, rapid and robust response in retinal morphology (central retinal thickness [CRT] as assessed by OCT). There was a statistically significant improvement in the EYLEA 2 mg group in comparison to the active control group treated with laser photocoagulation at week 24 (-280 microns vs. -128 microns). At week 24, the dosing interval was extended to every 2 months, and anatomic outcomes were maintained.

Retinal thickness on OCT at week 24 compared to baseline was a secondary efficacy variable in the VIBRANT study. This decrease from baseline was maintained to week 52, favouring EYLEA.

Table 2: Pharmacodynamic parameter at week 24 and at week 52 (Full Analysis Set with LOCF) in VIBRANT study

Efficacy Outcomes	**VIBRANT**			
	24 Weeks		**52 Weeks**	
	EYLEA 2 mg Q4 (N = 91)	**Active Control (laser) (N = 90)**	**EYLEA 2 mg Q8** (N = 91)[b)]	**Active Control[c)] (N = 90)**
Mean change in retinal thickness from baseline	-280	-128	-284	-249
Difference in LS mean (95% CI)[a)] p-value	-149 (-180, -117) p < 0.0001		-30 (-55, -4) p = 0.0218	

a) EYLEA administered as 2 mg every 4 weeks through week 24.
Laser treatment administered on day 1.

Last observation carried forward (LOCF) method was used to impute missing data.

Difference was EYLEA group minus laser group. Point estimate , 95% confidence interval (CI), and p-value were based on an analysis of covariance (ANCOVA) model with baseline measurement as covariate and treatment group, region, and baseline Best Corrected Visual Acuity (BCVA ≤ 20/200 and BCVA > 20/200) as fixed factors.

b) Starting from week 24, the treatment interval in the EYLEA treatment group was extended for all subjects from 4 weeks to 8 weeks through week 48.

c) Beginning at week 24, subjects in the Laser Group could receive rescue treatment with EYLEA, if they met at least one pre-specified eligibility criterion. A total of 67 subjects (74%) in this group received EYLEA rescue treatment. The fixed regimen for EYLEA rescue was EYLEA 2 mg every 4 weeks for three injections, followed by injections every 8 weeks.

PGR2026-00039
Biocon Ex.1065
Page 67 of 595

Diabetic macular oedema (DME)

Diabetic macular oedema is characterised by increased vasopermeability and damage to the retinal capillaries which may result in loss of visual acuity.

In patients treated with EYLEA, rapid and robust response in morphology (central retinal thickness [CRT]) as assessed by OCT was seen soon after treatment initiation. The mean change in CRT from baseline to week 52 was statistically significant favouring EYLEA and was maintained through week 100.

Table 3: Pharmacodynamic parameter at week 52 and week 100 (Full Analysis Set with LOCF) in VIVID^{DME} and VISTA^{DME}

Efficacy Outcomes	**VIVID^{DME}**					
	52 Weeks			**100 Weeks**		
	EYLEA 2 mg Q8 [a] (N = 135)	**EYLEA 2 mg Q4 (N = 136)**	**Active Control (laser) (N = 132)**	**EYLEA 2 mg Q8 [a] (N = 135)**	**EYLEA 2 mg Q4 (N = 136)**	**Active Control (laser) (N = 132)**
Mean change in CRT score from Baseline (SD)	-192.4 (149.89)	-195.0 (146.59)	-66.2 (138.99)	-195.8 (141.75)	-211.8 (150.87)	-85.7 (145.84)
Difference in LS mean [a, b] (97.5% CI) p-value	-142.8 (-179.3, -106.3) p < 0.0001	-157.0 (-190.9, -123.1) p < 0.0001		-126.8 (-164.6, -89.0) p < 0.0001	-154.4 (-189.1, -119.7) p < 0.0001	
Efficacy Outcomes	**VISTA^{DME}**					
	52 Weeks			**100 Weeks**		
	EYLEA 2 mg Q8 [a] (N = 151)	**EYLEA 2 mg Q4 (N = 154)**	**Active Control (laser) (N = 154)**	**EYLEA 2 mg Q8 [a] (N = 151)**	**EYLEA 2 mg Q4 (N = 154)**	**Active Control (laser) (N = 154)**
Mean change in CRT score from Baseline (SD)	-183.1 (153.50)	-185.9 (150.68)	-73.3 (176.72)	-191.1 (160.66)	-191.4 (180.01)	-83.9 (179.29)
Difference in LS mean [a, b] (97.5% CI) p-value	-113.47 (-144.19, -82.75) p < 0.0001	-110.78 (-141.34, -80.22) p < 0.0001		-110.99 (-142.94, -79.04) p < 0.0001	-104.89 (-139.58, -70.21) p < 0.0001	

a) LS mean and CI based on an ANCOVA model with baseline BCVA measurement as a covariate and a factor for treatment group. Additionally, region (Europe/Australia vs. Japan) had been included as factor for VIVID^{DME}, and history of MI and/or CVA as a factor for VISTA^{DME}).

b) Difference is EYLEA group minus active control (laser) group

Myopic choroidal neovascularisation (myopic CNV)

Myopic CNV is a frequent cause of vision loss in adults with pathologic myopia. Eyes with pathologic myopia are elongated, often excessively, and have, in addition, pathologic tissue alterations such as retinal pigment epithelial thinning and defects, lacquer cracks and Bruch's membrane ruptures, choroidal neovascularisation, subretinal haemorrhage and choroidal atrophy. As a consequence of ruptures of Bruch's membrane, myopic CNV develops as a wound healing mechanism and at the same time represents the most vision-threatening event in pathologic myopia.

PGR2026-00039
Biocon Ex.1065
Page 68 of 595

In patients treated with EYLEA (one injection given at the start of therapy, additional injection given in case of disease persistence or recurrence) retinal thickness assessed by OCT decreased soon after treatment initiation and the mean CNV lesion size was reduced. The mean change in CRT from baseline to week 24 was statistically significant favouring EYLEA.

Table 4: Pharmacodynamic parameter at week 24 and week 48 in MYRROR study (Full Analysis Set with LOCF[a)])

Efficacy Outcomes	MYRROR			
	24 Weeks		48 Weeks	
	EYLEA 2 mg [b] (N = 90)	Sham (N = 31)	EYLEA 2 mg [c] (N = 90)	Sham / EYLEA 2 mg [d] (N = 31)
Mean change in central retinal thickness from baseline	-79	-4	-83	-57
Difference in LS mean [e,f,g,h] (95% CI) p-value	-78 (-109, -47) p < 0.0001		-29 (-60, 2) P = 0.0650	

a) LOCF: Last Observation Carried Forward

b) EYLEA 2 mg administered at baseline and potentially every 4 weeks in case of disease persistence or recurrence.

c) EYLEA 2 mg administered from week 24 through week 44 potentially every 4 weeks in case of disease persistence or recurrence

d) Mandatory injection of EYLEA 2 mg at week 24, thereafter potentially every 4 weeks in case of disease persistence or recurrence through week 44.

e) Difference is EYLEA 2 mg minus sham at week 24; difference is EYLEA 2 mg minus sham/EYLEA 2 mg at week 48.

f) LS mean: Least square means derived from ANCOVA model

g) CI: Confidence Interval

h) LS mean difference and 95% CI based on an ANCOVA model with treatment group and country (country designations) as fixed effects, and baseline BCVA as covariant.

Pharmacokinetic properties

EYLEA is administered directly into the vitreous to exert local effects in the eye.

Absorption / Distribution

Aflibercept is slowly absorbed from the eye into the systemic circulation after intravitreal administration and is predominantly observed in the systemic circulation as an inactive, stable complex with VEGF; however only free aflibercept is able to bind endogenous VEGF.

In a pharmacokinetic sub-study with frequent sampling in patients with wet AMD, maximum plasma concentrations of free aflibercept (systemic C_{max}) were low, with a mean of approximately 0.02 µg/mL (range 0 to 0.054) within 1 to 3 days after 2 mg intravitreal injection, and were undetectable two weeks following dosage in almost all patients. Aflibercept does not accumulate in the plasma when administered intravitreally every 4 weeks.

PGR2026-00039
Biocon Ex.1065
Page 69 of 595

These pharmacokinetic results were consistent in pharmacokinetic sub-studies in patients with CRVO, BRVO, DME or myopic CNV, with mean Cmax of free aflibercept in plasma in the range of 0.03 to 0.05 microgram/mL and individual values not exceeding 0.14 microgram/mL. Thereafter, plasma concentrations of free aflibercept declined to values below or close to the lower limit of quantitation generally within one week; undetectable concentrations were reached before the next administration after 4 weeks in all patients.

Table 5: Tabulated summary of free aflibercept in plasma by indication

Indication	Mean C_{max} of free aflibercept (µg/mL)
Wet AMD	0.02 (0 – 0.054)
DME	0.03 (0 – 0.076)
CRVO	0.05 (0 – 0.081)
Myopic CNV	0.03*

* based on a single subject

The mean maximum plasma concentration of free aflibercept is approximately 50 to 500 times below the aflibercept concentration required to inhibit the biologic activity of systemic VEGF by 50% in animal models. It is estimated that after intravitreal administration of 2 mg to patients, the mean maximum plasma concentration of free aflibercept is more than 100-fold lower than the concentration of aflibercept required to half-maximally bind systemic VEGF. Therefore, systemic pharmacodynamic effects are unlikely.

Elimination

As EYLEA is a protein-based therapeutic, no metabolism studies have been conducted.

Free aflibercept binds VEGF to form a stable, inert complex. As with other large proteins, both free and bound aflibercept are expected to be cleared by proteolytic catabolism.

Patients with renal impairment

No special studies in patients with renal impairment were conducted with EYLEA. Pharmacokinetic analysis of patients with wet AMD in the VIEW 2 study, of which 40% had renal impairment (24% mild, 15% moderate, and 1% severe), revealed no differences with respect to plasma concentrations of active drug after intravitreal administration every 4 or 8 weeks.

Similar results were seen in patients with CRVO in the GALILEO study, with DME in the VIVID^{DME} study and with myopic CNV in the MYRROR study.

CLINICAL TRIALS

Neovascular (wet) age-related macular degeneration (wet AMD)

The safety and efficacy of EYLEA were assessed in two pivotal phase III randomised, multi-centre, double-masked, active-controlled studies in patients with wet AMD. A total of 2412 patients were treated and evaluable for efficacy (1817 with EYLEA) in the two studies (VIEW 1 and VIEW 2). In each study, patients were randomly assigned in a 1:1:1:1 ratio to 1 of 4 dosing regimens:

PGR2026-00039
Biocon Ex.1065
Page 70 of 595

1. EYLEA administered at 2 mg every 8 weeks following 3 initial monthly doses (EYLEA 2Q8)
2. EYLEA administered at 2 mg every 4 weeks (EYLEA 2Q4)
3. EYLEA administered at 0.5 mg every 4 weeks (EYLEA 0.5Q4)
4. Ranibizumab administered at 0.5 mg every 4 weeks (Ranibizumab 0.5Q4)

Patient ages ranged from 49 to 99 years with a mean of 76 years. Approximately 89% (1616/1817) of the patients randomised to treatment with EYLEA were 65 years of age or older and approximately 63% (1139/1817) were 75 years of age or older.

In the follow-up exploratory phase of the studies (i.e. from week 52 onwards to week 96), patients continued to receive the dosage strength to which they were initially randomised but on a modified dosing schedule. Injections were given as frequently as every 4 weeks, but no less frequently than every 12 weeks based upon pre-specified retreatment criteria guided by assessment of visual and/or anatomic outcomes. After the first year of the studies, 90% of patients originally treated with EYLEA 2Q8 received 6 doses or less and 72% received 4 doses or less among the patients completing the follow-up exploratory phase of the studies.

In both studies, the primary efficacy endpoint was the proportion of patients in the Per Protocol Set who maintained vision, defined as losing fewer than 15 letters of visual acuity at week 52 compared to baseline. The studies were intended to test for non-inferiority against ranibizumab 0.5 mg given every 4 weeks.

In the VIEW 1 study, at week 52, 95.1% of patients in the EYLEA 2Q8 treatment group maintained vision compared to 94.4% of patients in the ranibizumab 0.5Q4 group. EYLEA treatment was shown to be non-inferior to the ranibizumab 0.5Q4 group.

In the VIEW 2 study, at week 52, 95.6% of patients in the EYLEA 2Q8 treatment group maintained vision compared to 94.4% of patients in the ranibizumab 0.5Q4 group. EYLEA treatment was shown to be non-inferior to the ranibizumab 0.5Q4 group.

The VIEW 1 and VIEW 2 studies included four secondary efficacy endpoints: mean change in Best Corrected Visual Acuity (BCVA), proportion of patients who gained ≥15 letters, change in the total National Eye Institute Visual Function Questionnaire (NEI VFQ-25) score, and change in CNV area.

Detailed results from the combined analysis of both studies (primary[*] and secondary[#] endpoints) are shown in Table 6 and Figure 3 below.

Table 6: Efficacy outcomes at week 52 (primary analysis) and week 96; combined data from the VIEW 1 and VIEW 2 studies [(b)]

Efficacy Outcomes	**EYLEA 2 mg Q4 (N = 613)**		**EYLEA 2 mg Q8 [(e)] (N = 607)**		**Ranibizumab 0.5 mg Q4 (N = 595)**	
	Week 52	**Week 96[(h)]**	**Week 52**	**Week 96[(h)]**	**Week 52**	**Week 96[(h)]**
Mean number of injections from baseline	12.3	16.0	7.6	11.2	12.3	16.5
Mean number of injections during week 52 to week 96	N/A	4.1	N/A	4.2	N/A	4.7

PGR2026-00039
Biocon Ex.1065
Page 71 of 595

Efficacy Outcomes	EYLEA 2 mg Q4 (N = 613)		EYLEA 2 mg Q8 [e] (N = 607)		Ranibizumab 0.5 mg Q4 (N = 595)	
Proportion of patients with maintained visual acuity (<15 letters of BCVA [a] loss) (Per Protocol Set) *	95.35%[b]	92.17%	95.33%[b]	92.42%	94.42%[b]	91.60%
Difference [c] (95% CI) [d]	0.9% (-1.7, 3.5)[f]	0.6% (-2.5, 3.6)[f]	0.9% (-1.7, 3.5)[f]	0.8% (-2.3, 3.8)[f]	N/A	N/A
Mean change in BCVA as measured by ETDRS [a] letter score from baseline #	9.26	7.60	8.40	7.62	8.74	7.89
Difference in LS [a] mean (ETDRS letters) [c] (95% CI) [d]	0.60 (-0.94, 2.14)	-0.20 (-1.93, 1.53)	-0.32 (-1.87, 1.23)	-0.25 (-1.98, 1.49)	N/A	N/A
Proportion of patients who gained at least 15 letters of vision from baseline #	33.44%	31.16%	30.97%	33.44%	32.44%	31.60%
Difference [c] (95% CI) [d]	1.0% (-4.3, 6.3)	-0.4% (-5.6, 4.8)	-1.5% (-6.8, 3.8)	1.8% (-3.5, 7.1)	N/A	N/A
Mean change in total score as measured by NEI VFQ-25 from baseline #	5.60	5.03	5.00	5.31	5.56	5.24
Difference in LS [a] mean (NEI VFQ-25 score) [c] (95% CI) [d]	-0.75 (-2.20, 0.71)	-0.99 (-2.56, 0.58)	-1.26 (-2.72, 0.20)	-0.61 (-2.19, 0.97)	N/A	N/A
Mean change in CNV area as measured by FA [a] from baseline #	-5.30	-5.09	-4.28	-4.26	-4.21	-4.27
Difference in LS [a] mean (CNV area) [g] (95% CI) [d]	-0.74 (-1.27, -0.21)	-0.45 (-1.01, 0.10)	0.08 (-0.46, 0.61)	0.11 (-4.4, 0.67)	N/A	N/A

(a) BCVA: Best Corrected Visual Acuity; ETDRS: Early Treatment Diabetic Retinopathy Study; LS mean: least squares mean; FA: Fluorescein angiography

(b) Full Analysis Set (FAS), Last Observation Carried Forward (LOCF) for all analyses except proportion of patients with maintained visual acuity at week 52 which is Per Protocol Set (PPS)

(c) The difference is the value of the EYLEA group minus the value of the ranibizumab group. A positive value favours EYLEA.

(d) Confidence Interval (CI) calculated by normal approximation

(e) After treatment initiation with three monthly doses

(f) A confidence interval lying entirely above -10% indicates a non-inferiority of EYLEA to ranibizumab

(g) The difference is the value of the EYLEA group minus the value of the ranibizumab group

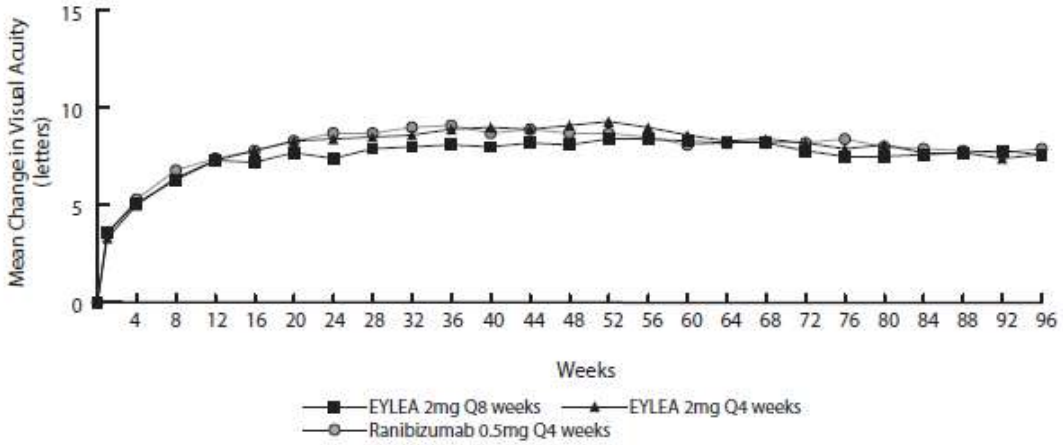
(h) Beginning at week 52, all groups were treated using a modified quarterly treatment paradigm where patients could be dosed as frequently as every 4 weeks but not less frequently than every 12 weeks based upon pre-specified retreatment criteria

* Primary endpoint

\# Secondary endpoint – see statistical comment below

PGR2026-00039
Biocon Ex.1065
Page 72 of 595

Figure 3: Mean change in visual acuity from baseline to week 96*; combined data from the VIEW1 and VIEW2 studies



* From Baseline to Week 52, EYLEA was dosed every 8 weeks following 3 initial monthly doses (EYLEA 2 mg Q8 weeks) or every 4 weeks (EYLEA 2 mg Q4 weeks). From Baseline to Week 52, ranibizumab 0.5 mg was dosed every 4 weeks (Ranibizumab 0.5 mg Q4 weeks). Beginning at Week 52, all groups were treated using a modified quarterly treatment paradigm where patients could be dosed as frequently as every 4 weeks but not less frequently than every 12 weeks based upon pre-specified retreatment criteria.

While there were small differences between EYLEA and ranibizumab, no clinically relevant differences were seen between the treatment groups across all four secondary efficacy endpoints, based on the confidence intervals for the differences between EYLEA and ranibizumab. All statistical tests on secondary efficacy endpoints were considered to be exploratory in the combined analysis of both studies. All secondary endpoint analyses supported the comparability of the efficacy of all 3 EYLEA treatment schedules and ranibizumab.

In combined data analysis of the VIEW 1 and VIEW 2 studies EYLEA demonstrated clinically meaningful changes from baseline in NEI VFQ-25 scores and subscales (near activities, distance activities, and vision-specific dependency). The magnitude of these changes was similar to that seen in published studies, which corresponded to a 15-letter gain in BCVA.

After the first year of the studies, efficacy was generally maintained through the last assessment at week 96. Over the 96 weeks period, patients in the EYLEA 2Q8 group received an average of 11.2 doses and patients in the ranibizumab group received an average of 16.5 doses.

Exploratory analyses of efficacy results in all evaluable subgroups (e.g. age, gender, race, baseline visual acuity, lesion type, lesion size) in each study and in the combined analysis were consistent with the results in the overall populations.

PGR2026-00039
Biocon Ex.1065
Page 73 of 595

Macular oedema secondary to central retinal vein occlusion (CRVO)

The safety and efficacy of EYLEA were assessed in two randomised, multi-centre, double-masked, sham-controlled studies in patients with macular oedema secondary to CRVO. A total of 358 patients were treated and evaluable for efficacy (217 with EYLEA) in the two studies (COPERNICUS and GALILEO). In both studies, patients were randomly assigned in a 3:2 ratio to either 2 mg EYLEA administered every 4 weeks (2Q4) or the control group receiving sham injections every 4 weeks for a total of 6 injections.

After 6 monthly injections, patients received treatment only if they met pre-specified retreatment criteria, except for patients in the control group in the GALILEO study who continued to receive sham (control to control) until week 52. Starting from this time point, all patients were offered treatment if they met pre-specified criteria.

Patient ages ranged from 22 to 89 years with a mean of 64 years. Approximately 52% (112/217) of the patients randomised to treatment with EYLEA were 65 years of age or older and approximately 18% (38/217) were 75 years of age or older.

In both studies, the primary efficacy endpoint was the proportion of patients who gained at least 15 letters in BCVA at week 24 compared to baseline. The studies were designed to evaluate superiority against the control group (receiving sham injections).

Change in visual acuity at week 24 compared to baseline was an important secondary endpoint in both COPERNICUS and GALILEO studies.

The difference between treatment groups was statistically significant in favour of EYLEA in both studies, for the proportion of patients who gained at least 15 letters in BCVA and for mean change in visual acuity, at week 24 compared to baseline. In both pivotal studies, the maximal improvement in visual acuity was achieved at month 3 with subsequent stabilisation of the effect on visual acuity and central retinal thickness until month 6. The statistically significant difference was maintained through week 52. A difference was maintained through week 76/100.

Three other secondary endpoints were included in the studies: change in central retinal thickness (CRT), as assessed by OCT, at week 24 compared to baseline (see **PHARMACOLOGY, Pharmacodynamic properties, Pharmacodynamic effects**); proportion of patients progressing to neovascularisation (anterior segment neovascularisation, neovascularisation of the optic disk, or neovascularisation of the retina elsewhere) at week 24; and change in the NEI VFQ-25 total score at week 24 compared to baseline.

Detailed results from the analysis of both studies (primary* and secondary# endpoints) are shown in Table 1 (see **PHARMACOLOGY**), Table 7 and Figure 4 below.

PGR2026-00039
Biocon Ex.1065
Page 74 of 595

Table 7: Efficacy outcomes at week 24, week 52 and week 76/100 (Full Analysis Set with LOCF[c)]) in COPERNICUS and GALILEO studies

Efficacy Outcomes	**COPERNICUS**						**GALILEO**					
	24 Weeks		**52 Weeks**		**100 Weeks**		**24 Weeks**		**52 Weeks**		**76 Weeks**	
	Control (N = 73)	**EYLEA 2 mg Q4 (N = 114)**	**Control [e)] (N = 73)**	**EYLEA 2 mg (N = 114)**	**Control [e,f)] (N = 73)**	**EYLEA [f)] 2 mg (N = 114)**	**Control (N = 68)**	**EYLEA 2 mg Q4 (N = 103)**	**Control (N = 68)**	**EYLEA 2 mg (N = 103)**	**Control [g)] (N = 68)**	**EYLEA [g)] 2 mg (N = 103)**
Proportion of patients who gained at least 15 letters in BCVA[c)] from baseline[*]	12%	56%	30%	55%	23.3%	49.1%	22%	60%	32%	60%	29.4%	57.3%
Weighted difference [a,b,e)] (95% CI) p-value		44.8% (33.0, 56.6) p < 0.0001		25.9% (11.8, 40.1) p = 0.0006		26.7% (13.1, 40.3) p = 0.0003		38.3% (24.4, 52.1) p < 0.0001		27.9% (13.0, 42.7) p = 0.0004		28.0% (13.3, 42.6) p = 0.0004
Mean change in BCVA as measured by ETDRS [c)] letter score from baseline (SD)[#]	-4.0 (18.0)	17.3 (12.8)	3.8 (17.1)	16.2 (17.4)	1.5 (17.7)	13.0 (17.7)	3.3 (14.1)	18.0 (12.2)	3.8 (18.1)	16.9 (14.8)	6.2 (17.7)	13.7 (17.8)
Difference in LS mean [a,c,d,e)] (95% CI) p-value		21.7 (17.4, 26.0) p < 0.0001		12.7 (7.7, 17.7) p < 0.0001		11.8 (6.7, 17.0) p < 0.0001		14.7 (10.8, 18.7) p < 0.0001		13.2 (8.2, 18.2) p < 0.0001		7.6 (2.1, 13.1) p = 0.0070
Proportion of patients who developed any neovascularisation[#]	6.8%	0%	6.8%	0%	11.0%	5.3%	4.4%	2.9%	8.8%	5.8%	8.8%	7.8%
CHM adjusted difference [a,c,d,e)] (95% CI) p-value		-6.8 (-12.4, -1.2) p = 0.0059		-6.8 (-12.4, -1.2) p = 0.0059		-5.4 (-13.7, 2.8) p = 0.1810		-1.5 (-7.4, 4.4) p = 0.5947		-2.5 (-10.8, 5.8) p = 0.5185		-0.6 (-9.3, 8.1) p = 0.8887
LS mean change in total score as measured by NEI VFQ-25 [c)] from baseline[# §]	2.5	8.8	6.9	9.3	3.6	6.3	0.3	4.5	1.7	5.3	1.1	4.0
Difference in LS mean [a,c,d,e)] (95% CI) p-value		6.3 (2.6, 9.9) p = 0.0009		2.4 (-1.4, 6.2) p = 0.2164		2.7 (-2.0, 7.3) p = 0.2628		4.2 (1.7, 6.8) p = 0.0013		3.6 (1.1, 6.0) p = 0.0049		2.9 (0.1, 5.7) p = 0.0445

PGR2026-00039
Biocon Ex.1065
Page 75 of 595

[a] Difference is EYLEA 2 mg Q4 weeks minus control

[b] Difference and confidence interval (CI) are calculated using Cochran-Mantel-Haenszel (CMH) test adjusted for region (America vs. rest of the world for COPERNICUS and Europe vs. Asia/Pacific for GALILEO) and baseline BCVA category (> 20/200 and ≤ 20/200)

[c] BCVA: Best Corrected Visual Acuity
ETDRS: Early Treatment Diabetic Retinopathy Study
LOCF: Last Observation Carried Forward
NEI VFQ-25: National Eye Institute Visual Function Questionnaire
LS: Least Square means derived from ANCOVA
SD: Standard Deviation

[d] LS mean difference and confidence interval based on an ANCOVA model with factors treatment group, region (America vs. rest of the world for COPERNICUS and Europe vs. Asia/Pacific for GALILEO) and baseline BCVA category (> 20/200 and ≤ 20/200)

[e] In COPERNICUS study, control group patients could receive EYLEA on an as-needed basis as frequently as every 4 weeks during week 24 to week 52; patients had visits every 4 weeks

[f] In COPERNICUS study, both control group and EYLEA 2 mg patients received EYLEA 2 mg on an as-needed basis as frequently as every 4 weeks starting from Week 52 to Week 96; patients had mandatory quarterly visits but may have been seen as frequently as every 4 weeks if necessary

[g] In GALILEO study, both control group and EYLEA 2 mg patients received EYLEA 2 mg on an as-needed basis every 8 weeks starting from Week 52 to Week 68; patients had mandatory visits every 8 weeks

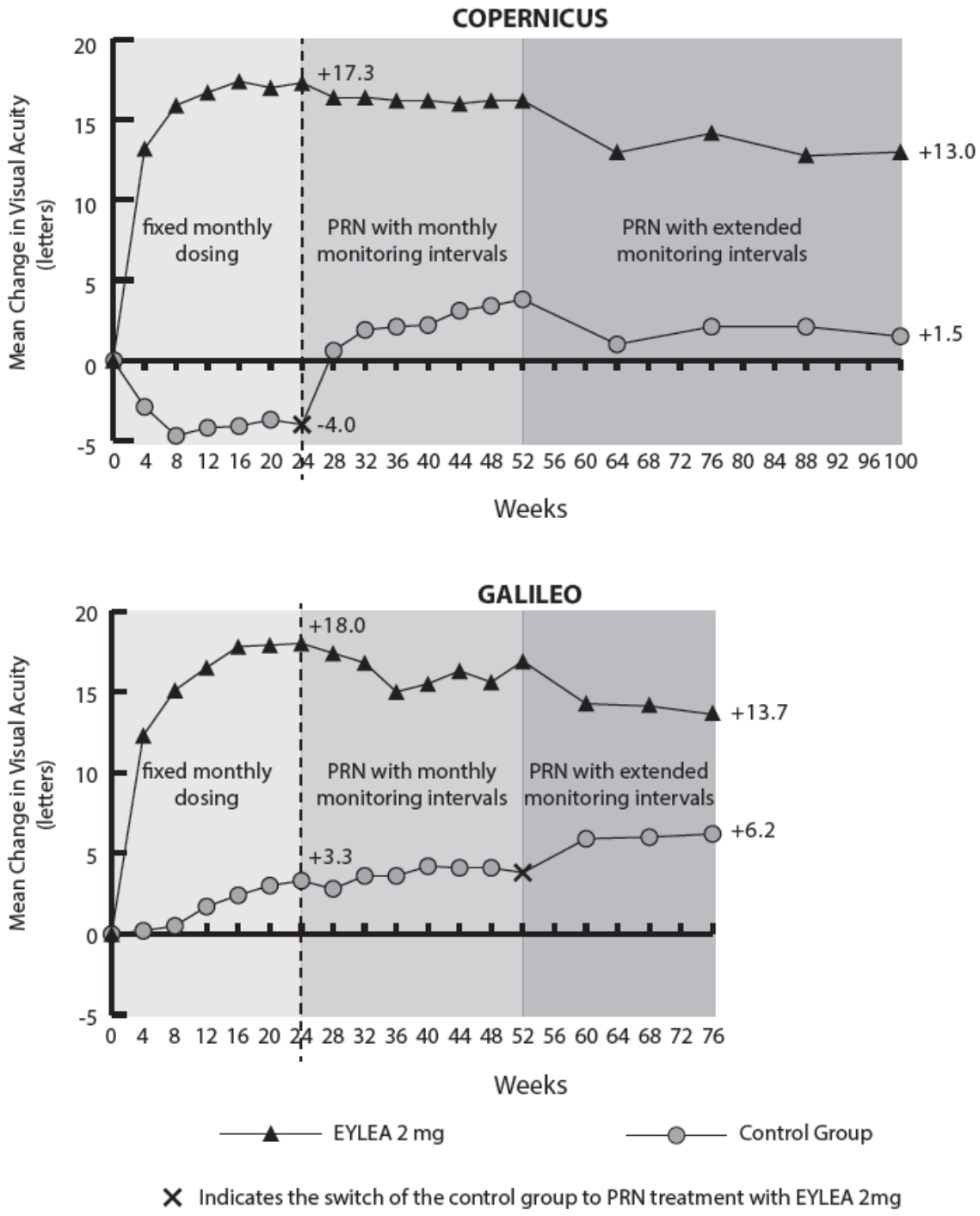
[*] Primary endpoint

[#] Secondary endpoint

[§] In GALILEO, n=65 in the control group and n=96 in the EYLEA group at week 24; n=67 in the control group and n=98 in the EYLEA group at week 52

PGR2026-00039
Biocon Ex.1065
Page 76 of 595

Figure 4: Mean change from baseline to week 52 and week 76/100 in visual acuity[#] by treatment group for the COPERNICUS and GALILEO studies (Full Analysis Set)



Exploratory analyses of efficacy results in all evaluable subgroups (e.g. age, gender, race, baseline visual acuity, retinal perfusion status, CRVO duration) in each study were in general consistent with the results in the overall populations.

PGR2026-00039
Biocon Ex.1065
Page 77 of 595

Macular oedema secondary to branch retinal vein occlusion (BRVO)

The safety and efficacy of EYLEA were assessed in a randomised, multi-centre, double-masked, active-controlled study in patients with macular oedema secondary to BRVO, which included Hemi-Retinal Vein Occlusion. A total of 181 patients were treated and evaluable for efficacy (91 with EYLEA) in the VIBRANT study. In the study, patients were randomly assigned in a 1:1 ratio to either 2 mg EYLEA administered every 4 weeks, with a total of 6 injections, or laser photocoagulation administered at baseline (laser control group). Patients in the laser control group could receive additional laser photocoagulation (called "rescue laser treatment") beginning at week 12, if at least one pre-specified rescue treatment criterion was met. The minimum interval between laser photocoagulation treatments was 12 weeks. After week 24, patients in the EYLEA group received 2 mg every 8 weeks through week 48, and patients in the control group could receive treatment with EYLEA 2 mg, if at least one pre-specified rescue criterion was met. EYLEA rescue treatment consisted of a fixed regimen with 2 mg EYLEA administered every 4 weeks for 3 injections, followed by intravitreal injections every 8 weeks through week 48.

Patient ages ranged from 42 to 94 years with a mean of 65 years. Approximately 58% (53/91) of the patients randomised to treatment with EYLEA were 65 years of age or older, and approximately 23% (21/91) were 75 years of age or older.

In the VIBRANT study, the primary efficacy endpoint was the proportion of patients who gained at least 15 letters in BCVA at Week 24 compared to baseline. At Week 24, the EYLEA group was superior to laser control for the primary endpoint.

Change in visual acuity at week 24 compared to baseline was a secondary efficacy variable in the VIBRANT study. The difference between treatment groups was statistically significant in favour of EYLEA. The course of visual improvement was rapid and maximal improvement was achieved at week 12, with subsequent stabilisation of the effect on visual acuity and central retinal thickness until week 24 and subsequent maintenance of the effect until week 52.

In the laser group 67 patients (74%) received rescue treatment with EYLEA beginning at week 24. In this treatment group, visual acuity improved by about 5 letters from week 24 to 52.

Detailed results from the analysis of the VIBRANT study are shown in Table 8 and Figure 5 below.

PGR2026-00039
Biocon Ex.1065
Page 78 of 595

Table 8: Efficacy outcomes at week 24, and week 52 (Full Analysis Set LOCF) in the VIBRANT study

Efficacy Outcomes	VIBRANT			
	EYLEA 2 mg Q4 (N = 91)	Active Control (laser) (N = 90)	EYLEA 2 mg Q8 (N = 91) [d]	Active Control [e] (N = 90)
Proportion of patients who gained at least 15 letters in BCVA from Baseline (%)	52.7%	26.7%	57.1%	41.1%
Weighted Difference [a,b] (%) (95% CI) p-value	26.6% (13.0, 40.1) p = 0.0003		16.2% (2.0, 30.5) p = 0.0296	
Mean change in BCVA as measured by ETDRS letter score from Baseline (SD)	17.0 (11.9)	6.9 (12.9)	17.1 (13.1)	12.2 (11.9)
Difference in LS mean [a,c] (95% CI) p-value	10.5 (7.1, 14.0) p < 0.0001		5.2 (1.7, 8.7) p = 0.0035	

a) Difference is EYLEA 2 mg Q4 weeks minus Laser Control

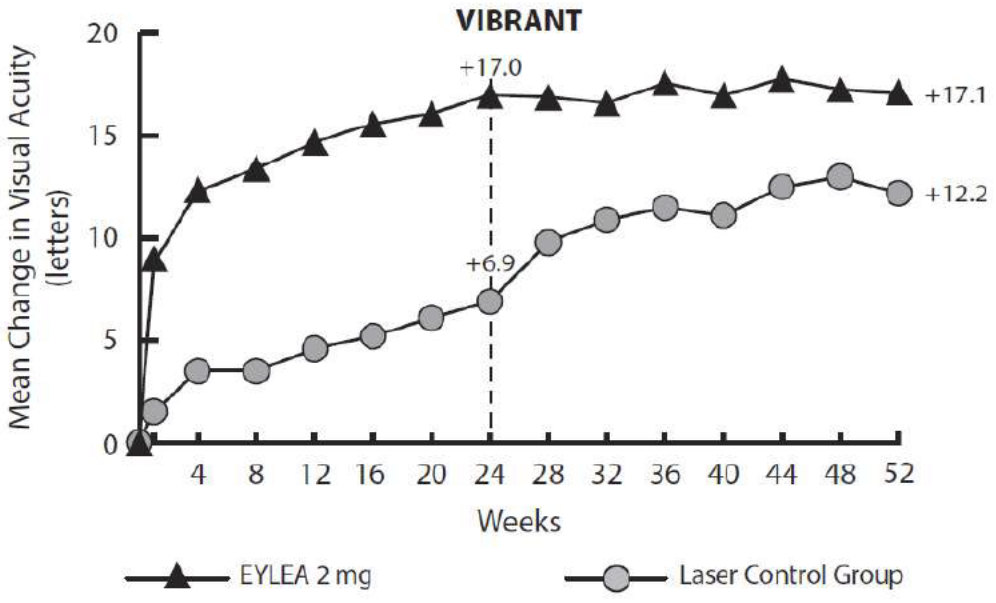
b) Difference and 95% CI are calculated using Mantel-Haenszel weighting scheme adjusted for region (North America vs. Japan) and baseline BCVA category (> 20/200 and ≤ 20/200)

c) LS mean difference and 95% CI based on an ANCOVA model with treatment group, baseline BCVA category (> 20/200 and ≤ 20/200) and region (North America vs. Japan) as fixed effects, and baseline BCVA as covariate.

d) Starting from week 24, the treatment interval in the EYLEA treatment group was extended for all subjects from 4 weeks to 8 weeks through week 48.

e) Beginning at week 24, subjects in the Laser Group could receive rescue treatment with EYLEA if they met at least one pre-specified eligibility criterion. A total of 67 subjects (74%) in this group received EYLEA rescue treatment. The fixed regimen for EYLEA rescue was EYLEA 2 mg every 4 weeks for three injections, followed by injections every 8 weeks.

Figure 5: Mean change in BCVA as measured by ETDRS letter score from baseline to week 52 in VIBRANT study (Full Analysis Set, LOCF)



PGR2026-00039
Biocon Ex.1065
Page 79 of 595

The proportion of retinal perfused patients in the EYLEA group at baseline was 60.4% (n = 55). At week 24, this proportion increased to 80.2% (n = 65) and was sustained at week 52 (77.9%, n = 67). The proportion of perfused patients that started on grid laser photocoagulation was 68.9% (n = 62) at baseline. Perfusion at the week 24 primary endpoint in the laser group was 67.1% (n = 55). Patients in the laser group were eligible for rescue treatment with EYLEA beginning at week 24 according to pre-specified criteria. At week 52, 78.0% (n = 64) were perfused at this time.

The beneficial effect of EYLEA treatment on visual function was similar in the baseline groups with perfused and non-perfused patients.

Treatment effects in evaluable subgroups (e.g., age, gender, and baseline retinal perfusion status) in the study were in general consistent with the results in the overall populations.

Diabetic macular oedema (DME)

The safety and efficacy of EYLEA were assessed in two randomised, multi-centre, double-masked, active-controlled studies in patients with DME. A total of 862 randomised and treated patients were evaluable for efficacy. Of those, 576 were randomised to the EYLEA groups in two studies (VIVID^{DME} and VISTA^{DME}). In each study, patients were randomly assigned in a 1:1:1 ratio to 1 of 3 dosing regimens:

1. EYLEA administered at 2 mg every 8 weeks following 5 initial monthly injections (EYLEA 2Q8);
2. EYLEA administered at 2 mg every 4 weeks (EYLEA 2Q4); and
3. macular laser photocoagulation (active control).

Beginning at week 24, patients meeting a pre-specified threshold of vision loss were eligible to receive additional treatment: patients in the EYLEA groups could receive laser and patients in the laser group could receive EYLEA.

Patient ages ranged from 23 to 87 years with a mean of 63 years. Approximately 47% (268/576) of the patients randomised to treatment with EYLEA were 65 years of age or older, and approximately 9% (52/576) were 75 years of age or older. Efficacy and safety outcomes were consistent with the outcomes of the overall population.

In both studies, the primary efficacy endpoint was the mean change from baseline in BCVA at Week 52 as measured by ETDRS letter score. Both EYLEA 2Q8 and EYLEA 2Q4 groups were shown to have efficacy that was statistically significantly superior to the laser control group. This benefit was maintained through week 100.

Detailed results from the analysis of the VIVID^{DME} and VISTA^{DME} studies are shown in Table 9 and Figure 6 below.

PGR2026-00039
Biocon Ex.1065
Page 80 of 595

Table 9: Efficacy Outcomes at week 52 and week 100 (Full Analysis Set with LOCF) in VIVID^{DME} and VISTA^{DME} studies

Efficacy Outcomes	VIVID^{DME}						VISTA^{DME}					
	52 Weeks			100 Weeks			52 Weeks			100 Weeks		
	EYLEA 2 mg Q8 [a] (N = 135)	EYLEA 2 mg Q4 (N = 136)	Active Control (laser) (N = 132)	EYLEA 2 mg Q8 [a] (N =135)	EYLEA 2 mg Q4 (N =136)	Active Control (laser) (N =132)	EYLEA 2 mg Q8 [a] (N = 151)	EYLEA 2 mg Q4 (N = 154)	Active Control (laser) (N = 154)	EYLEA 2 mg Q8 [a] (N = 151)	EYLEA 2 mg Q4 (N = 154)	Active Control (laser) (N = 154)
Mean change in BCVA as measured by ETDRS [e] letter score from Baseline (SD)	10.7 (9.32)	10.5 (9.55)	1.2 (10.65)	9.4 (10.53)	11.4 (11.21)	0.7 (11.77)	10.7 (8.21)	12.5 (9.54)	0.2 (12.53)	11.1 (10.70)	11.5 (13.75)	0.9 (13.94)
Difference in LS mean [b, c, e] (97.5% CI) p-value	9.1 (6.3, 11.8) p < 0.0001	9.3 (6.5, 12.0) p < 0.0001		8.2 (5.2, 11.3) p < 0.0001	10.7 (7.6, 13.8) p < 0.0001		10.45 (7.73, 13.17) p < 0.0001	12.19 (9.35, 15.04) p < 0.0001		10.14 (6.96, 13.32) p < 0.0001	10.64 (7.09, 14.18) p < 0.0001	
Proportion of patients who gained at least 10 letters in BCVA [e] from Baseline	53.3%	54.4%	25.8%	49.6%	58.1%	25.0%	58.3%	64.9%	19.5%	59.6%	63.6%	27.9%
Adjusted Difference [c, d, e] (97.5% CI) p-value	27.5 (14.6, 40.5) p < 0.0001	28.7 (15.8, 41.6) p < 0.0001		24.6 (11.9, 37.3) p < 0.0001	33.1 (20.3, 45.9) p < 0.0001		38.8 (27.2, 50.3) p < 0.0001	45.9 (34.7, 57.0) p < 0.0001		31.6 (19.5, 43.7) p < 0.0001	36.2 (24.3, 48.1) p < 0.0001	
Proportion of patients who gained at least 15 letters in BCVA [e] from Baseline	33.3%	32.4%	9.1%	31.1%	38.2%	12.1%	31.1%	41.6%	7.8%	33.1%	38.3%	13.0%
Adjusted Difference [c, d, e] (97.5% CI) p-value	24.2% (13.5, 34.9) p < 0.0001	23.3% (12.6, 33.9) p < 0.0001		19.0% (8.0, 29.9) p = 0.0001	26.1% (14.8, 37.5) p < 0.0001		23.3% (13.5, 33.1) p < 0.0001	34.2% (24.1, 44.4) p < 0.0001		20.1% (9.6, 30.6) p < 0.0001	25.8% (15.1, 36.6) p < 0.0001	
Proportion of patients with an improvement of >= 2 steps on the ETDRS DRSS [e, f] from Baseline	27.7%	33.3%	7.5%	32.6%	29.3%	8.2%	29.1%	33.8%	14.3%	37.1%	37.0%	15.6%
Adjusted Difference [c, d] (97.5% CI) p-value	19.3 (6.6, 32.1) p = 0.0006	25.8 (12.2, 39.4) p < 0.0001		24.4 (11.3, 37.4) p < 0.0001	20.9 (7.7, 34.2) p = 0.0004		14.9 (4.4, 25.4) p = 0.0017	19.7 (9.0, 30.4) p < 0.0001		21.5 (10.4, 32.5) p = 0.0001	21.7 (10.8, 32.6) p < 0.0001	
See Table 3 for Mean Change in CRT from Baseline												

PGR2026-00039
Biocon Ex.1065
Page 81 of 595

Efficacy Outcomes	VIVID^{DME}						VISTA^{DME}					
	52 Weeks			100 Weeks			52 Weeks			100 Weeks		
	EYLEA 2 mg Q8 [a] (N = 135)	EYLEA 2 mg Q4 (N = 136)	Active Control (laser) (N = 132)	EYLEA 2 mg Q8 [a] (N =135)	EYLEA 2 mg Q4 (N =136)	Active Control (laser) (N =132)	EYLEA 2 mg Q8 [a] (N = 151)	EYLEA 2 mg Q4 (N = 154)	Active Control (laser) (N = 154)	EYLEA 2 mg Q8 [a] (N = 151)	EYLEA 2 mg Q4 (N = 154)	Active Control (laser) (N = 154)
Mean change in NEI VFQ-25 [e] near activities subscale from Baseline	5.29 (19.058)	5.73 (18.932)	3.54 (16.768)	6.97 (19.280)	8.17 (20.193)	4.8 (15.433)	9.4 (18.50)	9.0 (20.60)	5.4 (20.44)	12.8 (21.36)	10.9 (23.12)	8.1 (22.10)
Difference in LS mean [b, c, e] (97.5% CI) p-value	-1.21 (-5.79, 3.37) p = 0.5537	2.41 (-2.01, 6.82) p = 0.2208		-0.74 (-5.25, 3.78) p = 0.7144	3.64 (-0.70, 7.98) p = 0.0596		4.36 (-0.21, 8.93) p = 0.0323	5.19 (0.33, 10.04) p = 0.0168		5.05 (0.12, 9.98) p = 0.0218	4.59 (-0.73, 9.90) p = 0.0529	
Mean change in NEI VFQ-25 [e] distance activities subscale from Baseline	5.32 (18.475)	0.94 (16.487)	2.26 (15.923)	4.94 (20.253)	4.62 (17.618)	2.2 (16.684)	7.3 (19.32)	8.6 (20.99)	6.7 (19.85)	8.5 (20.35)	10.9 (22.05)	6.1 (20.42)
Difference in LS mean [b, c, e] (97.5% CI) p-value	-0.37 (-4.79, 4.05) p = 0.8498	-1.19 (-5.29, 2.91) p = 0.5138		-1.30 (-6.00, 3.39) p = 0.5325	2.57 (-1.73, 6.86) p = 0.1792		1.65 (-2.83, 6.13) p = 0.4067	2.86 (-1.82, 7.54) p = 0.1702		3.57 (-0.96, 8.11) p = 0.0772	5.80 (0.97, 10.64) p = 0.0072	

[a] After treatment initiation with 5 monthly injections

[b] LS mean and CI based on an ANCOVA model with baseline BCVA measurement as a covariate and a factor for treatment group. Additionally, region (Europe/Australia vs. Japan) had been included as a factor for VIVID^{DME}, and history of MI and/or CVA as a factor for VISTA^{DME}.

[c] Difference is EYLEA group minus active control (laser) group

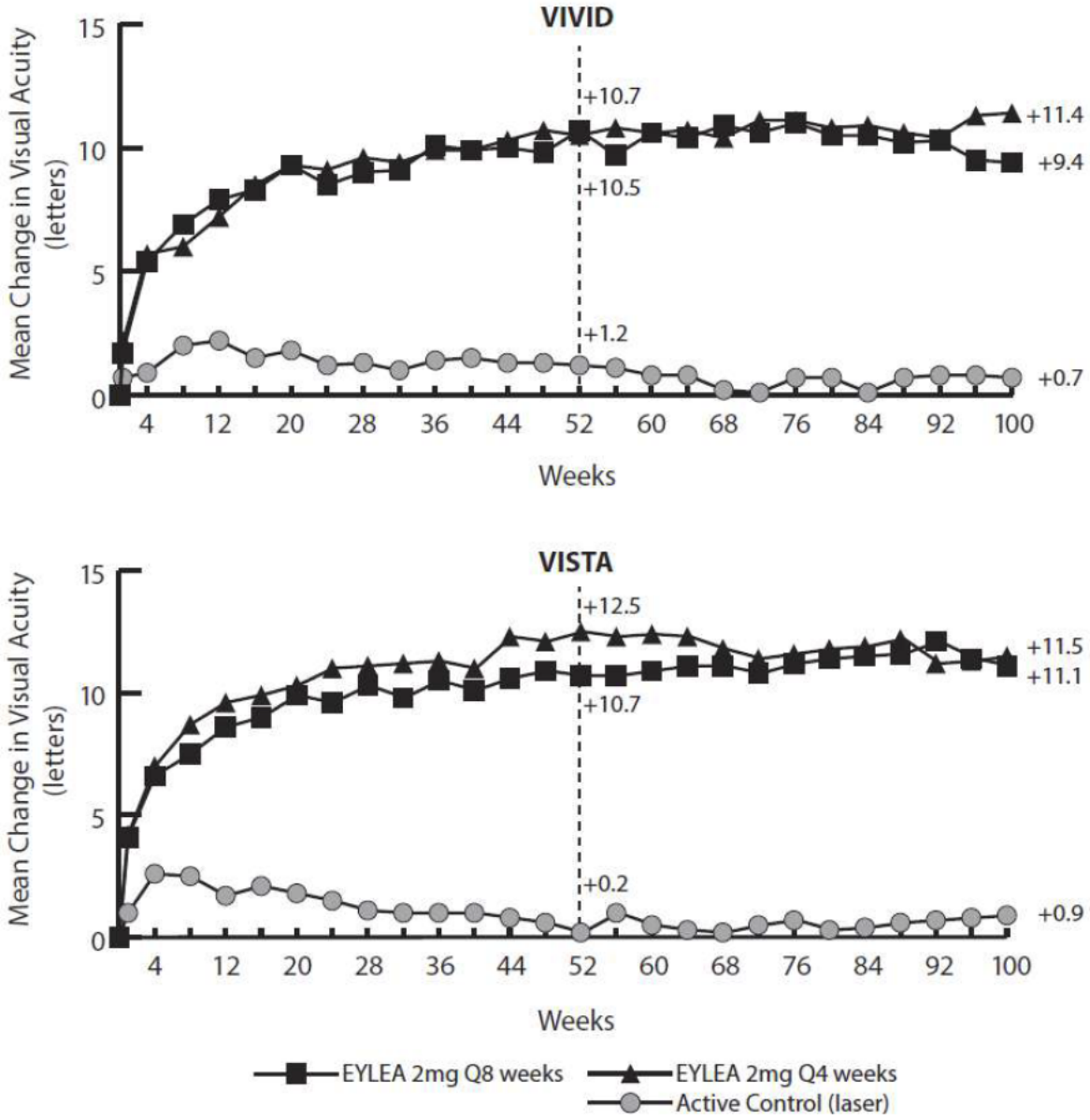
[d] Difference with confidence interval (CI) and statistical test is calculated using Mantel-Haenszel weighting scheme adjusted by region (Europe/Australia vs. Japan) for VIVID^{DME} and medical history of MI or CVA for VISTA^{DME}

[e] BCVA: Best Corrected Visual Acuity
ETDRS: Early Treatment Diabetic Retinopathy Study
LOCF: Last Observation Carried Forward
SD: Standard deviation
LS: Least square means derived from ANCOVA
DRSS: Diabetic Retinopathy Severity Scale
CI: Confidence interval
NEI VFQ-25: National Eye Institute Visual Function Questionnaire

[f] VIVID^{DME}: based on the patients with gradable images at baseline and post-baseline [week 52: n=83 (EYLEA 2mg Q8), n=81 (EYLEA 2mg Q4), n=80 (laser); week 100: n=86 (EYLEA 2mg Q8), n=82 (EYLEA 2mg Q4), n=85 (laser)]

PGR2026-00039
Biocon Ex.1065
Page 82 of 595

Figure 6: Mean change in BCVA as measured ETDRS letter score from baseline to Week 100 in VIVID^{DME} and VISTA^{DME} studies



At week 52, 33.3% and 33.8% of 2Q4 patients, 27.7% and 29.1% of 2Q8 patients, and 7.5% and 14.3% of laser control patients in the VIVID^{DME} and VISTA^{DME} studies, respectively experienced an improvement in the severity of diabetic retinopathy, as measured by a $\geq$ 2 step improvement in the diabetic retinopathy severity scale (DRSS). This improvement was maintained through week 100 (see Table 9).

Treatment effects in evaluable subgroups (e.g., age, gender, race, baseline HbA1c, baseline visual acuity, prior anti-VEGF therapy) in each study and in the combined analysis were generally consistent with the results in the overall populations.

In the VIVID^{DME} and VISTA^{DME} studies, 36 (8.9%) and 197 (42.9%) patients received prior anti-VEGF therapy, respectively, with a 3-month or longer washout period. Treatment effects in the subgroup of patients who had previously been treated with a VEGF inhibitor prior to study participation were similar to those seen in patients who were VEGF inhibitor naïve prior to study participation.

PGR2026-00039
Biocon Ex.1065
Page 83 of 595

Patients with bilateral disease were eligible to receive anti-VEGF treatment in their fellow eye. In the VISTA^{DME} study, 217 (70.7%) of EYLEA patients received bilateral EYLEA injections until week 100; in the VIVID^{DME} study, 97 (35.8%) of EYLEA patients received a different anti-VEGF treatment in their fellow eye until week 100.

Myopic choroidal neovascularisation (myopic CNV)

The safety and efficacy of EYLEA were assessed in a randomised, multi-centre, double-masked, sham-controlled study (MYRROR) in patients with myopic CNV. A total of 121 patients were treated and evaluable for efficacy (90 with EYLEA). Patients were randomly assigned in a 3:1 ratio to either 2 mg EYLEA administered once at study start (with additional injections given in the case of disease persistence or reoccurrence) or sham injections. In total 6 injections was possible until the week 24 primary endpoint assessment in the study.

After the first 6 months, patients initially randomised to sham were eligible to receive the first dose of EYLEA at week 24. Following this, patients in this former sham arm and also patients in the arm initially randomised to active treatment continued to be eligible for additional injections in case of disease persistence or recurrence.

Patient ages ranged from 27 to 83 years with a mean of 58 years. Approximately 36% (33/91) of the patients randomised to treatment with EYLEA were 65 years of age or older, and approximately 10% (9/91) were 75 years of age or older.

The primary efficacy endpoint was the change in visual acuity at week 24 compared to baseline. The confirmatory secondary efficacy endpoint was the proportion of patients who gained at least 15 letters in BCVA at week 24 compared to baseline.

The difference between treatment groups was statistically significant in favour of EYLEA for the primary and confirmatory secondary efficacy endpoints at week 24. Differences for both endpoints were maintained through week 48.

Detailed results from the analyses are shown in Table 10 and Figure 7 below.

Table 10: Efficacy outcomes at week 24 (primary analysis) and in week 48 in MYRROR study (Full Analysis Set with LOCF[a)])

Efficacy outcomes	**MYRROR**			
	24 Weeks		**48 Weeks**	
	EYLEA 2 mg [b] (N = 90)	**Sham (N = 31)**	**EYLEA 2 mg [c] (N = 90)**	**Sham / EYLEA 2 mg [d] (N = 31)**
Mean change in BCVA letter score as measured by ETDRS from baseline (SD)[e]	12.1 (8.3)	-2.0 (9.7)	13.5 (8.8)	3.9 (14.3)
Difference in LS mean [f,g,h,i] (95% CI)	14.1 (10.8, 17.4)		9.5 (5.4, 13.7)	
p-value	p < 0.0001		p < 0.0001	
Proportion of patients who gained at least 15 letters in BCVA[e] from baseline	38.9%	9.7%	50.0%	29.0%
Weighted difference [f,h,j] (95% CI)	29.2% (14.4, 44.0)		21.0% (1.9, 40.1)	
p-value	p = 0.0001		p = 0.0308	

PGR2026-00039
Biocon Ex.1065
Page 84 of 595

a) LOCF: Last Observation Carried Forward

b) EYLEA 2 mg administered at baseline and potentially every 4 weeks in case of disease persistence or recurrence.

c) EYLEA 2 mg administered from week 24 through week 44 potentially every 4 weeks in case of disease persistence or recurrence

d) Mandatory injection of EYLEA 2 mg at week 24, thereafter potentially every 4 weeks in case of disease persistence or recurrence through week 44.

e) BCVA: Best Corrected Visual Acuity; ETDRS: Early Treatment Diabetic Retinopathy Study; SD: Standard Deviation

f) Difference is EYLEA 2 mg minus sham at Week 24 and EYLEA 2 mg minus sham/EYLEA 2 mg at week 48.

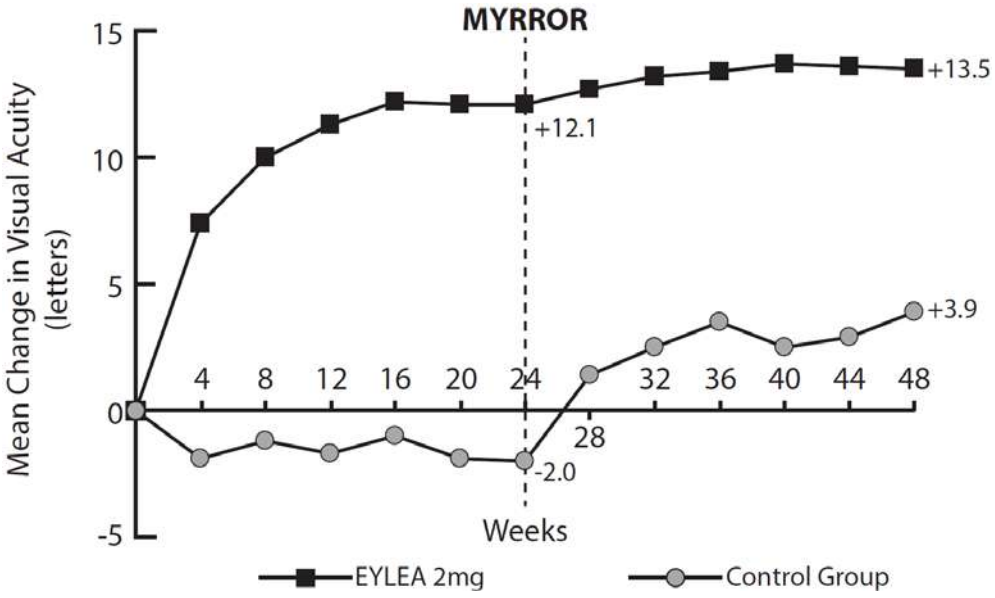
g) LS mean: Least square means derived from ANCOVA model

h) CI: Confidence Interval

i) LS mean difference and 95% CI based on an ANCOVA model with treatment group and country (country designations) as fixed effects, and baseline BCVA as covariant.

j) Difference and 95% CI are calculated using Cochran-Mantel-Haenszel (CMH) test adjusted for country (country designations)

Figure 7: Mean change from baseline to week 48 in visual acuity by treatment group for the MYRROR study (Full Analysis Set, LOCF)



Treatment effects in all evaluable subgroups were in general, consistent with the results in the overall populations.

PGR2026-00039
Biocon Ex.1065
Page 85 of 595

INDICATIONS

EYLEA (aflibercept) is indicated in adults for the treatment of:

- neovascular (wet) age-related macular degeneration (wet AMD)
- visual impairment due to macular oedema secondary to central retinal vein occlusion (CRVO)
- visual impairment due to macular oedema secondary to branch retinal vein occlusion (BRVO)
- diabetic macular oedema (DME)
- visual impairment due to myopic choroidal neovascularisation (myopic CNV).

CONTRAINDICATIONS

- Known hypersensitivity to aflibercept or to any of the excipients
- Ocular or periocular infection
- Active severe intraocular inflammation.

PRECAUTIONS

Endophthalmitis

Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis (see **ADVERSE EFFECTS**). Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis without delay and should be managed appropriately.

Increase in intraocular pressure

Increases in intraocular pressure have been seen within 60 minutes of an intravitreal injection, including with EYLEA (see **ADVERSE EFFECTS**). Special precaution is needed in patients with poorly controlled glaucoma. In all cases both the intraocular pressure and the perfusion of the optic nerve head must therefore be monitored and managed appropriately.

Immunogenicity

As this is a therapeutic protein, there is a potential for immunogenicity. Patients should be instructed to report any signs or symptoms of intraocular inflammation, e.g. pain, photophobia, or redness, which may be a clinical sign attributable to hypersensitivity.

Arterial thromboembolic events

There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors (see **ADVERSE EFFECTS**). ATEs include vascular death (e.g., due to stroke or myocardial infarction), non-fatal strokes and non-fatal myocardial infarction.

PGR2026-00039
Biocon Ex.1065
Page 86 of 595

The risk of stroke may be greater in patients with known risk factors including a history of stroke or transient ischaemic attack (TIA). Patients should be carefully evaluated by their doctor to assess whether the benefits of treatment outweigh the potential risks.

Other

The safety and efficacy of EYLEA therapy administered to both eyes concurrently have not been systematically studied (see **CLINICAL TRIALS**). As with other intravitreal injections, if bilateral treatment is performed at the same time this could lead to an increased systemic exposure, which could increase the risk of systemic adverse events.

Risk factors associated with the development of a retinal pigment epithelial tear after anti-VEGF therapy for wet AMD, include a large and/or high pigment epithelial retinal detachment. When initiating anti-VEGF therapy, caution should be used in patients with these risk factors for retinal pigment epithelial tears.

Treatment should be withheld in patients with rhegmatogenous retinal detachment or stage 3 or 4 macular holes.

In the event of a retinal break the dose should be withheld and treatment should not be resumed until the break is adequately repaired.

In the event of either a decrease in best-corrected visual acuity (BCVA) of ≥30 letters compared with the last assessment of visual acuity; or a subretinal haemorrhage involving the centre of the fovea or if the size of the haemorrhage is ≥50% of the total lesion area, the dose should be withheld and treatment should not be resumed earlier than the next scheduled treatment.

The dose should be withheld in the event of performed or planned intraocular surgery within the previous or next 28 days.

In patients presenting with clinical signs of irreversible ischaemic visual function loss, the treatment is not recommended.

<u>Populations with limited data</u>

- Diabetic macular oedema due to type 1 diabetes
- Diabetic patients with HbA1c > 12%
- Proliferative diabetic retinopathy
- Active systemic infections
- Concurrent eye conditions (e.g., retinal detachment, macular hole)
- Uncontrolled hypertension
- In myopic CNV there is no experience with EYLEA in the treatment of non-Asian patients, patients who have previously undergone treatment for myopic CNV, and patients with extrafoveal lesions.

PGR2026-00039
Biocon Ex.1065
Page 87 of 595

Effects on fertility

Effects on male and female fertility were assessed as part of a 6-month study in monkeys with intravenous administration of aflibercept at doses ranging from 3 to 30 mg/kg every one to two weeks. Absent or irregular menses associated with alterations in female reproductive hormone levels and changes in sperm morphology and motility (considered consequential to male fertility) were observed at all dose levels. Based on C_{max} and AUC for free aflibercept observed at the 3 mg/kg intravenous dose, the systemic exposures were approximately 4900-fold and 1500-fold higher, respectively, than the exposure observed in humans after an intravitreal dose of 2 mg. All changes were reversible.

Use in pregnancy (Category D)

There are no data on the use of aflibercept in pregnant women. Studies in animals have shown reproductive toxicity, including a series of external, visceral, skeletal malformations, after systemic administration. EYLEA should not be used during pregnancy unless the potential benefit outweighs the potential risk to the fetus. Women of childbearing potential have to use effective contraception during treatment and for at least 3 months after the last intravitreal injection of aflibercept.

Aflibercept produced malformations and other fetal abnormalities in pregnant rabbits with intravenous administration (at 3 to 60 mg/kg once every 3 days during the period of organogenesis) and with subcutaneous administration (0.1 to 1 mg/kg on gestational days 1, 7, and 13). A No Observed Effect Level (NOEL) for adverse effects on embryo-fetal development was not established. At the lowest dose tested (0.1 mg/kg), the systemic exposures based on C_{max} and cumulative AUC for free aflibercept were approximately 13- and 10-fold higher, respectively, when compared to corresponding values observed in humans after an intravitreal dose of 2 mg.

Use in lactation

It is unknown whether aflibercept is excreted in human milk. A risk to the breast-fed child cannot be excluded. EYLEA is not recommended during breast-feeding. A decision must be made whether to discontinue breast-feeding or to abstain from EYLEA therapy.

Paediatric use

The safety and efficacy of EYLEA have not been studied in children or adolescents.

Use in the elderly

No special considerations are needed. There is limited experience in patients older than 75 years with DME (see **CLINICAL TRIALS**).

Genotoxicity

No studies have been conducted on the mutagenic or clastogenic potential of aflibercept. As a large protein molecule, aflibercept is not expected to interact directly with DNA or other chromosomal material.

Carcinogenicity

No studies have been conducted on the carcinogenic potential of aflibercept.

PGR2026-00039
Biocon Ex.1065
Page 88 of 595

Effects on ability to drive or use machines

Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA and the associated eye examinations. They should not drive or use machinery until visual function has recovered sufficiently.

INTERACTIONS WITH OTHER MEDICINES

No formal drug interaction studies have been performed with EYLEA.

ADVERSE EFFECTS

Summary of the safety profile

A total of 3102 patients treated with EYLEA constituted the safety population in eight Phase III studies. Amongst those, 2501 patients were treated with the recommended dose of 2 mg.

Serious adverse reactions related to the injection procedure have occurred in less than 1 in 2400 intravitreal injections with EYLEA and included endophthalmitis, retinal detachment, cataract traumatic, cataract, vitreous detachment and intraocular pressure increased (see **PRECAUTIONS**).

The most frequently observed adverse reactions (in at least 5% of patients treated with EYLEA) were conjunctival haemorrhage (25.0%), visual acuity reduced (11.1%), eye pain (10.2%), cataract (7.6%), intraocular pressure increased (7.5%), vitreous detachment (7.4%), and vitreous floaters (6.9%).

In wet AMD, these adverse reactions occurred with a similar incidence in the ranibizumab treatment group.

Tabulated list of adverse reactions

The safety data described in Table 11 below include all adverse reactions (serious and non-serious) from eight Phase III studies with a reasonable possibility of causality to the injection procedure or medicinal product over the 96 weeks study duration for wet AMD, over 100 weeks for CRVO, over 100 weeks for DME, over 52 weeks for BRVO and over 48 weeks for myopic CNV.

The adverse reactions are listed by system organ class and frequency using the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥ 1/10,000 to < 1/1,000 patients). Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness.

Table 11: All treatment-emergent adverse drug reactions reported in patients in Phase III studies

System Organ Class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥ 1/10,000 to < 1/1,000)
Immune system disorders			Hypersensitivity***	

PGR2026-00039
Biocon Ex.1065
Page 89 of 595

System Organ Class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥ 1/10,000 to < 1/1,000)
Eye disorders	Visual acuity reduced, Conjunctival haemorrhage, Eye pain	Retinal pigment epithelial tear*, Detachment of the retinal pigment epithelium, Retinal degeneration, Vitreous haemorrhage, Cataract, Cataract cortical, Cataract nuclear, Cataract subcapsular, Corneal erosion, Corneal abrasion, Intraocular pressure increased, Vision blurred, Vitreous floaters, Vitreous detachment, Injection site pain, Foreign body sensation in eyes, Lacrimation increased, Eyelid oedema, Injection site haemorrhage, Punctate keratitis, Conjunctival hyperaemia Ocular hyperaemia	Endophthalmitis**, Retinal detachment, Retinal tear, Iritis, Uveitis, Iridocyclitis, Lenticular opacities, Corneal epithelium defect, Injection site irritation, Abnormal sensation in eye, Eyelid irritation, Anterior chamber flare, Corneal oedema	Blindness, Cataract traumatic, Vitritis, Hypopyon

* Conditions known to be associated with wet AMD. Observed in the wet AMD studies only.
** Culture positive and culture negative endophthalmitis
*** including allergic reactions

Post-Marketing Experience

In addition, the following adverse reactions have also been reported during the post-marketing period of EYLEA, for which a frequency could not be estimated.

Immune system disorders: hypersensitivity (including rash, pruritus, urticaria, and isolated cases of severe anaphylactic/anaphylactoid reactions).

Description of selected adverse reactions

In the wet AMD phase III studies, there was an increased incidence of conjunctival haemorrhage in patients receiving anti-thrombotic agents. This increased incidence was comparable between patients treated with ranibizumab and EYLEA.

Arterial thromboembolic events (ATEs) are adverse events potentially related to systemic VEGF inhibition. There is a theoretical risk of arterial thromboembolic events following intravitreal use of VEGF inhibitors.

ATEs, as defined by Antiplatelet Trialists' Collaboration (APTC) criteria, include nonfatal myocardial infarction, nonfatal stroke, or vascular death (including deaths of

PGR2026-00039
Biocon Ex.1065
Page 90 of 595

unknown cause). The incidence of adjudicated APTC ATEs in the VIEW 1 and VIEW 2 wet AMD studies during the 96 weeks study period was 3.3% (60 out of 1824) in the combined group of patients treated with EYLEA (2.4% in the EYLEA 2Q4 arm and 3.6% in the EYLEA 2Q8 arm), compared to 3.2% (19 out of 595) in patients treated with ranibizumab.

The incidence of adjudicated APTC ATEs in the CRVO studies (GALILEO and COPERNICUS) during the 76/100 weeks study duration was 0.6% (2 out of 317) in patients treated with at least one dose of EYLEA compared to 1.4% (2 out of 142) in the group of patients receiving only sham treatment.

The incidence of adjudicated APTC ATEs in the DME studies (VIVID^{DME} and VISTA^{DME}) during the 100 weeks study duration was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group.

The incidence of APTC ATEs in the BRVO study (VIBRANT) during the 52 week study duration was 0% (0 out of 91) in patients treated with EYLEA compared with 2.2% (2 out of 92) in the control group.

The incidence of APTC ATEs in the myopic CNV study (MYRROR) during the 48 week study duration was 1.1% (1 out of 91) in the group of patients treated with EYLEA compared to 0% (0 out of 31) in the group of patients in the control group.

As with all therapeutic proteins, there is a potential for immunogenicity with EYLEA.

DOSAGE AND ADMINISTRATION

EYLEA is for intravitreal injection only.

It must only be administered by a qualified ophthalmologist experienced in administering intravitreal injections.

Dosage regimen

The recommended dose for EYLEA is 2 mg aflibercept, equivalent to an injection volume of 50 μL. The interval between doses injected into the same eye should not be shorter than one month.

Advice on treatment initiation and maintenance of therapy specific to each patient population is described in the section below. Once optimal visual acuity is achieved and/or there are no signs of disease activity, treatment may then be continued with a treat-and-extend regimen with gradually increased treatment intervals to maintain stable visual and/or anatomic outcomes. If disease activity persists or recurs, the treatment interval may be shortened accordingly. Monitoring should be done at injection visits. There is limited information on the optimal dosing interval and monitoring interval especially for long-term (e.g. > 12 months) treatment. The monitoring and treatment schedule should be determined by the treating ophthalmologist based on the individual patient's response. If visual and anatomic outcomes indicate that the patient is not benefiting from continued treatment, EYLEA should be discontinued.

PGR2026-00039
Biocon Ex.1065
Page 91 of 595

Treatment of neovascular (wet) age-related macular degeneration (wet AMD)

EYLEA treatment is initiated with one injection per month for three consecutive months, followed by one injection every two months. Long term, it is recommended that patients continue to be treated with EYLEA every two months.

Generally, once optimal visual acuity is achieved and/or there are no signs of disease activity, the treatment interval may be adjusted based on visual and/or anatomic outcomes.

The dosing interval can be extended up to every three months (see **CLINICAL TRIALS** for dosing experience).

Treatment of visual impairment due to macular oedema secondary to central retinal vein occlusion (CRVO)

EYLEA treatment is initiated with one injection per month for three consecutive months. After the first three monthly injections, the treatment interval may be adjusted based on visual and/or anatomic outcomes.

Treatment of visual impairment due to macular oedema secondary to branch retinal vein occlusion (BRVO)

EYLEA treatment is initiated with one injection per month for three consecutive months. After the first three monthly injections, the treatment interval may be adjusted based on visual and/or anatomic outcomes.

Treatment of diabetic macular oedema (DME)

EYLEA treatment is initiated with one injection per month for five consecutive months, followed by one injection every two months. After the first 12 months, the treatment interval may be adjusted based on visual and/or anatomic outcomes.

Treatment of visual impairment due to myopic choroidal neovascularisation (myopic CNV)

EYLEA treatment is initiated with one injection of 2 mg aflibercept (equivalent to 50 µL).

Additional doses should be administered only if visual and/or anatomic outcomes indicate that the disease persists. Recurrences are treated like a new manifestation of the disease.

Special populations

Patients with hepatic and/or renal impairment

No specific studies in patients with hepatic and/or renal impairment were conducted with EYLEA. Available data do not suggest a need for a dose adjustment with EYLEA in these patients (see **Pharmacokinetic properties**).

Method of administration

Intravitreal injections must be carried out according to medical standards and applicable guidelines by a qualified ophthalmologist experienced in administering intravitreal injections. In general, adequate anaesthesia and asepsis, including topical broad

PGR2026-00039
Biocon Ex.1065
Page 92 of 595

spectrum microbicide, have to be ensured. Surgical hand disinfection, sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent) are recommended.

Immediately following the intravitreal injection, patients should be monitored for elevation in intraocular pressure. Appropriate monitoring may consist of a check for perfusion of the optic nerve head or tonometry. If required, sterile equipment for paracentesis should be available.

Following intravitreal injection patients should be instructed to report any symptoms suggestive of endophthalmitis (e.g. eye pain, redness of the eye, photophobia, blurring of vision) without delay.

Each pre-filled syringe or vial should only be used for the treatment of a single eye.

The pre-filled syringe and the glass vial contain more than the recommended dose of 2 mg. The excess volume should be expelled before injecting. Injecting the entire volume of the glass vial or the pre-filled syringe could result in overdose.

After injection any unused product must be discarded.

Instructions for use / handling

The pre-filled syringe and the vial are for single use in one eye only.

Prior to administration visually inspect the solution for injection. Do not use the vial or pre-filled syringe if particulates, cloudiness, or discolouration are visible.

Prior to usage, the EYLEA unopened vial or pre-filled syringe blister pack may be stored at room temperature (25°C) for up to 24 hours. After opening the vial or blister pack, proceed under aseptic conditions.

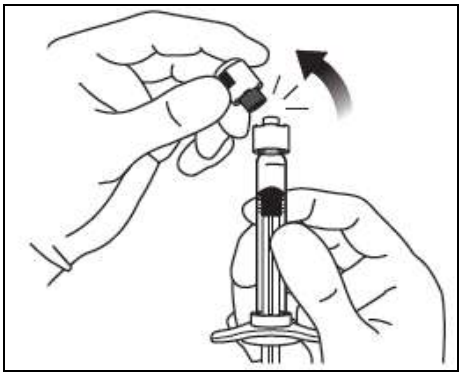
For the intravitreal injection a 30 G x ½ inch injection needle should be used.

Pre-filled syringe

1. When ready to administer EYLEA, open the carton and remove the sterilised blister pack. Carefully peel open the blister pack ensuring the sterility of its contents. Keep the syringe in the sterile tray until you are ready for assembly.

2. Using aseptic technique, remove the syringe from the sterilised blister pack.

3. To remove the syringe cap, hold the syringe in one hand while using your other hand to grasp the syringe cap with the thumb and forefinger. Please note: Snap off (do not turn or twist) the syringe cap.

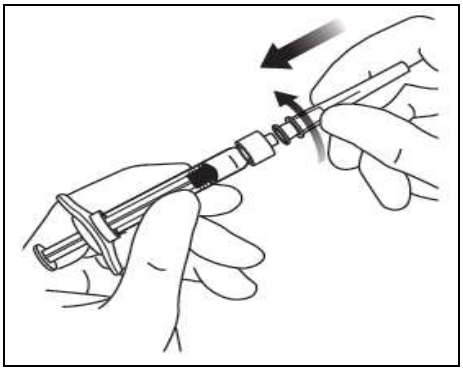


4. To avoid compromising the sterility of the

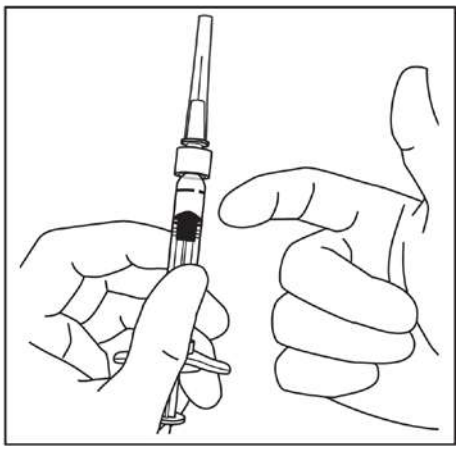
PGR2026-00039
Biocon Ex.1065
Page 93 of 595

product, do not pull back on the plunger.

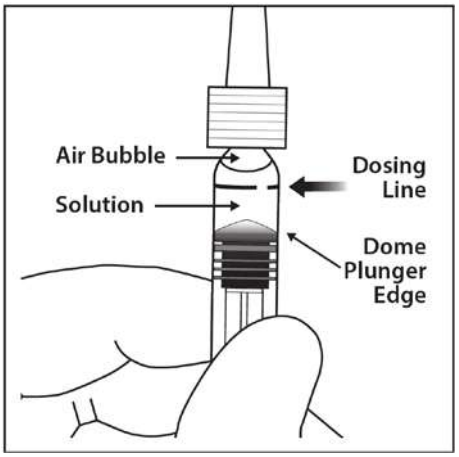
5. Using aseptic technique, firmly twist the injection needle onto the Luer-lock syringe tip.

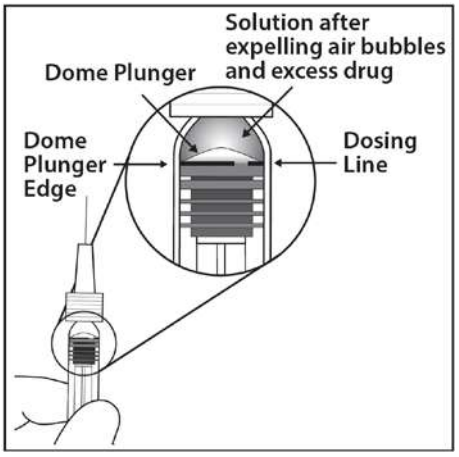


6. Holding the syringe with the needle pointing up, check the syringe for bubbles. If there are bubbles, gently tap the syringe with your finger until the bubbles rise to the top.



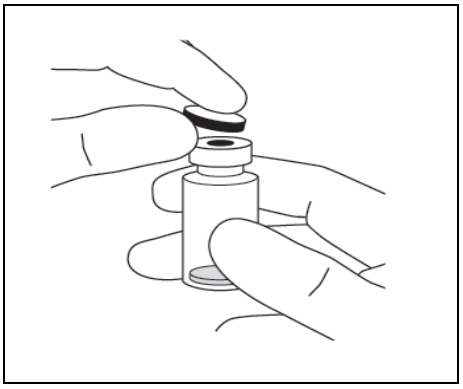
7. To eliminate all bubbles and to expel excess drug, slowly depress the plunger to align the cylindrical base of the dome plunger with the black dosing line on the syringe (equivalent to 50 µL).



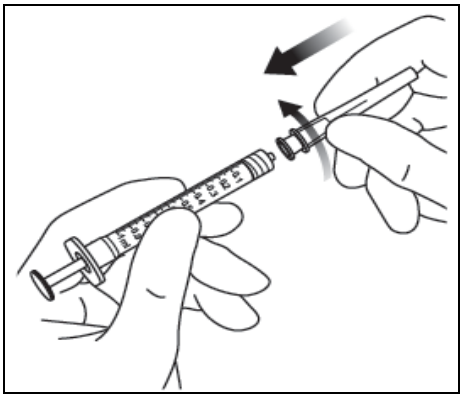


Vial

1. Remove the plastic cap and disinfect the outer part of the rubber stopper of the vial.

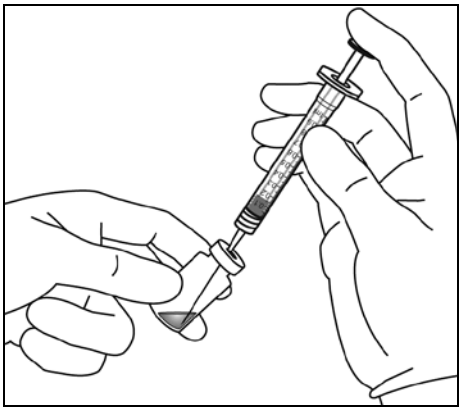


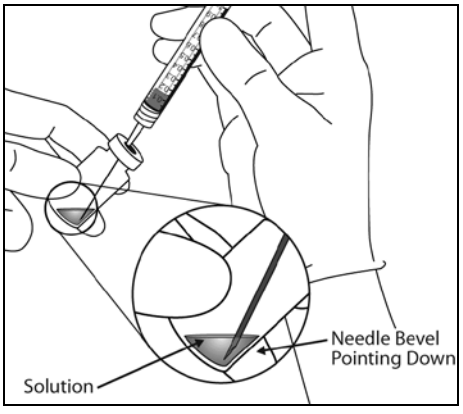
2. Attach the 18 G, 5-micron filter needle supplied in the carton to a 1 mL sterile, Luer-lock syringe.



3. Push the filter needle into the centre of the vial stopper until the needle is completely inserted into the vial and the tip touches the bottom or bottom edge of the vial.

4. Using aseptic technique withdraw all of the EYLEA vial contents into the syringe, keeping the vial in an upright position, slightly inclined to ease complete withdrawal. To deter the introduction of air, ensure the bevel of the filter needle is submerged into the liquid. Continue to tilt the vial during withdrawal keeping the bevel of the filter needle submerged in the liquid.



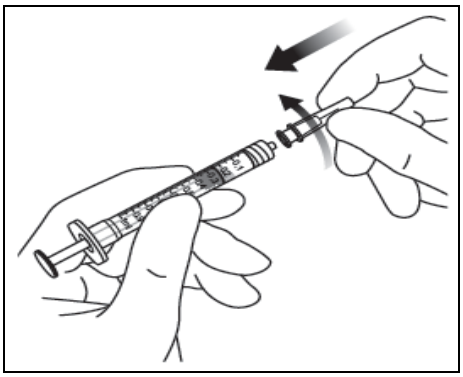


PGR2026-00039
Biocon Ex.1065
Page 95 of 595

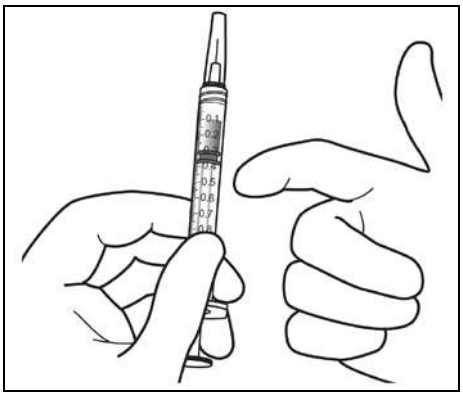
5. Ensure that the plunger rod is drawn sufficiently back when emptying the vial in order to completely empty the filter needle.

6. Remove the filter needle and properly dispose of it. **Note:** Filter needle is **not** to be used for intravitreal injection.

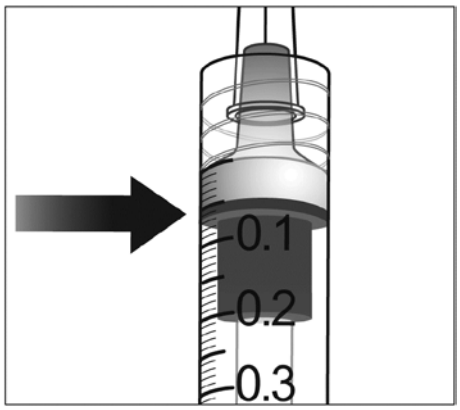
7. Using aseptic technique, firmly twist a 30 G x ½ inch injection needle to the Luer-lock syringe tip.

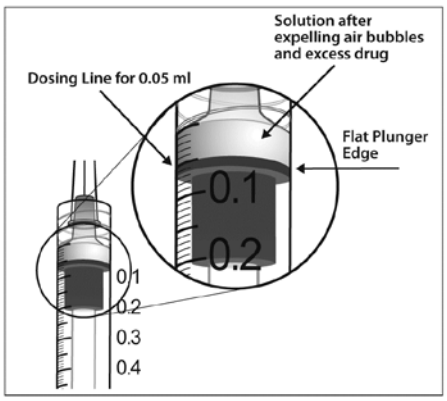


8. Holding the syringe with the needle pointing up, check the syringe for bubbles. If there are bubbles, gently tap the syringe with your finger until the bubbles rise to the top.



9. Eliminate all bubbles and expel excess drug by slowly depressing the plunger so that the plunger tip aligns with the line that marks 0.05 mL (equivalent to 50 µL) on the syringe.





PGR2026-00039
Biocon Ex.1065
Page 96 of 595

Incompatibilities

EYLEA must not be mixed with other medicinal products.

OVERDOSAGE

In clinical trials doses of up to 4 mg in monthly intervals and isolated cases of overdoses with 8 mg were generally well tolerated. Overdosing was associated with increased injection volume and subsequently with increased intraocular pressure. Therefore, in case of overdosage intraocular pressure should be monitored and if deemed necessary by the treating physician, adequate treatment should be initiated. It is advisable to contact the Poisons Information Centre (131126) for recommendations on the management and treatment of overdose.

PRESENTATION AND STORAGE CONDITIONS

Presentation

EYLEA is a sterile, clear, colourless to pale yellow, preservative-free, iso-osmotic aqueous solution for intravitreal injection containing 40 mg/mL aflibercept.

EYLEA is supplied in a single-use vial or pre-filled syringe.

Each vial and pre-filled syringe provides a usable amount to deliver a single dose of 50 µL solution for intravitreal injection containing 2 mg aflibercept.

Not all presentations are being distributed in Australia.

Pre-filled syringe

Each carton includes a sealed blister pack with a sterile pre-filled type I glass syringe, containing approximately 90 µL of extractable volume, sealed with an elastomeric plunger stopper and an elastomeric tip cap that is part of a closure system with Luer lock adaptor. The syringe has a pre-attached plunger rod and a finger plate.

Vial

Each carton includes a type I glass vial containing approximately 100 µL of extractable volume, with an elastomeric rubber stopper, and an 18 G filter needle.

Storage conditions

Store at 2°C to 8°C (Refrigerate. Do not freeze). Protect from light.

Keep the pre-filled syringe in its blister pack and carton in order to protect from light.

Keep the vial in its carton in order to protect from light.

NAME AND ADDRESS OF THE SPONSOR

Bayer Australia Ltd

ABN 22 000 138 714

875 Pacific Highway

Pymble, NSW 2073

PGR2026-00039
Biocon Ex.1065
Page 97 of 595

POISON SCHEDULE OF THE MEDICINE

PRESCRIPTION ONLY MEDICINE (S4)

DATE OF FIRST INCLUSION IN THE ARTG

7 March 2012

Date of most recent amendment: 13 July 2016

® Registered Trademark of the Bayer Group, Germany

PGR2026-00039
Biocon Ex.1065
Page 98 of 595

APPENDIX REGENERON01

Regeneron Pharmaceuticals, Inc.

Lehman Brothers

9th Annual Global Healthcare Conference

March 8, 2006

PGR2026-00039
Biocon Ex.1065
Page 100 of 595

Safe Harbor Statement

Except for historical information, the matters contained in this presentation may constitute forward-looking statements that involve risks and uncertainties, including uncertainties related to product development and clinical trials, unforeseen safety issues resulting from the administration of products in patients, uncertainties related to the need for regulatory and other government approvals, patents and proprietary technology, the need for additional capital, uncertainty of market acceptance of Regeneron's product candidates, the receipt of future payments, the continuation of business partnerships, and additional risks detailed from time to time in Regeneron's filings with the Securities and Exchange Commission (SEC). Please refer to Regeneron's recent Forms 10-K, 10-Q, and 8-K for additional information on the uncertainties and risk factors related to our business.

Because forward-looking statements involve risks and uncertainties, actual results may differ materially from current results expected by Regeneron. Regeneron is providing this information as of the original date of this presentation and expressly disclaims any duty to update any information contained in these materials.

REGENERON

PGR2026-00039
Biocon Ex.1065
Page 101 of 595

Regeneron Overview

- 3 major clinical programs
  - Oncology
  - Eye Diseases
  - Inflammatory Diseases
- Major collaboration with sanofi-aventis
- Manufacturing expertise at 10,000 liter scale
- Next generation platform for monoclonal antibodies
- Strong financial position
  - Approximately $316 million cash on hand at 12/31/05

REGENERON

PGR2026-00039
Biocon Ex.1065
Page 102 of 595

Current Events

- Oncology
  - Three phase 2 trials announced
  - Completing preparations for combination studies
  - FDA submission targeted for 2007/2008 timeframe
- Eye diseases
  - Reported positive preliminary results in wet AMD
  - Phase 2 study ready to go
  - Phase 3 planned for initiation early 2007
- IL-1 Trap – Inflammatory Diseases
  - Phase 3 study enrollment on plan
  - BLA submission targeted for 1H 2007
- Human monoclonal antibody platform
  - Source of new drug candidates and potential partnerships

REGENERON

PGR2026-00039
Biocon Ex.1065
Page 103 of 595

"Mechanism" vs. "Execution" Risk

- **Mechanism Risk**
  - Target not validated; no approved products with same molecular target
  - Mechanism-based toxicity ill-defined
  - Historically high rate of failure
- **Execution Risk**
  - Approved product validates molecular target and safety profile
  - Higher probability of successful development
  - 2nd and 3rd entries to "blockbuster" categories have history of strong commercial success

REGENERON

PGR2026-00039
Biocon Ex.1065
Page 104 of 595

Regeneron Clinical Product Candidates

- Each candidate designed to address clinically validated target
- Each has opportunity to expand to new disease settings
- Clinical evidence already obtained indicating that each candidate addresses its target
- Regulatory approval strategy defined for each candidate

Execution vs. Mechanism Risk!

REGENERON

PGR2026-00039
Biocon Ex.1065
Page 105 of 595

VEGF Trap Oncology
The sanofi-aventis Collaboration

Strong partner
- Leader in oncology marketplace
- Expertise in clinical development and therapeutic research
- Sanofi-aventis leads the global development program

Commitment to broad VEGF Trap oncology program
- Single agent studies
- Chemotherapy combination studies
- Expanding number of therapeutic indications

Favorable financial opportunity for Regeneron
- sanofi-aventis funds global development
  - Repayment of 50% out of profits according to formula
- $400 MM in commercial approval milestones
- 50:50 global profit split (35% royalty in Japan)
- Co-promotion rights

REGENERON

PGR2026-00039
Biocon Ex.1065
Page 106 of 595

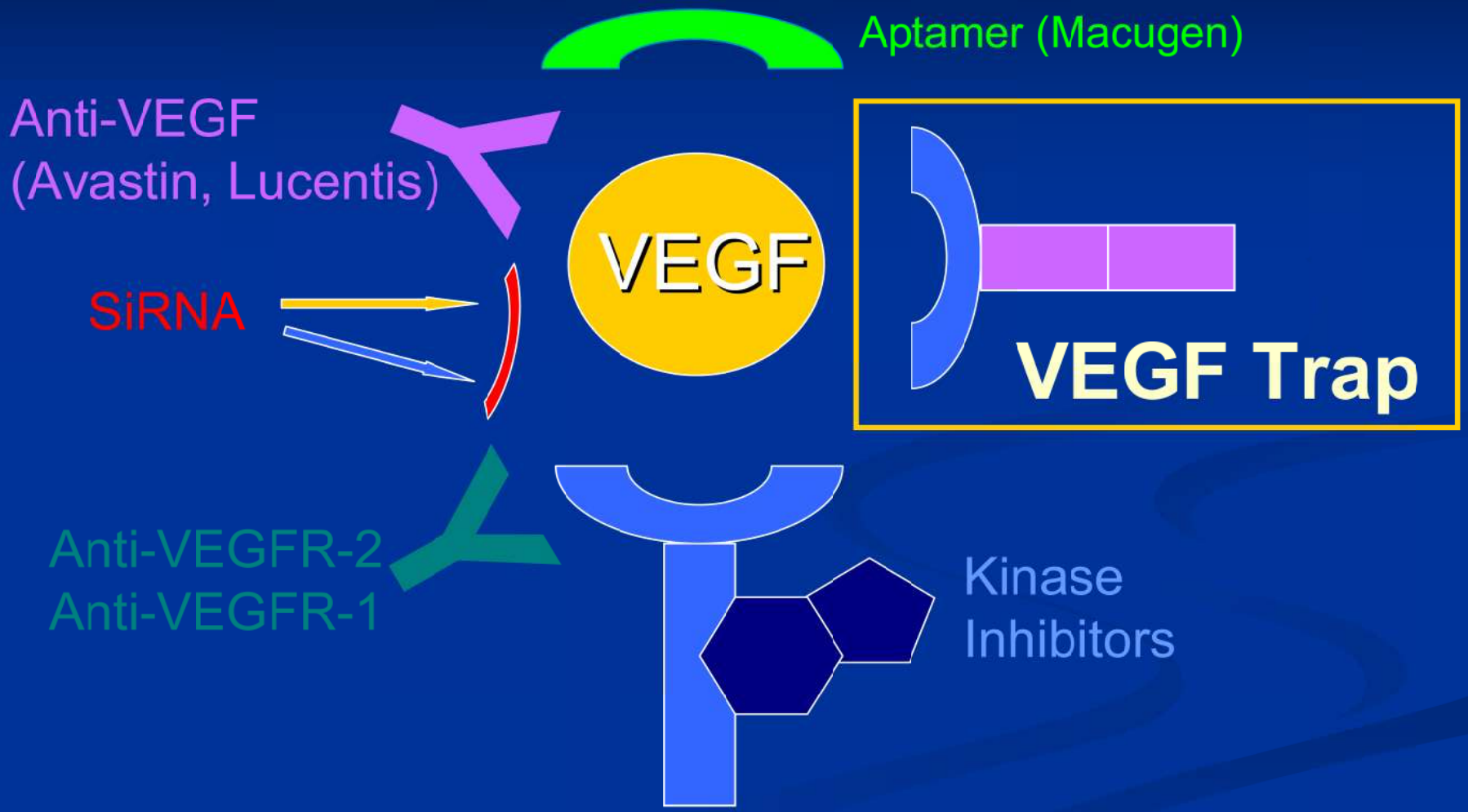
Blocking VEGF with VEGF Trap

- Clinical evidence that VEGF Trap can address "VEGF target"
  - Blood samples demonstrate "trapping" of VEGF
  - Decreased perfusion/vascular permeability after single dose
  - Adverse events of hypertension and proteinuria; expected based on Avastin® results
  - Responses observed in individual patients previously treated with multiple chemotherapy regimens

REGENERON

PGR2026-00039
Biocon Ex.1065
Page 107 of 595

Targeting the VEGF Pathway

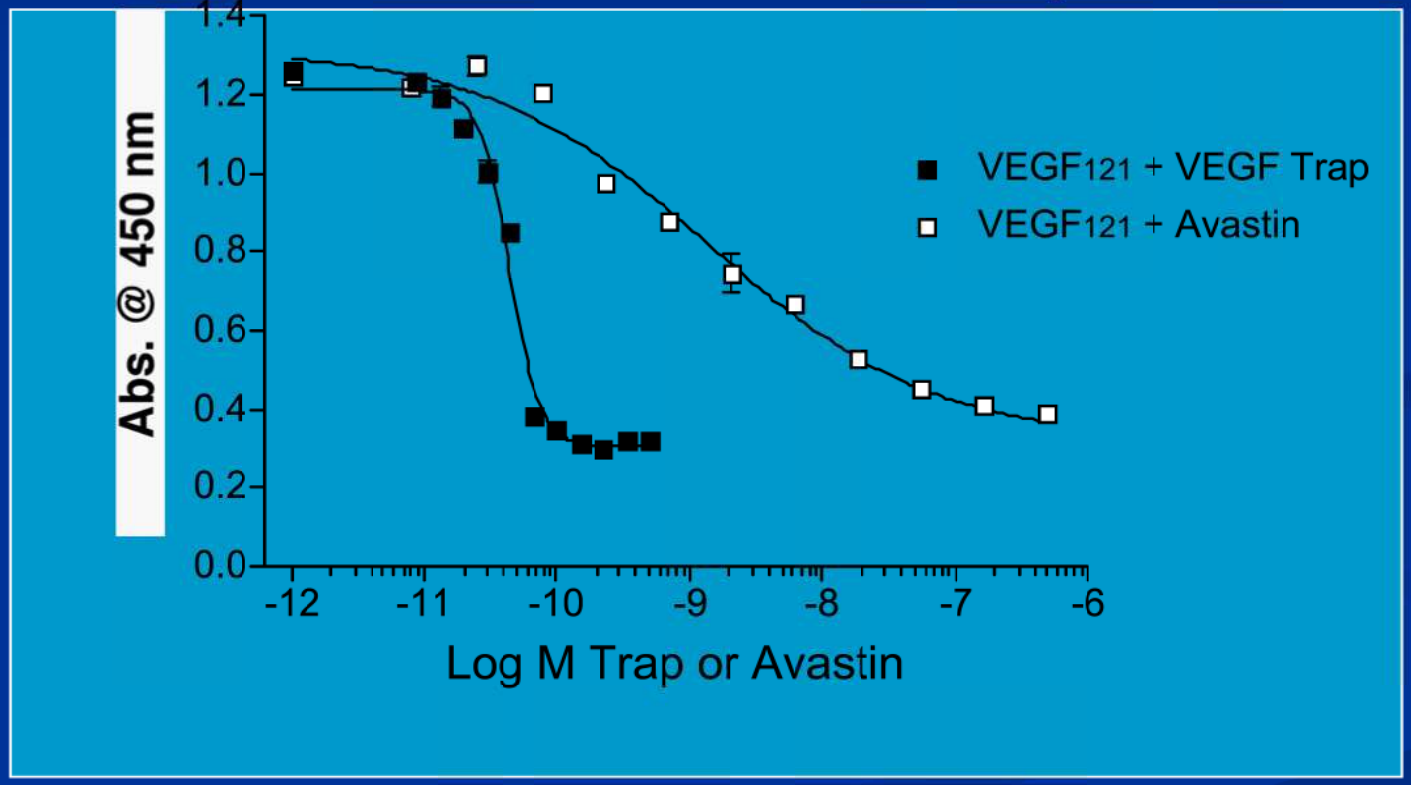


REGENERON

PGR2026-00039
Biocon Ex.1065
Page 108 of 595

Comparison of VEGF Trap and Avastin®

VEGF Trap has markedly higher affinity for VEGF than Avastin based on in vitro bioassay



IC50 for VEGF Trap = 44pM

IC50 for Avastin = 1400pM

REGENERON

PGR2026-00039
Biocon Ex.1065
Page 109 of 595

VEGF Trap Oncology

Single Agent Studies in Late-stage Cancer Patients

- Non-small Cell Lung Adenocarcinoma (NSCLA)
  - Trial initiated January 2006
  - Single arm, open label design
  - Primary endpoint objective response rate
- Ovarian Cancer
  - Randomized comparison of 2 doses of VEGF Trap
- Symptomatic Malignant Ascites (SMA)
  - Randomized, placebo controlled study
  - Fast track designation granted by FDA

REGENERON

PGR2026-00039
Biocon Ex.1065
Page 110 of 595

Preliminary Anti-tumor Activity
Ovarian Cancer Patient

VEGF Trap 4.0 mg/kg IV biweekly x 4

Baseline | Week 8



Diagnosis: Recurrent Advanced Ovarian Epithelial Adenocarcinoma

Prior Treatments: Carboplatinum + Paclitaxel; Carboplatinum + Gemcitabine

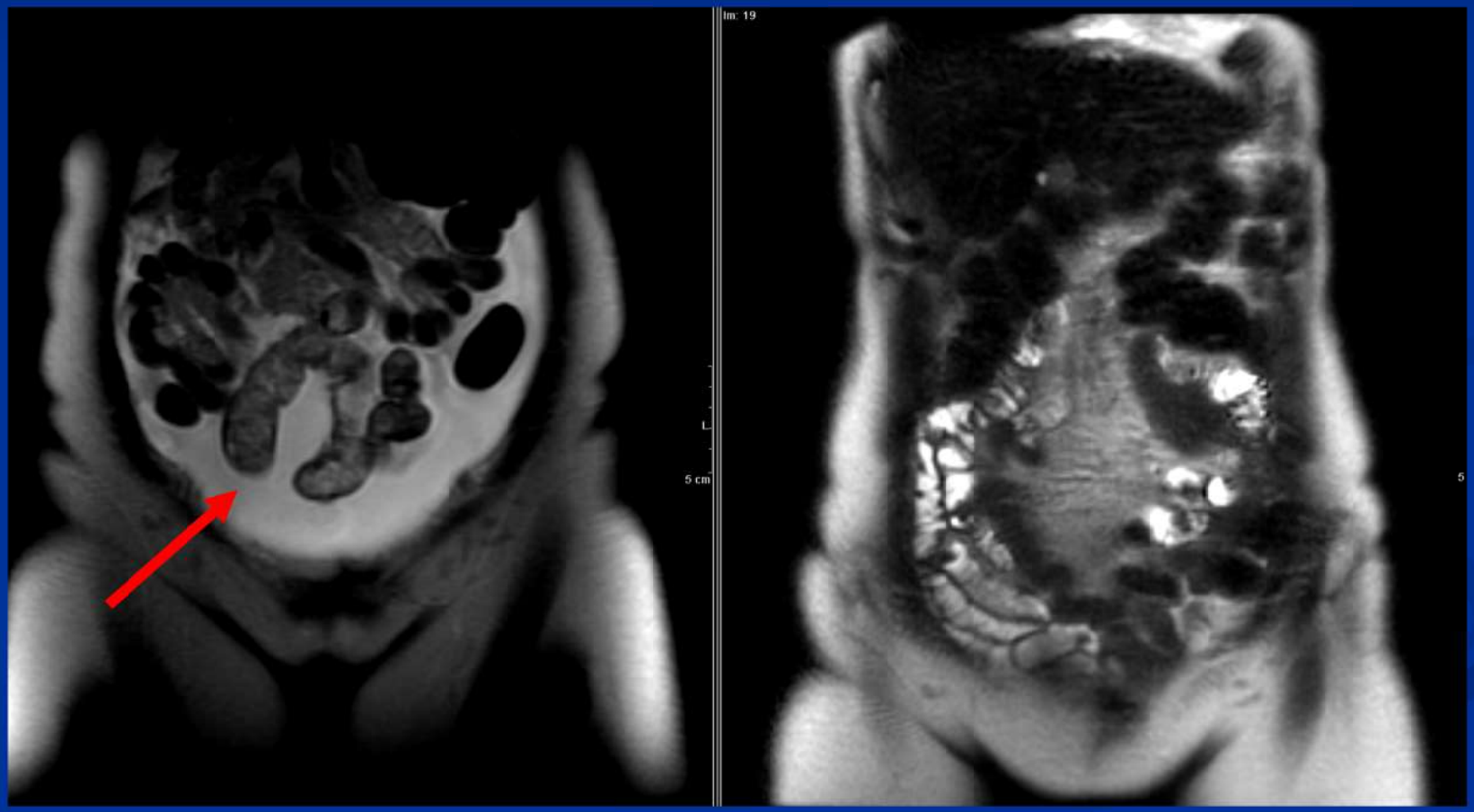
REGENERON

PGR2026-00039
Biocon Ex.1065
Page 111 of 595

Symptomatic Malignant Ascites
Complete Resolution after 4 Doses of VEGF Trap

VEGF Trap 4.0 mg/kg IV biweekly x 4

Baseline | Week 8



Prior Treatments: Carboplatinum + Paclitaxel; Carboplatinum + Gemcitabine

REGENERON

PGR2026-00039
Biocon Ex.1065
Page 112 of 595

VEGF Trap Oncology

VEGF Trap Studies in Combination with Standard Chemotherapy Regimens

- 5 phase 1b studies in different chemotherapy regimens
  - 3 trials initiated in 2005
  - 2 additional trials to begin in near term
- Efficacy studies to begin 2H 2006
  - 2 studies currently in late-stage planning

REGENERON

PGR2026-00039
Biocon Ex.1065
Page 113 of 595

VEGF Trap Oncology

VEGF Trap Studies being planned with National Cancer Institute

- National Cancer Institute to conduct trials of VEGF Trap under Clinical Trials Agreement between CTEP, NCI, and sanofi-aventis
- Up to 10 efficacy/safety studies planned for 2006

REGENERON

PGR2026-00039
Biocon Ex.1065
Page 114 of 595

VEGF Trap Oncology Summary

- VEGF confirmed as validated target
- Preliminary clinical evidence already obtained that VEGF Trap addresses target
- Clinical program being rapidly expanded
- Sanofi-aventis responsible for execution of clinical trials
- Submission for approval planned for 2007/2008 timeframe

REGENERON

PGR2026-00039
Biocon Ex.1065
Page 115 of 595

VEGF Trap – Eye Development Program

- Wet AMD is major cause of blindness in adults over 60
- Blocking VEGF validated as a means to treat wet AMD
- Opportunity for VEGF Trap – Eye to emerge as "best-in-class" treatment for wet AMD
  - Potential for greater efficacy related to unique characteristics
    - Higher affinity for VEGF than Lucentis®
    - Ability to block all forms of VEGF-A and Placental Growth Factor (PlGF)
  - Potential for greater patient convenience/safety by requiring less frequent injections
- Positive preliminary phase 1 data reported

REGENERON

PGR2026-00039
Biocon Ex.1065
Page 116 of 595

Phase 1 Intravitreal Trial

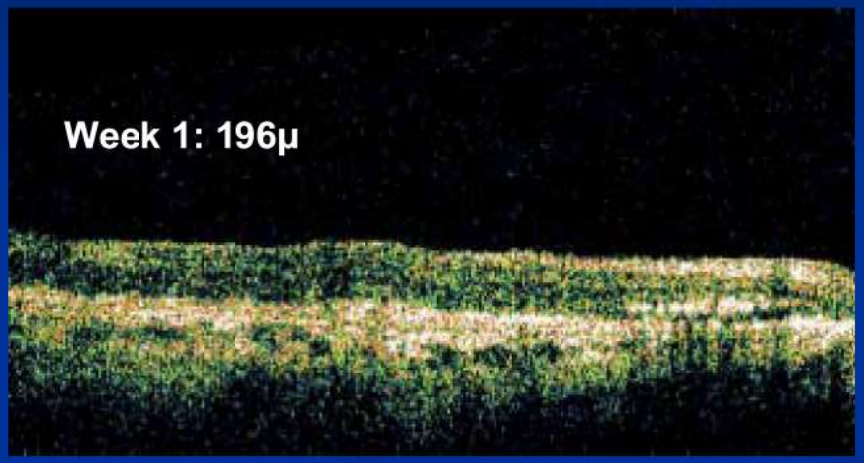
- Dose-ascending cohorts of 3-6 subjects given single intravitreal injection to determine maximum tolerated dose
- Primary endpoint safety and tolerability
  - Ocular coherence tomography (OCT) to assess retinal thickness
- Status and preliminary results
  - Dose levels of 0.05, 0.15, 0.5, 1.0, 2.0, and 4.0 mg completed
  - All planned dose levels completed: maximum tolerated dose not reached
  - Rapid, substantial, and prolonged (up to at least 4 weeks) reduction in retinal thickness demonstrated by OCT

REGENERON

PGR2026-00039
Biocon Ex.1065
Page 117 of 595

Intravitreal VEGF Trap – Eye
1.0 mg Single Dose









REGENERON

PGR2026-00039
Biocon Ex.1065
Page 118 of 595

VEGF Trap – Eye Summary

- Confirmed evidence of biological activity
  - Rapid and substantial reduction in retinal thickness
  - Prolonged effect appears to be at least 4 weeks
- Positioned for rapid expansion of program
  - Phase 2 wet AMD trial to begin in next few months
  - New indications being reviewed
- Phase 3 program in US likely to be comparison to ranibizumab (Lucentis™)
  - Initiation of phase 3 planned for 1Q 07
- Additional data at ARVO 2006

REGENERON

PGR2026-00039
Biocon Ex.1065
Page 119 of 595

The IL-1 Trap Development Program

Registration study initiated in rare genetic diseases
4Q 2005

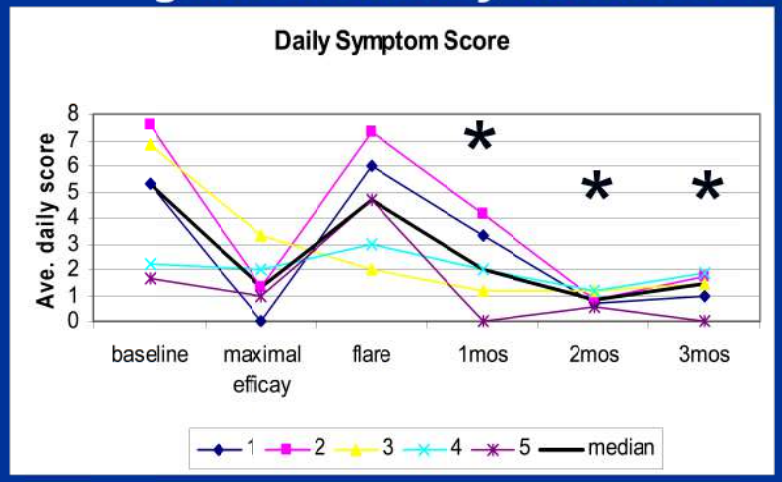
Proof-of-concept trial initiated in
Systemic Onset Juvenile Idiopathic Arthritis (SJIA)
4Q 2005

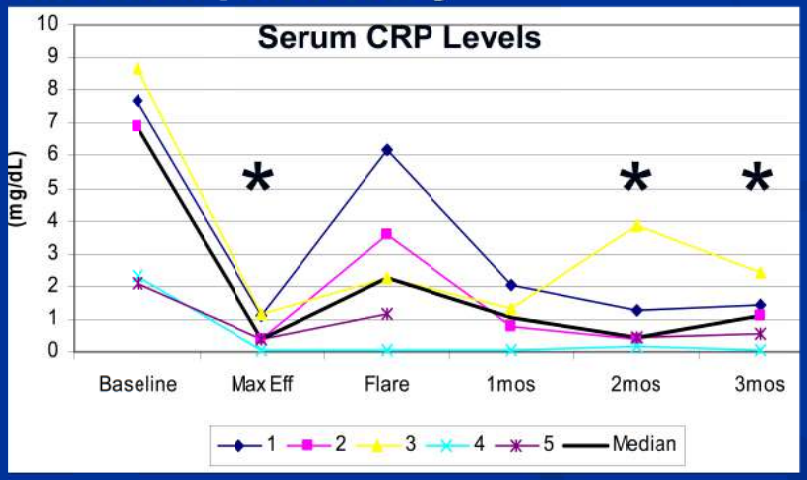
REGENERON

PGR2026-00039
Biocon Ex.1065
Page 120 of 595

IL-1 Trap CAPS POC Study (5 patients)

- IL-1 Trap rapidly and dramatically:
  - Improves subjective measures of disease
  - Lowers blood markers of inflammation (e.g., CRP, SAA, ESR)
  - "Traps" IL-1 and convincingly confirms markedly increased IL-1 levels in this disease
- No significant safety concerns noted in small pilot study





* : p<0.05 for comparison to baseline

* : p<0.05 for comparison to baseline

The daily diary score is the sum of symptoms on an ordinal (0-4) scale. Symptoms include fever, rash, joint pain, headache, hearing loss, fatigue, sleep problems, eye redness, & difficulties walking

REGENERON

PGR2026-00039
Biocon Ex.1065
Page 121 of 595

IL-1 Trap CAPS Registration Study

- Orphan drug designation
- 160 mg/week dose
- Study phases include
  - 6 month placebo controlled, double blind (efficacy/safety)
  - 6 month label extension (safety)
- Study cohort identified and enrollment in progress
  - Enrollment on target for completion 1H 06
  - BLA submission planned for 1H 2007

REGENERON

PGR2026-00039
Biocon Ex.1065
Page 122 of 595

Velocimmune: Proprietary New Approach for Therapeutic Human Monoclonal Antibodies

- Produces wide variety of high affinity human antibodies against target
- Synergizes with commercial-scale manufacturing and proprietary approach to cell line development
- Applicable to both validated and novel targets
- Overcomes many issues currently used to produce human antibodies

Future Pipeline Development Platform

REGENERON

PGR2026-00039
Biocon Ex.1065
Page 123 of 595

Regeneron's major development programs mid 2007: future plans

- Oncology
  - 3 single agent efficacy studies well under way
  - 3 large studies in combination with chemotherapy underway
  - About 12 studies underway in collaboration with NCI CTEP program
- Eye
  - Phase 2 data completed and data reported
  - Phase 3 underway in AMD
  - Additional indications being explored
- IL-1 Trap
  - BLA submitted for CAPS
  - Phase 3 under way for systemic onset JIA

REGENERON

PGR2026-00039
Biocon Ex.1065
Page 124 of 595

Regeneron Pharmaceuticals, Inc.

Lehman Brothers

9th Annual Global Healthcare Conference

March 8, 2006

PGR2026-00039
Biocon Ex.1065
Page 125 of 595

APPENDIX FDA02

https://web.archive.org/web/20151015000000*/https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021756s018lbl.pdf September 13, 2025

INTERNET ARCHIVE WEB TEXTS VIDEO AUDIO SOFTWARE IMAGES SIGN UP | LOG IN UPLOAD Search

ABOUT BLOG PROJECTS HELP DONATE CONTACT JOBS VOLUNTEER PEOPLE

DONATE INTERNET ARCHIVE WayBackMachine Explore more than 946 billion web pages saved over time

https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021

Calendar · Collections · Changes · Summary · Site Map · URLs

Saved **25 times** between January 17, 2015 and August 23, 2025.

002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 **2015** 2016 2017 2018 2019 2020 2021 2022 2023 2024 2025

JAN

			1	2	3	
4	5	6	7	8	9	10
11	12	13	14	15	16	17
18	19	20	21	22	23	24
25	26	27	28	29	30	31

FEB

1	2	3	4	5	6	7
8	9	10	11	12	13	14
15	16	17	18	19	20	21
22	23	24	25	26	27	28

MAR

1	2	3	4	5	6	7
8	9	10	11	12	13	14
15	16	17	18	19	20	21
22	23	24	25	26	27	28
29	30	31				

APR

			1	2	3	4
5	6	7	8	9	10	11
12	13	14	15	16	17	18
19	20	21	22	23	24	25
26	27	28	29	30		

MAY

				1	2	
3	4	5	6	7	8	9
10	11	12	13	14	15	16
17	18	19	20	21	22	23
24	25	26	27	28	29	30
31						

JUN

	1	2	3	4	5	6
7	8	9	10	11	12	13
14	15	16	17	18	19	20
21	22	23	24	25	26	27
28	29	30				

JUL

			1	2	3	4
5	6	7	8	9	10	11
12	13	14	15	16	17	18
19	20	21	22	23	24	25
26	27	28	29	30	31	

AUG

						1
2	3	4	5	6	7	8
9	10	11	12	13	14	15
16	17	18	19	20	21	22
23	24	25	26	27	28	29
30	31					

SEP

	1	2	3	4	5	
6	7	8	9	10	11	12
13	14	15	16	17	18	19
20	21	22	23	24	25	26
27	28	29	30			

OCT

				1	2	3
4	5	6	7	8	9	10
11	12	13	14	15	16	17
18	19	20	21	22	23	24
25	26	27	28	29	30	31

NOV

1	2	3	4	5	6	7
8	9	10	11	12	13	14
15	16	17	18	19	20	21
22	23	24	25	26	27	28
29	30					

DEC

		1	2	3	4	5
6	7	8	9	10	11	12
13	14	15	16	17	18	19
20	21	22	23	24	25	26
27	28	29	30	31		

Note

This calendar view maps the number of times **https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021756s018lbl.pdf** was crawled by the Wayback Machine, *not* how many times the site was actually updated. More info in the FAQ.

FAQ | Contact Us | Terms of Service (Dec 31, 2014)

The Wayback Machine is an initiative of the Internet Archive, a 501(c)(3) non-profit, building a digital library of Internet sites and other cultural artifacts in digital form. Other projects include Open Library & archive-it.org.

Your use of the Wayback Machine is subject to the Internet Archive's Terms of Use.

https://web.archive.org/web/20150117045738/https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021756s018lbl.pdf September 13, 2025

INTERNET ARCHIVE WayBack Machine https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021756s018lbl.pdf Go DEC JAN 17 JUN 2014 2015 2016 About this capture
25 captures
17 Jan 2015 - 23 Aug 2025

label 1 / 10 100%


1


2


3

----------DOSAGE AND ADMINISTRATION----------

- FOR OPHTHALMIC INTRAVITREAL INJECTION ONLY (2.1).
- Macugen 0.3 mg should be administered once every six weeks by intravitreous injection into the eye to be treated (2.2).

----------DOSAGE FORMS AND STRENGTHS----------

- 0.3 mg/90 µL solution in a single-use syringe for intravitreal injection (3).

----------CONTRAINDICATIONS----------

- Ocular or periocular infections (4.1).
- Hypersensitivity (4.2).

----------ADVERSE REACTIONS----------

Most common adverse reactions (reported in 10-40% of patients treated with Macugen for up to two years) are anterior chamber inflammation, blurred vision, cataract, conjunctival hemorrhage, corneal edema, eye discharge, eye irritation, eye pain, hypertension, increased intraocular pressure (IOP), ocular discomfort, punctate keratitis, reduced visual acuity, visual disturbance, vitreous floaters, and vitreous opacities (6.2).

To report SUSPECTED ADVERSE REACTIONS, contact Eyetech Inc. at 1-866-MACUGEN (1-866-622-8436) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION

Revised: 07/2011

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
2. DOSAGE AND ADMINISTRATION
2.1 General Dosing Information
2.2 Dosing
2.3 Preparation for Administration
2.4 Administration
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
4.1 Ocular or Periocular Infections
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1Mechanism of Action
12.3Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1Carcinogenesis, Mutagenesis, Impairment of Fertility

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all of the information needed to use MACUGEN® safely and effectively. See full prescribing information for MACUGEN®.
MACUGEN®(pegaptanib sodium injection)
Intravitreal Injection
Initial U.S. Approval: 2004

----------INDICATIONS AND USAGE----------
Macugen is indicated for the treatment of neovascular (wet) age-related macular degeneration (1).

----------DOSAGE AND ADMINISTRATION----------
- FOR OPHTHALMIC INTRAVITREAL INJECTION ONLY (2.1).
- Macugen 0.3 mg should be administered once every six weeks by intravitreous injection into the eye to be treated (2.2).

----------DOSAGE FORMS AND STRENGTHS----------
- 0.3 mg/90 µL solution in a single-use syringe for intravitreal injection (3).

----------CONTRAINDICATIONS----------
- Ocular or periocular infections (4.1).
- Hypersensitivity (4.2).

----------WARNINGS AND PRECAUTIONS----------
- Endophthalmitis may occur following intravitreous injections. Proper aseptic injection technique should always be utilized when administering Macugen. Patients should be monitored during the week following the injection (5.1).
- Increases in intraocular pressure have been seen within 30 minutes of injection of Macugen (5.2).
- Rare cases of anaphylaxis/anaphylactoid reactions, including angioedema, have been reported in the post-marketing experience (5.3).

----------ADVERSE REACTIONS----------
Most common adverse reactions (reported in 10-40% of patients treated with Macugen for up to two years) are anterior chamber inflammation, blurred vision, cataract, conjunctival hemorrhage, corneal edema, eye discharge, eye irritation, eye pain, hypertension, increased intraocular pressure (IOP), ocular discomfort, punctate keratitis, reduced visual acuity, visual disturbance, vitreous floaters, and vitreous opacities (6.2).

To report SUSPECTED ADVERSE REACTIONS, contact Eyetech Inc. at 1-866-MACUGEN (1-866-622-8436) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION

Revised: 07/2011

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
2. DOSAGE AND ADMINISTRATION
2.1 General Dosing Information
2.2 Dosing
2.3 Preparation for Administration
2.4 Administration
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
4.1 Ocular or Periocular Infections
4.2 Hypersensitivity
5 WARNINGS AND PRECAUTIONS
5.1 Endophthalmitis
5.2 Increases in Intraocular Pressure
5.3 Anaphylaxis
6 ADVERSE REACTIONS
6.1 Injection Procedure
6.2 Clinical Studies Experience
6.3 Postmarketing Experience
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1Mechanism of Action
12.3Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Macugen is indicated for the treatment of neovascular (wet) age-related macular degeneration.

2. DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

FOR OPHTHALMIC INTRAVITREAL INJECTION ONLY.

2.2 Dosing

Macugen 0.3 mg should be administered once every six weeks by intravitreous injection into the eye to be treated.

2.3 Preparation for Administration

Macugen should be inspected visually for particulate matter and discoloration prior to administration. If visible particulates are observed and/or the liquid in the syringe is discolored, the syringe must not be used.

Administration of the syringe contents involves assembly of the syringe with the administration needle. The injection procedure should be carried out under controlled aseptic conditions, which includes the use of sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent). When ready to assemble syringe and administer injection, carefully peel open pouches, remove contents, and place on sterile field. If upon opening the pouch, the plastic clip is missing or not attached to the syringe, the syringe should not be used.

To avoid compromising the sterility of the product, do not pull back on the plunger.

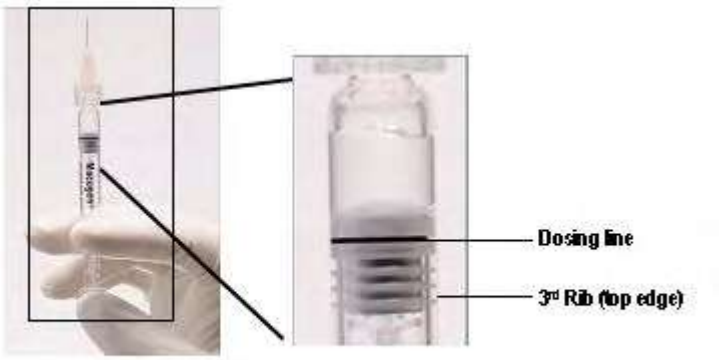
1. Remove the syringe from the plastic clip.
2. Twist off cap.
3. Attach the sterile BD® 30G ½" Precision Glide® administration needle (included) to the syringe by screwing it into the syringe tip.

--Another sterile BD® 30G ½" Precision Glide® administration needle may be used in lieu of the one included. Remove the plastic needle shield from the needle.

4. Holding the syringe with the needle pointing up, check the syringe for bubbles. If there are bubbles, gently tap the syringe with your finger until the bubbles rise to the top of the syringe. **SLOWLY** depress the plunger to eliminate all the bubbles and to expel the excess drug so that the **top edge of the 3rd rib on the plunger stopper aligns with the pre-printed black dosing line (See Figure 2, below).**
5. Inject the entire contents of the syringe.

PRIOR to Injection

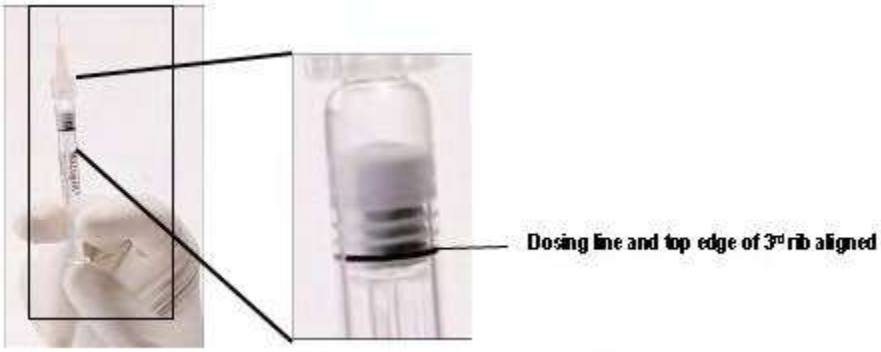
Figure1. **Before** expelling air bubble and excess drug



(Actual air bubble formation may vary)

READY for Injection

Figure 2. **After** expelling air bubble and excess drug



2.4 Administration

The injection procedure should be carried out under controlled aseptic conditions, which includes the use of sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent). Adequate anesthesia and a broad-spectrum microbicide should be given prior to the injection.

The patient's medical history for hypersensitivity reactions should be evaluated prior to performing the intravitreal procedure [*see Warnings and Precautions (5) and Adverse Events (6)*].

Following the injection, patients should be monitored for elevation in intraocular pressure and for endophthalmitis. Monitoring may consist of a check for perfusion of the optic nerve head immediately after the injection, tonometry within 30 minutes following the injection, and monitoring during the week following the injection. Patients should be instructed to report any symptoms suggestive of endophthalmitis without delay.

No special dosage modification is required for any of the populations that have been studied (i.e. gender, elderly).

The safety and efficacy of Macugen therapy administered to both eyes concurrently have not been studied.

3 DOSAGE FORMS AND STRENGTHS

Single-use glass syringe pre-filled with 0.3 mg of Macugen® in a nominal 90 µL solution for intravitreal injection.

4 CONTRAINDICATIONS

4.1 Ocular or Periocular Infections

Macugen is contraindicated in patients with ocular or periocular infections.

4.2 Hypersensitivity

Macugen is contraindicated in patients with known hypersensitivity to pegaptanib sodium or any other excipient in this product.

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis

Intravitreous injections, including those with Macugen, have been associated with endophthalmitis. Proper aseptic injection technique should always be utilized when administering Macugen. In addition, patients should be monitored during the week following the injection to permit early treatment, should an infection occur [*see Dosage and Administration (2.4)*].

5.2 Increases in Intraocular Pressure

Increases in intraocular pressure have been seen within 30 minutes of injection with Macugen. Therefore, intraocular pressure as well as the perfusion of the optic nerve head should be monitored and managed appropriately [*see Dosage and Administration (2.4)*].

5.3 Anaphylaxis

Rare cases of anaphylaxis/anaphylactoid reactions, including angioedema, have been reported in the post-marketing experience following the Macugen intravitreal administration procedure [*see Adverse Events (6.3) and Dosage and Administration (2.4)*].

6 ADVERSE REACTIONS

6.1 Injection Procedure

Serious adverse events related to the injection procedure occurring in < 1% of intravitreous injections included endophthalmitis [*see Warnings and Precautions (5.1)*], retinal detachment, and iatrogenic traumatic cataract.

6.2 Clinical Studies Experience

The most frequently reported adverse events in patients treated with Macugen 0.3 mg for up to two years were anterior chamber inflammation, blurred vision, cataract, conjunctival hemorrhage, corneal edema, eye discharge, eye irritation, eye pain, hypertension, increased intraocular pressure (IOP), ocular discomfort, punctate keratitis, reduced visual acuity, visual disturbance, vitreous floaters, and vitreous opacities. These events occurred in approximately 10-40% of patients.

The following events were reported in 6-10% of patients receiving Macugen 0.3 mg therapy:
Ocular: blepharitis, conjunctivitis, photopsia, vitreous disorder.
Non-Ocular: bronchitis, diarrhea, dizziness, headache, nausea, urinary tract infection.

The following events were reported in 1-5% of patients receiving Macugen 0.3 mg therapy:
Ocular: allergic conjunctivitis, conjunctival edema, corneal abrasion, corneal deposits, corneal epithelium disorder, endophthalmitis, eye inflammation, eye swelling, eyelid irritation, meibomianitis, mydriasis, periorbital hematoma, retinal edema, vitreous hemorrhage.
Non-Ocular: arthritis, bone spur, carotid artery occlusion, cerebrovascular accident, chest pain, contact dermatitis, contusion, diabetes mellitus, dyspepsia, hearing loss, pleural effusion, transient ischemic attack, urinary retention, vertigo, vomiting.

6.3 Postmarketing Experience

Anaphylaxis/anaphylactoid reactions, including angioedema, have been identified during postapproval use of Macugen. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure [*see Warnings and Precautions (5.3) and Dosage and Administration (2.4)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category B. Pegaptanib produced no maternal toxicity and no evidence of teratogenicity or fetal mortality in mice at intravenous doses of up to 40 mg/kg/day (about 7,000 times the recommended human monocular ophthalmic dose of 0.3 mg/eye). Pegaptanib crosses the placenta in mice.

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

8.3 Nursing Mothers

It is not known whether pegaptanib is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Macugen is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness of Macugen in pediatric patients have not been established.

8.5 Geriatric Use

Approximately 94% (834/892) of the patients treated with Macugen were ≥ 65 years of age and approximately 62% (553/892) were ≥ 75 years of age. No difference in treatment effect or systemic exposure was seen with increasing age.

10 OVERDOSAGE

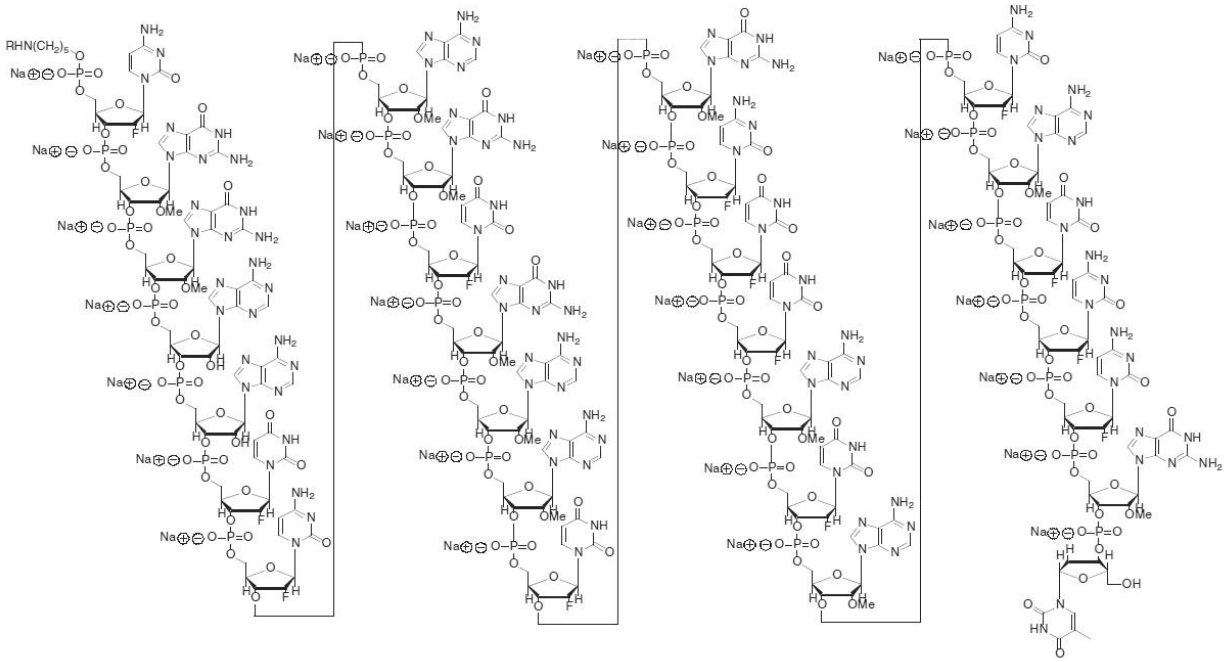
Doses of Macugen up to 10 times the recommended dosage of 0.3 mg have been studied. No additional adverse events have been noted but there is decreased efficacy with doses above 1 mg.

11 DESCRIPTION

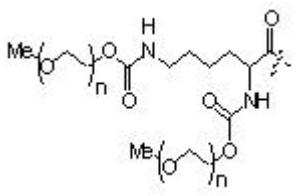
Macugen (pegaptanib sodium injection) is a sterile, aqueous solution containing pegaptanib sodium for intravitreous injection. Macugen is supplied in a single-dose, pre-filled syringe and is formulated as a 3.47 mg/mL solution, measured as the free acid form of the oligonucleotide. The active ingredient is 0.3 mg of the free acid form of the oligonucleotide without polyethylene glycol, in a nominal volume of 90 µL. This dose is equivalent to 1.6 mg of pegaptanib sodium (pegylated oligonucleotide) or 0.32 mg when expressed as the sodium salt form of the oligonucleotide moiety. The product is a sterile, clear, preservative-free solution containing sodium chloride, monobasic sodium phosphate monohydrate, dibasic sodium phosphate heptahydrate, hydrochloric acid, and/or sodium hydroxide to adjust the pH and water for injection.

Pegaptanib sodium is a covalent conjugate of an oligonucleotide of twenty-eight nucleotides in length that terminates in a pentylamino linker, to which two 20-kilodalton monomethoxy polyethylene glycol (PEG) units are covalently attached via the two amino groups on a lysine residue.

Pegaptanib sodium is represented by the following structural formula:



Where R is



and n is approximately 450.

PGR2026-00039
Biocon Ex.1065
Page 134 of 595

The chemical name for pegaptanib sodium is as follows: RNA, ((2'-deoxy-2'-fluoro)C-G_m-G_m-A-A-(2'-deoxy-2'-fluoro)U-(2'-deoxy-2'-fluoro)C-A_m-G_m-(2'-deoxy-2'-fluoro)U-G_m-A_m-A_m-(2'-deoxy-2'-fluoro)U-G_m-(2'-deoxy-2'-fluoro)C-(2'-deoxy-2'-fluoro)U-(2'-deoxy-2'-fluoro)U-A_m-(2'-deoxy-2'-fluoro)U-A_m-(2'-deoxy-2'-fluoro)C-A_m-(2'-deoxy-2'-fluoro)U-(2'-deoxy-2'-fluoro)C-(2'-deoxy-2'-fluoro)C-G_m-(3'→3')-dT), 5'-ester with α,α'-[4,12-dioxo-6-[[[5-(phosphoonoxy)pentyl]amino] carbonyl]-3,13-dioxa-5,11-diaza-1,15-pentadecanediyl]bis[ω-methoxypoly(oxy-1,2-ethanediyl)], sodium salt.

The molecular formula for pegaptanib sodium is $C_{294}H_{342}F_{13}N_{107}Na_{28}O_{188}P_{28}[C_2H_4O]_n$ (where n is approximately 900) and the molecular weight is approximately 50 kilodaltons.

Macugen is formulated to have an osmolality of 280-360 mOsm/Kg, and a pH of 6–7.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Pegaptanib is a selective vascular endothelial growth factor (VEGF) antagonist. VEGF is a secreted protein that selectively binds and activates its receptors located primarily on the surface of vascular endothelial cells. VEGF induces angiogenesis, and increases vascular permeability and inflammation, all of which are thought to contribute to the progression of the neovascular (wet) form of age-related macular degeneration (AMD), a leading cause of blindness. VEGF has been implicated in blood retinal barrier breakdown and pathological ocular neovascularization.

Pegaptanib is an aptamer, a pegylated modified oligonucleotide, which adopts a three-dimensional conformation that enables it to bind to extracellular VEGF. Under in vitro testing conditions, pegaptanib binds to the major pathological VEGF isoform, extracellular $VEGF_{165}$, thereby inhibiting $VEGF_{165}$ binding to its VEGF receptors. The inhibition of $VEGF_{164}$, the rodent counterpart of human $VEGF_{165}$, was effective at suppressing pathological neovascularization.

12.3 Pharmacokinetics

Absorption

In animals, pegaptanib is slowly absorbed into the systemic circulation from the eye after intravitreous administration. The rate of absorption from the eye is the rate limiting step in the disposition of pegaptanib in animals and is likely to be the rate limiting step in humans.

In humans, a mean maximum plasma concentration of about 80 ng/mL occurs within 1 to 4 days after a 3 mg monocular dose (10 times the recommended dose). The mean area under the plasma concentration-time curve (AUC) is about 25 µg·hr/mL at this dose.

Pegaptanib is metabolized by nucleases and is generally not affected by the cytochrome P450 system.

Two early clinical studies conducted in patients who received Macugen alone and in combination with photodynamic therapy (PDT) revealed no apparent difference in the plasma pharmacokinetics of pegaptanib.

Distribution/Metabolism/Excretion

Twenty-four hours after intravitreous administration of a radiolabeled dose of pegaptanib to both eyes of rabbits, radioactivity was mainly distributed in vitreous fluid, retina, and aqueous fluid. After intravitreous and intravenous administrations of radiolabeled pegaptanib to rabbits, the highest concentrations of radioactivity (excluding the eye for the intravitreous dose) were obtained in the kidney. In rabbits, the component nucleotide, 2'-fluorouridine is found in plasma and urine after single radiolabeled pegaptanib intravenous and intravitreous doses. In rabbits, pegaptanib is eliminated as parent drug and metabolites primarily in the urine.

Based on preclinical data, pegaptanib is metabolized by endo- and exonucleases.

In humans, after a 3 mg monocular dose (10 times the recommended dose), the average (± standard deviation) apparent plasma half-life of pegaptanib is 10 (±4) days.

Special Populations
Plasma concentrations do not appear to be affected by age or gender, but have not been studied in patients under the age of 50.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with pegaptanib have not been conducted. No data are available to evaluate male or female mating or fertility indices.

13.2 Animal Toxicology and/or Pharmacology

Pegaptanib and its monomer component nucleotides (2'-MA, 2'-MG, 2'-FU, 2'-FC) were evaluated for genotoxicity in a battery of *in vitro* and *in vivo* assay systems. Pegaptanib, 2'-O-methyladenosine (2'-MA), and 2'-O-methylguanosine (2'-MG) were negative in all assay systems evaluated. 2'-fluorouridine (2'-FU) and 2'-fluorocytidine (2'-FC) were nonclastogenic and were negative in all *S. typhimurium* tester strains, but produced a non-dose related increase in revertant frequency in a single *E. coli* tester strain. Pegaptanib, 2'-FU, and 2'-FC tested negative in cell transformation assays.

14 CLINICAL STUDIES

Macugen was studied in two controlled, double-masked, and identically designed randomized studies in patients with neovascular AMD. Patients were randomized to receive control (sham treatment) or 0.3 mg, 1 mg or 3 mg Macugen administered as intravitreous injections every 6 weeks for 48 weeks. A total of approximately 1200 patients were enrolled with 892 patients receiving Macugen and 298 receiving a sham injection. The median age of the patients was 77 years. Patients received a mean 8.5 treatments out of a possible 9 total treatments across all treatment arms. Patients were re-randomized between treatment and no treatment during the second year. Patients who continued treatment in year 2 received a mean of 16 treatments out of a possible total 17 overall.

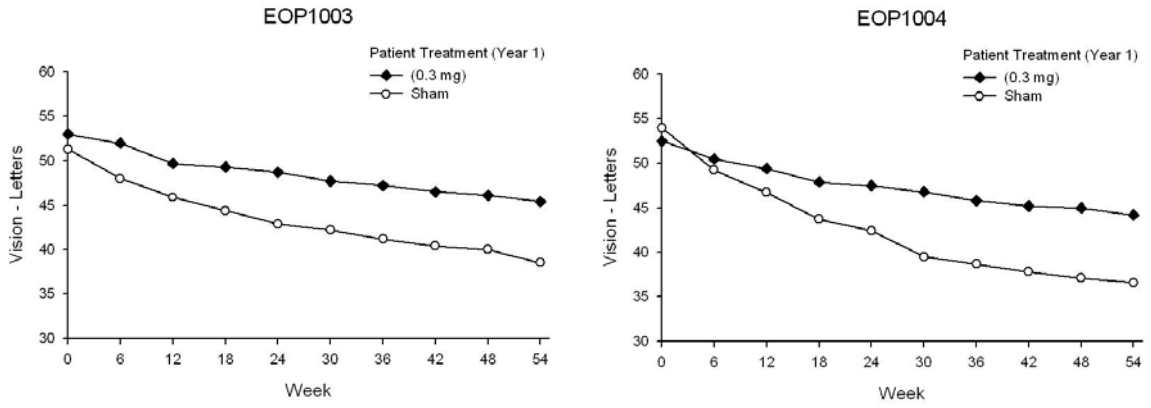
The two trials enrolled patients with neovascular AMD characteristics including classic, occult, and mixed lesions of up to 12 disc areas and baseline visual acuity in the study eye between 20/40 and 20/320. The primary efficacy endpoint was the proportion of patients losing less than 15 letters of visual acuity, from baseline up to 54 week assessment.

Verteporfin PDT usage was permitted at the discretion of the investigators in patients with predominantly classic lesions.

The groups treated with Macugen 0.3 mg exhibited a statistically significant result in both trials for the primary efficacy endpoint at 1 year: Study EOP1003, Macugen 73% vs. Sham 60%; Study EOP1004, Macugen 67% vs. Sham 53%. Concomitant use of PDT overall was low. More sham treated patients (75/296) received PDT than Macugen 0.3 mg treated patients (58/294).

On average, Macugen 0.3 mg treated patients and sham treated patients continued to experience vision loss. However, the rate of vision decline in the Macugen treated group was slower than the rate in the patients who received sham treatment. See Figure 1.

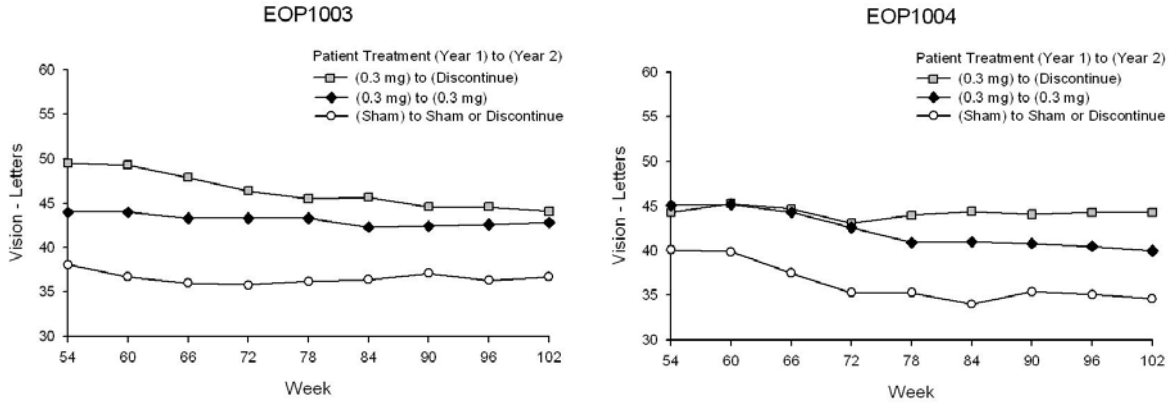
Figure 1
Mean Visual Acuity: Year 1



At the end of the first year (week 54), approximately 1050 of the original 1200 patients were re-randomized to either continue the same treatment or to discontinue treatment through week 102. See Figure 2.

Macugen was less effective during the second year than during the first year. The percentage of patients losing less than 15 letters from baseline to week 102 was: Study EOP1003, Macugen 38/67 (57%); Sham 30/54 (56%); Study EOP1004, Macugen 40/66 (61%); Sham 18/53 (34%).

Figure 2
Mean Visual Acuity: Year 2



Dose levels above 0.3 mg did not demonstrate any additional benefit.
The safety or efficacy of Macugen beyond 2 years has not been demonstrated.

16 HOW SUPPLIED/STORAGE AND HANDLING

Macugen (pegaptanib sodium injection) is supplied in a sterile foil pouch as a single-use glass syringe pre-filled with 0.3 mg of Macugen® in a nominal 90 µL deliverable volume pack. A sterile packaged BD® single use 30G x ½" Precision Glide® Luer Lok® needle is supplied in a separate pouch. The foil pouch and needle are packaged together in a carton (NDC 68782-001-02).

Store in the refrigerator at 2° to 8°C (36° to 46°F). Do not freeze or shake vigorously.
Rx only.

17 PATIENT COUNSELING INFORMATION

In the days following Macugen administration, patients are at risk for the development of endophthalmitis. If the eye becomes red, sensitive to light, painful or develops a change in vision, the patient should seek the immediate care with their ophthalmologist [*see Warnings and Precautions (5.1)*].

MACUGEN®(pegaptanib sodium injection)

Manufactured by:
Gilead Sciences, Inc
650 Cliffside Drive
San Dimas, CA 91773

For:
Eyetech Inc.
11360 Jog Road, Suite 200
Palm Beach Gardens, Florida 33418

BD and Precision Glide Luer Lok® are registered trademarks of Becton Dickinson & CO, Franklin Lakes, New Jersey 07417

APPENDIX FDA03

https://web.archive.org/web/20190715000000*/https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761125s000lbl.pdf September 13, 2025

INTERNET ARCHIVE WEB TEXTS VIDEO AUDIO SOFTWARE IMAGES SIGN UP | LOG IN UPLOAD Search

ABOUT BLOG PROJECTS HELP DONATE CONTACT JOBS VOLUNTEER PEOPLE

DONATE

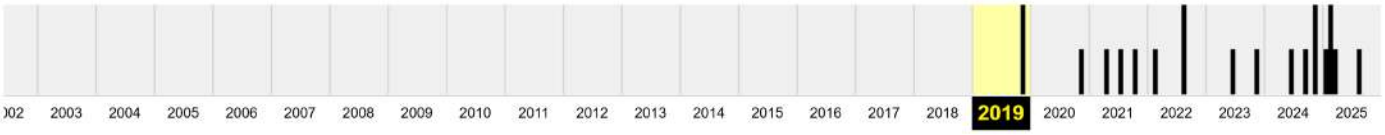
INTERNET ARCHIVE WayBackMachine

Explore more than 946 billion web pages saved over time

https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761

Calendar · Collections · Changes · Summary · Site Map · URLs

Saved **20 times** between November 17, 2019 and August 22, 2025.



JAN

	1	2	3	4	5	
6	7	8	9	10	11	12
13	14	15	16	17	18	19
20	21	22	23	24	25	26
27	28	29	30	31		

FEB

					1	2
3	4	5	6	7	8	9
10	11	12	13	14	15	16
17	18	19	20	21	22	23
24	25	26	27	28		

MAR

					1	2
3	4	5	6	7	8	9
10	11	12	13	14	15	16
17	18	19	20	21	22	23
24	25	26	27	28	29	30
31						

APR

	1	2	3	4	5	6
7	8	9	10	11	12	13
14	15	16	17	18	19	20
21	22	23	24	25	26	27
28	29	30				

MAY

		1	2	3	4	
5	6	7	8	9	10	11
12	13	14	15	16	17	18
19	20	21	22	23	24	25
26	27	28	29	30	31	

JUN

						1
2	3	4	5	6	7	8
9	10	11	12	13	14	15
16	17	18	19	20	21	22
23	24	25	26	27	28	29
30						

JUL

	1	2	3	4	5	6
7	8	9	10	11	12	13
14	15	16	17	18	19	20
21	22	23	24	25	26	27
28	29	30	31			

AUG

				1	2	3
4	5	6	7	8	9	10
11	12	13	14	15	16	17
18	19	20	21	22	23	24
25	26	27	28	29	30	31

SEP

1	2	3	4	5	6	7
8	9	10	11	12	13	14
15	16	17	18	19	20	21
22	23	24	25	26	27	28
29	30					

OCT

		1	2	3	4	5
6	7	8	9	10	11	12
13	14	15	16	17	18	19
20	21	22	23	24	25	26
27	28	29	30	31		

NOV

					1	2
3	4	5	6	7	8	9
10	11	12	13	14	15	16
17	18	19	20	21	22	23
24	25	26	27	28	29	30

DEC

1	2	3	4	5	6	7
8	9	10	11	12	13	14
15	16	17	18	19	20	21
22	23	24	25	26	27	28
29	30	31				

Note

This calendar view maps the number of times **https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761125s000lbl.pdf** was crawled by the Wayback Machine, *not* how many times the site was actually updated. More info in the FAQ.

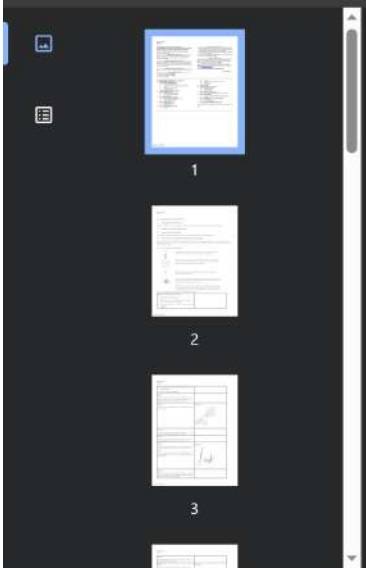
FAQ | Contact Us | Terms of Service (Dec 31, 2014)

The Wayback Machine is an initiative of the Internet Archive, a 501(c)(3) non-profit, building a digital library of Internet sites and other cultural artifacts in digital form. Other projects include Open Library & archive-it.org.

Your use of the Wayback Machine is subject to the Internet Archive's Terms of Use.

https://web.archive.org/web/20191117202243/https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761125s000lbl.pdf September 13, 2025

INTERNET ARCHIVE WayBackMachine https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761125s000lbl.pdf Go OCT NOV 17 2019 NOV 2020 About this capture
20 captures
17 Nov 2019 - 22 Aug 2025



HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use BEOVU safely and effectively. See full prescribing information for BEOVU.

BEOVU® (brolucizumab-dbll) injection, for intravitreal injection
Initial U.S. Approval: 2019

----------INDICATIONS AND USAGE----------
BEOVU is a human vascular endothelial growth factor (VEGF) inhibitor indicated for the treatment of Neovascular (Wet) Age-Related Macular Degeneration (AMD) (1).

----------DOSAGE AND ADMINISTRATION----------
BEOVU is administered by intravitreal injection. The recommended dose for BEOVU is 6 mg (0.05 mL of 120 mg/mL solution) monthly (approximately every 25-31 days) for the first three doses, followed by one dose of 6 mg (0.05 mL) every 8-12 weeks (2).

----------DOSAGE FORMS AND STRENGTHS----------
Injection: 6 mg/0.05 mL solution for intravitreal injection in a single-dose vial (3).

----------CONTRAINDICATIONS----------
- Ocular or periocular infections (4.1).
- Active intraocular inflammation (4.2).
- Hypersensitivity (4.3).

----------WARNINGS AND PRECAUTIONS----------
- Endophthalmitis and retinal detachments may occur following intravitreal injections. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay (5.1).
- Increases in intraocular pressure (IOP) have been seen within 30 minutes of an intravitreal injection (5.2).
- There is a potential risk of arterial thromboembolic events (ATE) following intravitreal use of VEGF inhibitors (5.3).

----------ADVERSE REACTIONS----------
The most common adverse reactions (≥ 5%) reported in patients receiving BEOVU are vision blurred (10%), cataract (7%), conjunctival hemorrhage (6%), eye pain (5%), and vitreous floaters (5%) (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 10/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 General Dosing Information
8.2 Lactation
8.3 Females and Males of Reproductive Potential
8.4 Pediatric Use
8.5 Geriatric Use

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use BEOVU safely and effectively. See full prescribing information for BEOVU.

BEOVU® (brolucizumab-dbll) injection, for intravitreal injection
Initial U.S. Approval: 2019

----------INDICATIONS AND USAGE----------
BEOVU is a human vascular endothelial growth factor (VEGF) inhibitor indicated for the treatment of Neovascular (Wet) Age-Related Macular Degeneration (AMD) (1).

----------DOSAGE AND ADMINISTRATION----------
BEOVU is administered by intravitreal injection. The recommended dose for BEOVU is 6 mg (0.05 mL of 120 mg/mL solution) monthly (approximately every 25-31 days) for the first three doses, followed by one dose of 6 mg (0.05 mL) every 8-12 weeks (2).

----------DOSAGE FORMS AND STRENGTHS----------
Injection: 6 mg/0.05 mL solution for intravitreal injection in a single-dose vial (3).

----------CONTRAINDICATIONS----------
- Ocular or periocular infections (4.1).
- Active intraocular inflammation (4.2).
- Hypersensitivity (4.3).

----------WARNINGS AND PRECAUTIONS----------
- Endophthalmitis and retinal detachments may occur following intravitreal injections. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay (5.1).
- Increases in intraocular pressure (IOP) have been seen within 30 minutes of an intravitreal injection (5.2).
- There is a potential risk of arterial thromboembolic events (ATE) following intravitreal use of VEGF inhibitors (5.3).

----------ADVERSE REACTIONS----------
The most common adverse reactions (≥ 5%) reported in patients receiving BEOVU are vision blurred (10%), cataract (7%), conjunctival hemorrhage (6%), eye pain (5%), and vitreous floaters (5%) (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 10/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 General Dosing Information
2.2 Neovascular (Wet) Age-Related Macular Degeneration (AMD)
2.3 Preparation for Administration
2.4 Injection Procedure
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
4.1 Ocular or Periocular Infections
4.2 Active Intraocular Inflammation
4.3 Hypersensitivity
5 WARNINGS AND PRECAUTIONS
5.1 Endophthalmitis and Retinal Detachments
5.2 Increase in Intraocular Pressure
5.3 Thromboembolic Events
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Immunogenicity
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation
8.3 Females and Males of Reproductive Potential
8.4 Pediatric Use
8.5 Geriatric Use
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
14.1 Neovascular (Wet) Age-Related Macular Degeneration (AMD)
16 HOW SUPPLIED/STORAGE AND HANDLING
16.1 How Supplied
16.2 Storage and Handling
17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

BEOVU® is indicated for the treatment of Neovascular (Wet) Age-related Macular Degeneration (AMD).

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

For ophthalmic intravitreal injection. BEOVU must be administered by a qualified physician.

2.2 Neovascular (Wet) Age-Related Macular Degeneration (AMD)

The recommended dose for BEOVU is 6 mg (0.05 mL of 120 mg/mL solution) administered by intravitreal injection monthly (approximately every 25-31 days) for the first three doses, followed by 6 mg (0.05 mL) by intravitreal injection once every 8-12 weeks.

2.3 Preparation for Administration



Store BEOVU in the refrigerator between 2 to 8°C (36 to 46°F); do not freeze. Keep the vial in the outer carton to protect from light.



Prior to use, the unopened glass vial of BEOVU may be kept at room temperature, 20 to 25°C (68 to 77°F) for up to 24 hours. After opening the glass vial, proceed under aseptic conditions.



BEOVU is a clear to slightly opalescent and colorless to slightly brownish-yellow solution.

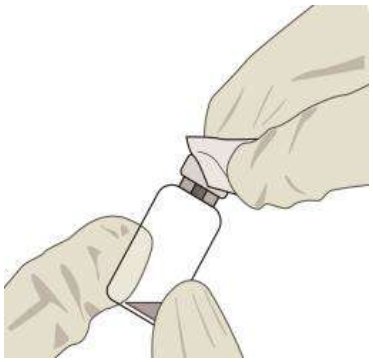
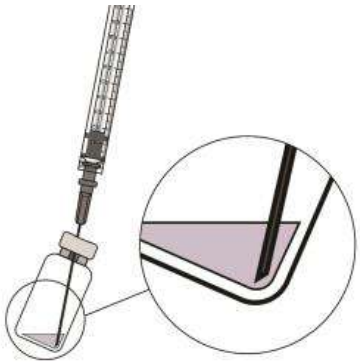


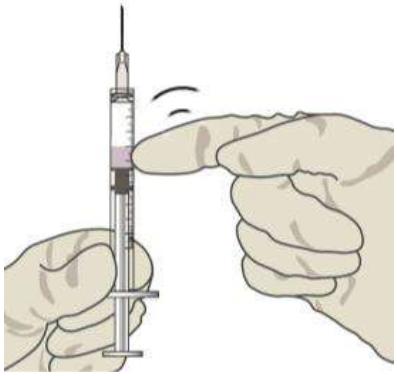
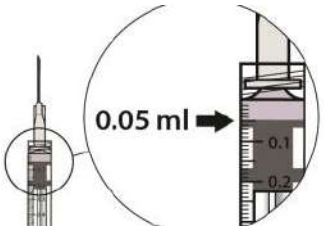
BEOVU should be inspected visually upon removal from the refrigerator and prior to administration. If particulates, cloudiness, or discoloration are visible, the glass vial must not be used.

The BEOVU kit includes the sterile glass vial and filter needle which are for single use only. Do not use if the packaging, vial and/or filter needle are damaged or expired *[see How Supplied/Storage and Handling (16)]*.

Use aseptic technique for preparation of the intravitreal injection.

STEP 1: Gather the supplies needed. • One BEOVU vial (included) • One sterile 5-micron blunt filter needle (18-gauge x 1½ inch, 1.2 mm x 40 mm) (included) • One sterile 30-gauge x ½ inch injection needle **(not included)**	

• One sterile 1 mL syringe with a 0.05 mL dose mark **(not included)** • Alcohol swab **(not included)**	
STEP 2 Allow vial to come to room temperature and inspect the solution. If particulates, cloudiness, or discoloration are visible, discard the vial and obtain a new vial.	
STEP 3 Remove the vial cap and clean the vial septum (e.g., with alcohol swab).	**Figure 1:** 
STEP 4 Assemble the 5-micron filter needle (18-gauge x 1½ inch) onto a 1-mL syringe using aseptic technique.	
STEP 5 Push the filter needle into the center of the vial septum until the needle touches the bottom of the vial.	
STEP 6 To withdraw the liquid, hold the vial slightly inclined and slowly withdraw all the liquid from the vial and filter needle. Ensure that the plunger rod is drawn sufficiently back when emptying the vial in order to completely empty the filter needle.	**Figure 2:** 
STEP 7 Disconnect the filter needle from the syringe in an aseptic manner and dispose of it. **The filter needle is not to be used for the intravitreal injection**.	

STEP 8 Aseptically and firmly assemble a 30-gauge x ½ inch injection needle onto the syringe.	
STEP 9 Check for air bubbles by holding the syringe with the needle pointing up. If there are any air bubbles, gently tap the syringe with your finger until the bubbles rise to the top.	**Figure 3:** 
STEP 10 Carefully expel the air from the syringe and adjust the dose to the 0.05 mL mark. The syringe is ready for the injection.	**Figure 4:** 

2.4 Injection Procedure

Ensure that the injection is given immediately after preparation of the dose.

The intravitreal injection procedure must be carried out under aseptic conditions, which includes the use of surgical hand disinfection, sterile gloves, a sterile drape and a sterile eyelid speculum (or equivalent), and the availability of sterile paracentesis equipment (if required). Adequate anesthesia and a broad-spectrum topical microbicide to disinfect the periocular skin, eyelid, and ocular surface should be administered prior to the injection.

Inject slowly until the rubber stopper reaches the end of the syringe to deliver the volume of 0.05 mL. Confirm delivery of the full dose by checking that the rubber stopper has reached the end of the syringe barrel.

Immediately following the intravitreal injection, patients should be monitored for elevation in intraocular pressure (IOP). Appropriate monitoring may consist of a check for perfusion of the optic nerve head or tonometry. If required, a sterile paracentesis needle should be available.

Following intravitreal injection, patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment (e.g., eye pain, redness of the eye, photophobia, blurring of vision) without delay *[see Patient Counseling Information (17)]*.

Each vial should only be used for the treatment of a single eye. If the contralateral eye requires treatment, a new vial should be used and the sterile field, syringe, gloves, drapes, eyelid speculum, filter, and injection needles should be changed before BEOVU is administered to the other eye.

Any unused medicinal product or waste material should be disposed of in accordance with local regulations.

3 DOSAGE FORMS AND STRENGTHS

Intravitreal Injection: 6 mg/0.05 mL, clear to slightly opalescent and colorless to slightly brownish-yellow solution in a single-dose vial.

4 CONTRAINDICATIONS

4.1 Ocular or Periocular Infections

BEOVU is contraindicated in patients with ocular or periocular infections.

4.2 Active Intraocular Inflammation

BEOVU is contraindicated in patients with active intraocular inflammation.

4.3 Hypersensitivity

BEOVU is contraindicated in patients with known hypersensitivity to brolucizumab or any of the excipients in BEOVU. Hypersensitivity reactions may manifest as rash, pruritus, urticaria, erythema, or severe intraocular inflammation.

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis and Retinal Detachments

Intravitreal injections, including those with BEOVU, have been associated with endophthalmitis and retinal detachments *[see Adverse Reactions (6.1)]*. Proper aseptic injection techniques must always be used when administering BEOVU. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately *[see Dosage and Administration (2.4) and Patient Counseling Information (17)]*.

5.2 Increase in Intraocular Pressure

Acute increases in intraocular pressure (IOP) have been seen within 30 minutes of intravitreal injection including with BEOVU *[see Adverse Reactions (6.1)]*. Sustained IOP increases have also been reported. Both IOP and perfusion of the optic nerve head must be monitored and managed appropriately *[see Dosage and Administration (2.4)]*.

5.3 Thromboembolic Events

Although there was a low rate of arterial thromboembolic events (ATEs) observed in the BEOVU clinical trials, there is a potential risk of ATEs following intravitreal use of VEGF inhibitors. Arterial thromboembolic events are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause).

The ATE rate in the two controlled 96-week neovascular AMD studies (HAWK and HARRIER) during the first 96-weeks was 4.5% (33 of 730) in the pooled brolucizumab arms compared with 4.7% (34 of 729) in the pooled aflibercept arms *[see Clinical Studies (14.1)]*.

6 ADVERSE REACTIONS

The following potentially serious adverse reactions are described elsewhere in the labeling:

- Hypersensitivity *[see Contraindications (4.3)]*
- Endophthalmitis and Retinal Detachments *[see Warnings and Precautions (5.1)]*
- Increase in intraocular pressure *[see Warnings and Precautions (5.2)]*
- Thromboembolic Events *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in one clinical trial of a drug cannot be directly compared with rates in the clinical trials of the same or another drug and may not reflect the rates observed in practice.

PGR2026-00039
Biocon Ex.1065
Page 146 of 595

A total of 1088 patients, treated with brolucizumab, constituted the safety population in the two controlled neovascular AMD Phase 3 studies (HAWK and HARRIER) with a cumulative 96 week exposure to BEOVU, and 730 patients treated with the recommended dose of 6 mg *[see Clinical Studies (14.1)]*

Adverse reactions reported to occur in ≥ 1% of patients who received treatment with BEOVU pooled across HAWK and HARRIER, are listed below in Table 1.

Table 1: Common Adverse Reactions (≥ 1%) in the HAWK and HARRIER wet AMD Clinical Trials

Adverse Drug Reactions	**BEOVU (N = 730)**	**Active Control (aflibercept) (N = 729)**
Vision blurred[a]	10%	11%
Cataract	7%	11%
Conjunctival hemorrhage	6%	7%
Vitreous floaters	5%	3%
Eye pain	5%	6%
Intraocular inflammation[b]	4%	1%
Intraocular pressure increased	4%	5%
Retinal hemorrhage	4%	3%
Vitreous detachment	4%	3%
Conjunctivitis	3%	2%
Retinal pigment epithelial tear	3%	1%
Corneal abrasion	2%	2%
Hypersensitivity[c]	2%	1%
Punctate keratitis	1%	2%
Retinal tear	1%	1%
Endophthalmitis	1%	< 1%
Blindness[d]	1%	< 1%
Retinal artery occlusion	1%	< 1%
Retinal detachment	1%	< 1%
Conjunctival hyperemia	1%	1%
Lacrimation increased	1%	1%
Abnormal sensation in eye	1%	2%
Detachment of retinal pigment epithelium	1%	< 1%

[a]Including vision blurred, visual acuity reduced, visual acuity reduced transiently and visual impairment.
[b]Including anterior chamber cell, anterior chamber flare, anterior chamber inflammation, chorioretinitis, eye inflammation, iridocyclitis, iritis, uveitis, vitreous haze, vitritis.
[c]Including urticaria, rash, pruritus, erythema.
[d]Including blindness, blindness transient, amaurosis, and amaurosis fugax.

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for an immune response in patients treated with BEOVU. The immunogenicity of BEOVU was evaluated in serum samples. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to BEOVU in immunoassays. The detection of an immune response is highly dependent on the sensitivity and specificity of the assays used, sample handling, timing of sample

collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to BEOVU with the incidence of antibodies to other products may be misleading.

Anti-brolucizumab antibodies were detected in the pre-treatment sample of 36% to 52% of treatment naive patients. After initiation of dosing, anti-brolucizumab antibodies were detected in at least one serum sample in 53% to 67% of patients treated with BEOVU. Intraocular inflammation was observed in 6% of patients with anti-brolucizumab antibodies detected during dosing with BEOVU.

The significance of anti-brolucizumab antibodies on the clinical effectiveness and safety of BEOVU is not known.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies of BEOVU administration in pregnant women.

Based on the anti-VEGF mechanism of action for brolucizumab *[see Clinical Pharmacology (12.1)]*, treatment with BEOVU may pose a risk to human embryo-fetal development. BEOVU should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

All pregnancies have a background risk of birth defect, loss, and other adverse outcomes. The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects is 2%-4% and of miscarriage is 15%-20% of clinically recognized pregnancies.

Data

Animal Data

VEGF inhibition has been shown to cause malformations, embryo-fetal resorption, and decreased fetal weight. VEGF inhibition has also been shown to affect follicular development, corpus luteum function, and fertility.

8.2 Lactation

Risk Summary

There is no information regarding the presence of brolucizumab in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production/excretion. Because many drugs are transferred in human milk and because of the potential for absorption and adverse reactions in the breastfed child, breastfeeding is not recommended during treatment and for at least one month after the last dose when stopping treatment with BEOVU.

8.3 Females and Males of Reproductive Potential

Contraception

Females

Females of reproductive potential should use highly effective contraception (methods that result in less than 1% pregnancy rates) during treatment with BEOVU and for at least one month after the last dose when stopping treatment with BEOVU.

Infertility

No studies on the effects of brolucizumab on fertility have been conducted and it is not known whether brolucizumab can affect reproductive capacity. Based on its anti-VEGF mechanism of action, treatment with BEOVU may pose a risk to reproductive capacity.

8.4 Pediatric Use

The safety and efficacy of BEOVU in pediatric patients has not been established.

PGR2026-00039
Biocon Ex.1065
Page 148 of 595

8.5 Geriatric Use

In the two Phase 3 clinical studies, approximately 90% (978/1089) of patients randomized to treatment with BEOVU were ≥ 65 years of age and approximately 60% (648/1089) were ≥ 75 years of age. No significant differences in efficacy or safety were seen with increasing age in these studies. No dosage regimen adjustment is required in patients 65 years and above.

11 DESCRIPTION

Brolucizumab-dbll is a recombinant human vascular endothelial growth factor inhibitor. Brolucizumab-dbll is a humanized monoclonal single-chain Fv (scFv) antibody fragment. Brolucizumab-dbll has a molecular weight of ~26 kilodaltons and is produced in *Escherichia coli* cells by recombinant DNA technology.

BEOVU (brolucizumab-dbll) injection is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly brownish-yellow solution in a single-dose vial for intravitreal administration. Each vial is designed to deliver 0.05 mL of solution containing 6 mg brolucizumab-dbll, polysorbate 80 (0.02%), sodium citrate (10 mM), sucrose (5.8%), and Water for Injection, USP and with a pH of approximately 7.2.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Brolucizumab is a human VEGF inhibitor. Brolucizumab binds to the three major isoforms of VEGF-A (e.g., $VEGF_{110}$, $VEGF_{121}$, and $VEGF_{165}$), thereby preventing interaction with receptors VEGFR-1 and VEGFR-2. By inhibiting VEGF-A, brolucizumab suppresses endothelial cell proliferation, neovascularization, and vascular permeability.

12.2 Pharmacodynamics

Leakage of blood and fluid from choroidal neovascularization (CNV) may cause retinal thickening or edema. Reductions in central retinal subfield thickness (CST) were observed across all treatment arms.

12.3 Pharmacokinetics

Following a single intravitreal dose of 6 mg BEOVU to 25 AMD patients, the mean (range) serum C_{max} of free brolucizumab (unbound to VEGF-A) was 49 ng/mL (9 to 548 ng/mL) and was attained at 24 hours post-dose. Brolucizumab concentrations were near or less than 0.5 ng/mL (lower limit of assay quantitation) at approximately 4 weeks after repeat dose administration and no accumulation in serum was observed in most patients.

Elimination

The estimated mean (± standard deviation) systemic half-life of brolucizumab is 4.4 days (± 2.0 days) after a single intravitreal dose.

Metabolism

Metabolism of brolucizumab has not been fully characterized. However, free brolucizumab is expected to undergo metabolism via proteolysis.

Excretion

The excretion of brolucizumab has not been fully characterized. However, free brolucizumab is expected to undergo target-mediated disposition and/or passive renal excretion.

Specific Populations

Following repeat intravitreal dose administration of 6 mg BEOVU, no differences in the systemic pharmacokinetics of brolucizumab were observed based on age (50 years and above), sex, or mild to moderate renal impairment (glomerular filtration rate (GFR) = 30 to 70 mL/min, estimated using the Modification of Diet in Renal Disease (MDRD) equation). The effect of severe renal impairment or any degree of hepatic impairment on the pharmacokinetics of BEOVU is unknown. As significant increases in serum brolucizumab exposures are not expected with intravitreal route of administration, no dosage adjustment is needed based on renal or hepatic impairment status.

Drug Interaction Studies

No studies evaluating the drug interaction potential of BEOVU have been conducted.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been conducted on the carcinogenic or mutagenic potential of BEOVU. Based on the anti-VEGF mechanism of action, treatment with BEOVU may pose a risk to reproductive capacity *[see Use in Specific Populations (8.3)]*.

14 CLINICAL STUDIES

14.1 Neovascular (Wet) Age-Related Macular Degeneration (AMD)

The safety and efficacy of BEOVU were assessed in two randomized, multi-center, double-masked, active-controlled studies (HAWK - NCT02307682 and HARRIER - NCT02434328) in patients with neovascular AMD. A total of 1817 patients were treated in these studies for two years (1088 on brolucizumab and 729 on control). Patient ages ranged from 50 to 97 years with a mean of 76 years.

In HAWK, patients were randomized in a 1:1:1 ratio to the following dosing regimens:

1) brolucizumab 3 mg administered every 8 or 12 weeks after the first 3 monthly doses,
2) brolucizumab 6 mg administered every 8 or 12 weeks after the first 3 monthly doses,
3) aflibercept 2 mg administered every 8 weeks after the first 3 monthly doses.

In HARRIER, patients were randomized in a 1:1 ratio to the following dosing regimens:

1) brolucizumab 6 mg administered every 8 or 12 weeks after the first 3 monthly doses,
2) aflibercept 2 mg administered every 8 weeks after the first 3 monthly doses.

In both studies, after three initial monthly doses (Week 0, 4, and 8), treating physicians decided whether to treat each individual patient on an every 8 week or 12 week dosing interval guided by visual and anatomical measures of disease activity, although the utility of these measures has not been established. Patients on 12 week dosing intervals could be changed based on the same measures to an 8 week schedule after subsequent treatment visits. Any patient placed on an 8 week schedule, remained on the 8 week dosing interval until the end of the study. Protocol-specified visits in the initial three months occurred every 28 ± 3 days followed by every 28 ± 7 days for the remainder of the studies. Baseline anatomical measures may have contributed to the regimen selection because the majority of patients on the 12-week dosing schedule at the end of the trial had less baseline macular edema and/or smaller baseline lesions.

Both studies demonstrated efficacy in the primary endpoint defined as the change from baseline in Best Corrected Visual Acuity (BCVA) at Week 48, measured by the Early Treatment Diabetic Retinopathy Study (ETDRS) Letter Score. In both studies, BEOVU treated patients had a similar mean change from baseline in BCVA as the patients treated with aflibercept 2 mg (fixed every 8 weeks). Detailed results of both studies are shown in the Table 2 and Figures 5 and 6 below.

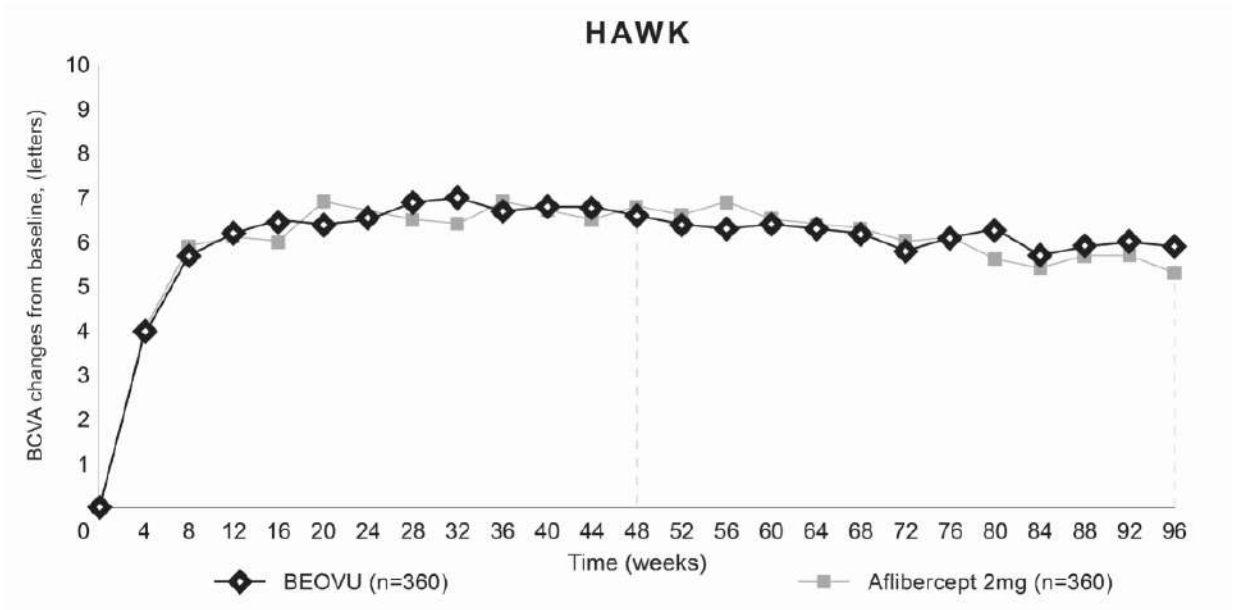
PGR2026-00039
Biocon Ex.1065
Page 150 of 595

Table 2: Efficacy Outcomes at Week 48 and 96 in Phase 3 HAWK and HARRIER Studies

		HAWK			HARRIER		
Efficacy outcome	**At week**	**BEOVU (n = 360)**	**Aflibercept 2 mg (n = 360)**	**Difference (95% CI) brolucizumab – aflibercept**	**BEOVU (n = 370)**	**Aflibercept 2 mg (n = 369)**	**Difference (95% CI) brolucizumab – aflibercept**
Mean (SD) BCVA at Baseline		60.8 (13.7)	60.0 (13.9)		61.5 (12.6)	60.8 (12.9)	
Mean (SE) change from baseline in BCVA (measured by ETDRS letters score)	48	6.6 (0.71)	6.8 (0.71)	-0.2 (-2.1, 1.8)	6.9 (0.61)	7.6 (0.61)	-0.7 (-2.4, 1.0)
	96	5.9 (0.78)	5.3 (0.78)	+0.5 (-1.6, 2.7)	6.1 (0.73)	6.6 (0.73)	-0.4 (-2.5, 1.6)
Proportion of patients who gained visual acuity (%) (≥ 15 letters of BCVA)	48	33.6	25.4	8.2 (2.2, 15.0)	29.3	29.9	-0.6 (-7.1, 5.8)
	96	34.2	27	7.2 (1.4, 13.8)	29.1	31.5	-2.4 (-8.8, 4.1)
Proportion of patients who lost visual acuity (%) (≥ 15 letters of BCVA)	48	6.4	5.5	0.9 (-2.7, 4.3)	3.8	4.8	-1.0 (-3.9, 2.2)
	96	8.1	7.4	0.7 (-3.6, 4.6)	7.1	7.5	-0.4 (-3.8, 3.3)

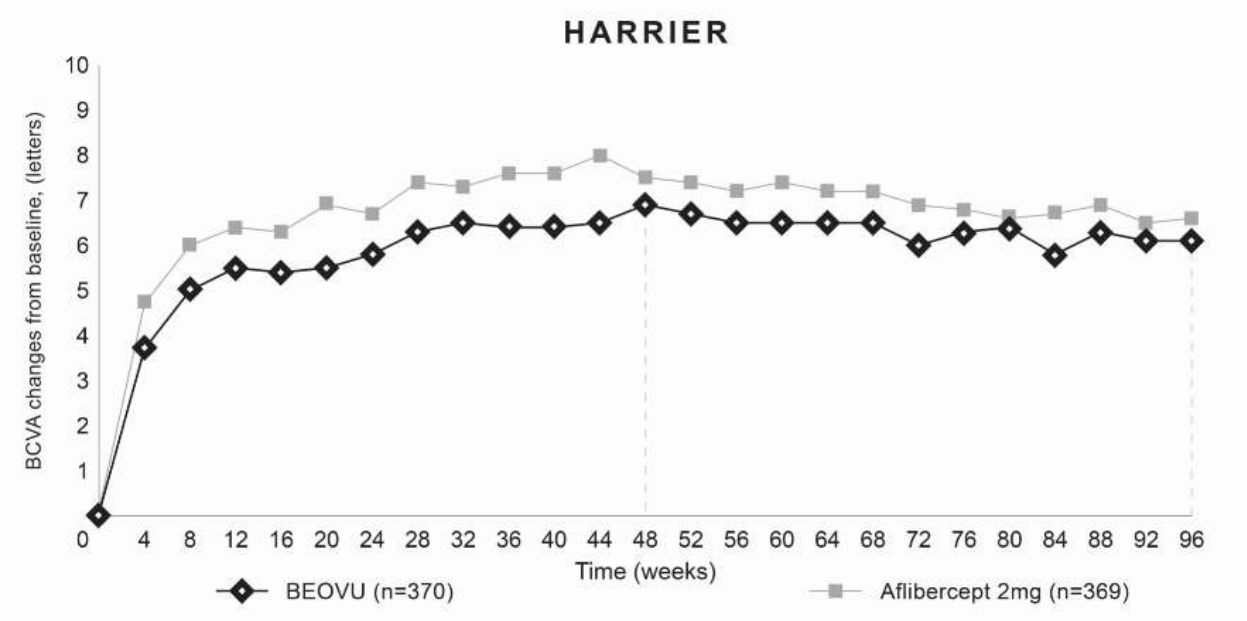
Abbreviations - BCVA: Best Corrected Visual Acuity; missing data are imputed using last observation carried forward (LOCF) method, ETDRS: Early Treatment Diabetic Retinopathy Study, SE: standard error.

Figure 5: Mean Change in Visual Acuity From Baseline to Week 96 in HAWK



PGR2026-00039
Biocon Ex.1065
Page 151 of 595

Figure 6: Mean Change in Visual Acuity From Baseline to Week 96 in HARRIER



Through Week 48, 56% (HAWK) and 51% (HARRIER) of patients remained on BEOVU every 12 weeks. The proportion of patients who were maintained on every 12 week dosing through Week 96 was 45% and 39% in HAWK and HARRIER, respectively. The probability of remaining on every 12 week dosing from Week 20 to Week 48 was 85% and 82%, and from Week 48 to Week 96 was 82% and 75% in HAWK and HARRIER, respectively.

Treatment effects in evaluable subgroups (e.g., age, gender, race, baseline visual acuity) in each study were generally consistent with the results in the overall populations.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

BEOVU (brolucizumab-dbll) injection is supplied as a clear to slightly opalescent and colorless to slightly brownish-yellow 6 mg/0.05 mL solution in a single-dose vial. Each BEOVU carton (NDC 0078-0827-61) contains one BEOVU vial and one sterile 5 µm blunt filter needle (18-gauge x 1½ inch, 1.2 mm x 40 mm).

16.2 Storage and Handling

Refrigerate BEOVU between 2 to 8°C (36 to 46°F). Do not freeze. Store the vial in the outer carton to protect from light.

Prior to use, the unopened glass vial of BEOVU may be kept at room temperature, 20 to 25°C (68 to 77°F) for up to 24 hours.

17 PATIENT COUNSELING INFORMATION

Endophthalmitis and Retinal Detachments

Advise patients that in the days following BEOVU administration, patients are at risk of developing endophthalmitis. If the eye becomes red, sensitive to light, painful, or develops a change in vision, advise the patient to seek immediate care from an ophthalmologist *[see Warnings and Precautions (5.1)]*.

Patients may experience temporary visual disturbances after an intravitreal injection with BEOVU and the associated eye examination *[see Adverse Reactions (6.1)]*. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

Manufactured by:

PGR2026-00039
Biocon Ex.1065
Page 152 of 595

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936
U.S. License Number: 1244

© Novartis

T20XX-XX

PGR2026-00039
Biocon Ex.1065
Page 153 of 595

APPENDIX FDA04

https://web.archive.org/web/20140701000000*/http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/125387lbl.pdf September 17, 2025

INTERNET ARCHIVE WEB TEXTS VIDEO AUDIO SOFTWARE IMAGES SIGN UP | LOG IN UPLOAD Search

ABOUT BLOG PROJECTS HELP DONATE CONTACT JOBS VOLUNTEER PEOPLE

DONATE INTERNET ARCHIVE WayBackMachine Explore more than 946 billion web pages saved over time

http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/1253

Calendar · Collections · Changes · Summary · Site Map · URLs

Saved **18 times** between April 30, 2014 and August 23, 2025.

002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 **2014** 2015 2016 2017 2018 2019 2020 2021 2022 2023 2024 2025

JAN

		1	2	3	4	
5	6	7	8	9	10	11
12	13	14	15	16	17	18
19	20	21	22	23	24	25
26	27	28	29	30	31	

FEB

						1
2	3	4	5	6	7	8
9	10	11	12	13	14	15
16	17	18	19	20	21	22
23	24	25	26	27	28	

MAR

						1
2	3	4	5	6	7	8
9	10	11	12	13	14	15
16	17	18	19	20	21	22
23	24	25	26	27	28	29
30	31					

APR

		1	2	3	4	5
6	7	8	9	10	11	12
13	14	15	16	17	18	19
20	21	22	23	24	25	26
27	28	29	30			

MAY

				1	2	3
4	5	6	7	8	9	10
11	12	13	14	15	16	17
18	19	20	21	22	23	24
25	26	27	28	29	30	31

JUN

1	2	3	4	5	6	7
8	9	10	11	12	13	14
15	16	17	18	19	20	21
22	23	24	25	26	27	28
29	30					

JUL

		1	2	3	4	5
6	7	8	9	10	11	12
13	14	15	16	17	18	19
20	21	22	23	24	25	26
27	28	29	30	31		

AUG

					1	2
3	4	5	6	7	8	9
10	11	12	13	14	15	16
17	18	19	20	21	22	23
24	25	26	27	28	29	30
31						

SEP

	1	2	3	4	5	6
7	8	9	10	11	12	13
14	15	16	17	18	19	20
21	22	23	24	25	26	27
28	29	30				

OCT

			1	2	3	4
5	6	7	8	9	10	11
12	13	14	15	16	17	18
19	20	21	22	23	24	25
26	27	28	29	30	31	

NOV

						1
2	3	4	5	6	7	8
9	10	11	12	13	14	15
16	17	18	19	20	21	22
23	24	25	26	27	28	29
30						

DEC

	1	2	3	4	5	6
7	8	9	10	11	12	13
14	15	16	17	18	19	20
21	22	23	24	25	26	27
28	29	30	31			

Note

This calendar view maps the number of times **http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/125387lbl.pdf** was crawled by the Wayback Machine, *not* how many times the site was actually updated. More info in the FAQ.

FAQ | Contact Us | Terms of Service (Dec 31, 2014)

The Wayback Machine is an initiative of the Internet Archive, a 501(c)(3) non-profit, building a digital library of Internet sites and other cultural artifacts in digital form. Other projects include Open Library & archive-it.org.

Your use of the Wayback Machine is subject to the Internet Archive's Terms of Use.

https://web.archive.org/web/20140430031100/http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/125387lbl.pdf September 17, 2025

INTERNET ARCHIVE Wayback Machine http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/125387lbl.pdf Go MAR APR 30 MAY 2013 2014 2016 About this capture

18 captures 30 Apr 2014 - 23 Aug 2025



1



2



HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use EYLEA safely and effectively. See full prescribing information for EYLEA.

EYLEA™ (aflibercept) Injection
For Intravitreal Injection
Initial U.S. Approval: 2011

INDICATIONS AND USAGE

EYLEA is indicated for the treatment of patients with Neovascular (Wet) Age-Related Macular Degeneration (AMD). (1)

DOSAGE AND ADMINISTRATION

- For ophthalmic intravitreal injection only. (2.1)
- The recommended dose for EYLEA is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (monthly) for the first 3 months, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). (2.2)
- Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated when EYLEA was dosed every 4 weeks compared to every 8 weeks. (2.2)

DOSAGE FORMS AND STRENGTHS

40 mg/mL solution for intravitreal injection in a single-use vial (3)

CONTRAINDICATIONS

- Ocular or periocular infection (4.1)
- Active intraocular inflammation (4.2)
- Hypersensitivity (4.3)

WARNINGS AND PRECAUTIONS

- Endophthalmitis and retinal detachments may occur following intravitreal injections. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately. (5.1)
- Increases in intraocular pressure have been seen within 60 minutes of an intravitreal injection. (5.2)

ADVERSE REACTIONS

The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and increased intraocular pressure. (6.2)

To report SUSPECTED ADVERSE REACTIONS, contact Regeneron at 1-855-395-3248 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 11/2011

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 General Dosing Information
2.2 Dosing
2.3 Preparation for Administration
6.3 Immunogenicity
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
11 DESCRIPTION

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use EYLEA safely and effectively. See full prescribing information for EYLEA.

EYLEA™ (aflibercept) Injection
For Intravitreal Injection
Initial U.S. Approval: 2011

INDICATIONS AND USAGE

EYLEA is indicated for the treatment of patients with Neovascular (Wet) Age-Related Macular Degeneration (AMD). (1)

DOSAGE AND ADMINISTRATION

- For ophthalmic intravitreal injection only. (2.1)

- The recommended dose for EYLEA is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (monthly) for the first 3 months, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). (2.2)
- Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated when EYLEA was dosed every 4 weeks compared to every 8 weeks. (2.2)

DOSAGE FORMS AND STRENGTHS

40 mg/mL solution for intravitreal injection in a single-use vial (3)

CONTRAINDICATIONS

- Ocular or periocular infection (4.1)
- Active intraocular inflammation (4.2)
- Hypersensitivity (4.3)

WARNINGS AND PRECAUTIONS

- Endophthalmitis and retinal detachments may occur following intravitreal injections. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately. (5.1)
- Increases in intraocular pressure have been seen within 60 minutes of an intravitreal injection. (5.2)

ADVERSE REACTIONS

The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and increased intraocular pressure. (6.2)

To report SUSPECTED ADVERSE REACTIONS, contact Regeneron at 1-855-395-3248 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 11/2011

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 General Dosing Information
2.2 Dosing
2.3 Preparation for Administration
2.4 Administration
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
4.1 Ocular or Periocular Infections
4.2 Active Intraocular Inflammation
4.3 Hypersensitivity
5 WARNINGS AND PRECAUTIONS
5.1 Endophthalmitis and Retinal Detachments
5.2 Increase in Intraocular Pressure
5.3 Thromboembolic Events
6 ADVERSE REACTIONS
6.1 Injection Procedure
6.2 Clinical Studies Experience
6.3 Immunogenicity
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

***Sections or subsections omitted from the full prescribing information are not listed.**

PGR2026-00039
Biocon Ex.1065
Page 157 of 595

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

EYLEA is indicated for the treatment of patients with Neovascular (Wet) Age-Related Macular Degeneration (AMD).

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

FOR OPHTHALMIC INTRAVITREAL INJECTION ONLY. EYLEA must only be administered by a qualified physician.

2.2 Dosing

The recommended dose for EYLEA is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (monthly) for the first 12 weeks (3 months), followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated when EYLEA was dosed every 4 weeks compared to every 8 weeks [*see Clinical Studies (14)*].

2.3 Preparation for Administration

EYLEA should be inspected visually prior to administration. If particulates, cloudiness, or discoloration are visible, the vial must not be used.

Using aseptic technique, the intravitreal injection should be performed with a 30-gauge x ½-inch injection needle.

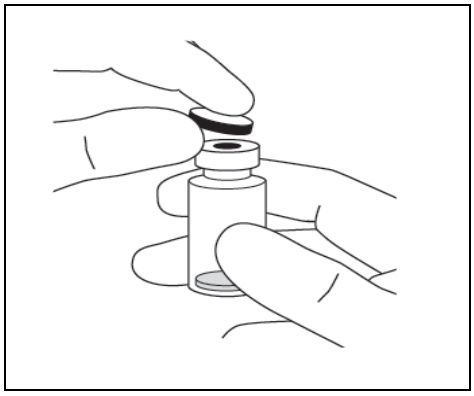
Vial

The glass vial is for single use only.

1. Remove the protective plastic cap from the vial (see Figure 1).

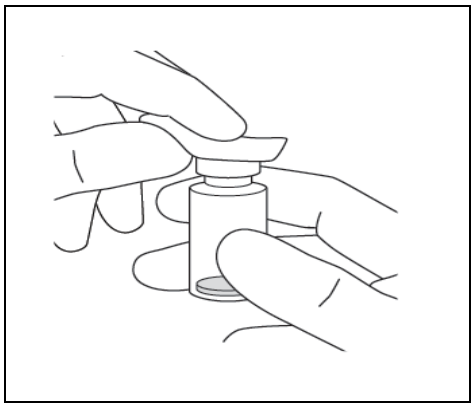
PGR2026-00039
Biocon Ex.1065
Page 158 of 595

Figure 1:



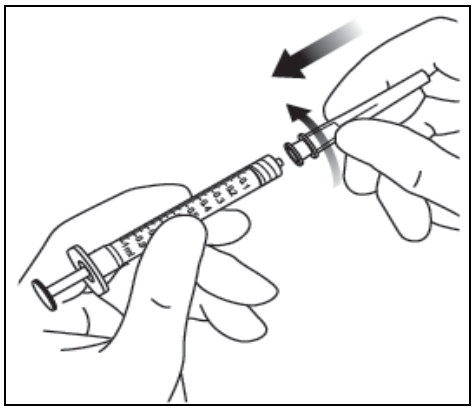
2. Clean the top of the vial with an alcohol wipe (see Figure 2).

Figure 2:



3. Remove the 19-gauge x 1½-inch, 5-micron, filter needle from its pouch and remove the 1-mL syringe supplied in the carton from its pouch. Attach the filter needle to the syringe by twisting it onto the Luer lock syringe tip (see Figure 3).

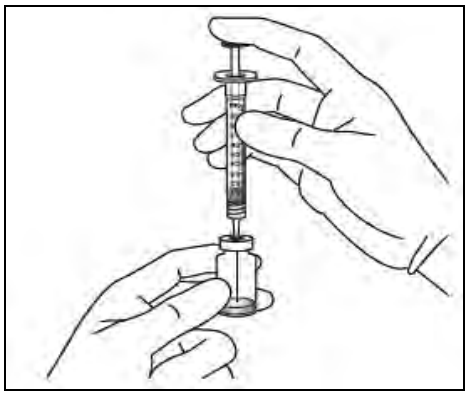
Figure 3:



PGR2026-00039
Biocon Ex.1065
Page 159 of 595

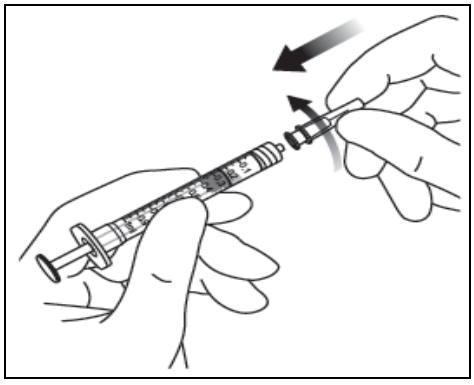
4. Push the filter needle into the center of the vial stopper until the needle touches the bottom edge of the vial.
5. Using aseptic technique withdraw all of the EYLEA vial contents into the syringe, keeping the vial in an upright position, slightly inclined to ease complete withdrawal (see Figure 4).

Figure 4:



6. Ensure that the plunger rod is drawn sufficiently back when emptying the vial in order to completely empty the filter needle.
7. Remove the filter needle from the syringe and properly dispose of the filter needle.
   Note: Filter needle is **not** to be used for intravitreal injection.
8. Remove the 30-gauge x ½-inch injection needle from the plastic pouch and attach the injection needle to the syringe by firmly twisting the injection needle onto the Luer lock syringe tip (see Figure 5).

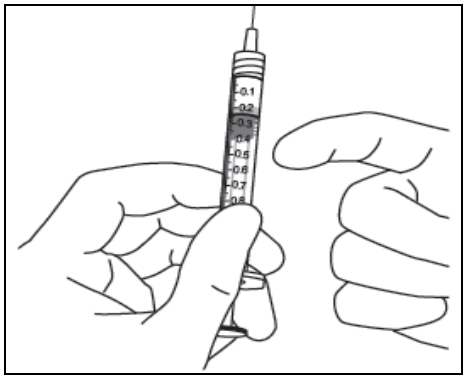
Figure 5:



9. When ready to administer EYLEA, remove the plastic needle shield from the needle.
10. Holding the syringe with the needle pointing up, check the syringe for bubbles. If there are bubbles, gently tap the syringe with your finger until the bubbles rise to the top (see Figure 6).

PGR2026-00039
Biocon Ex.1065
Page 160 of 595

Figure 6:



11. To eliminate all of the bubbles and to expel excess drug, SLOWLY depress the plunger so that the plunger tip aligns with the line that marks 0.05 mL on the syringe (see Figures 7 and 8).

Figure 7:

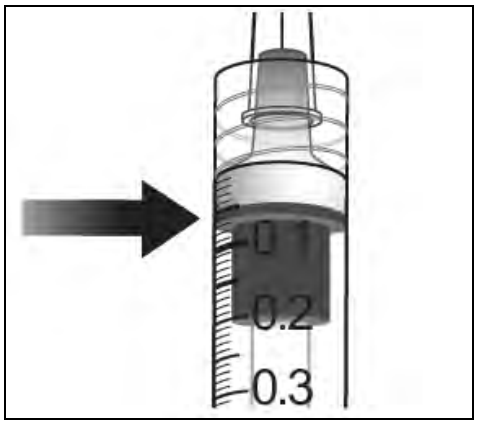
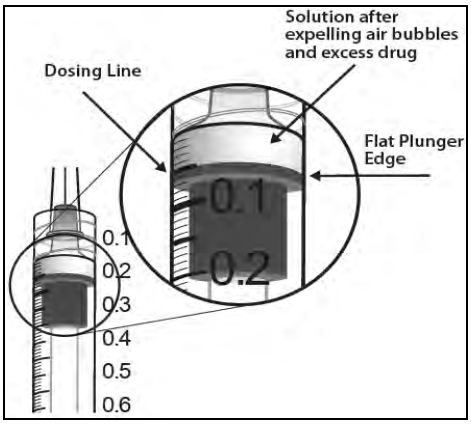


Figure 8:



2.4 Administration

The intravitreal injection procedure should be carried out under controlled aseptic conditions, which include surgical hand disinfection and the use of sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent). Adequate anesthesia and a topical broad–spectrum microbicide should be given prior to the injection.

Immediately following the intravitreal injection, patients should be monitored for elevation in intraocular pressure. Appropriate monitoring may consist of a check for perfusion of the optic nerve head or tonometry. If required, a sterile paracentesis needle should be available.

Following intravitreal injection, patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment (e.g., eye pain, redness of the eye, photophobia, blurring of vision) without delay [*see Patient Counseling Information (17)*].

Each vial should only be used for the treatment of a single eye. If the contralateral eye requires treatment, a new vial should be used and the sterile field, syringe, gloves, drapes, eyelid

PGR2026-00039
Biocon Ex.1065
Page 161 of 595

speculum, filter, and injection needles should be changed before EYLEA is administered to the other eye.

After injection, any unused product must be discarded.

No special dosage modification is required for any of the populations that have been studied (e.g., gender, elderly).

3 DOSAGE FORMS AND STRENGTHS

Single-use, glass vial designed to provide 0.05 mL of 40 mg/mL solution for intravitreal injection.

4 CONTRAINDICATIONS

4.1 Ocular or Periocular Infections

EYLEA is contraindicated in patients with ocular or periocular infections.

4.2 Active Intraocular Inflammation

EYLEA is contraindicated in patients with active intraocular inflammation.

4.3 Hypersensitivity

EYLEA is contraindicated in patients with known hypersensitivity to aflibercept or any of the excipients in EYLEA.

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis and Retinal Detachments

Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments [*see Adverse Reactions (6.1)*]. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately [*see Dosage and Administration (2.4) and Patient Counseling Information (17)*].

5.2 Increase in Intraocular Pressure

Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA [*see Adverse Reactions (6.1)*]. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with VEGF inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately [*see Dosage and Administration (2.4)*].

PGR2026-00039
Biocon Ex.1065
Page 162 of 595

5.3 Thromboembolic Events

There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence in the VIEW1 and VIEW2 wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA [*see Clinical Studies (14)*].

6 ADVERSE REACTIONS

The following adverse reactions are discussed in detail in other sections of the labeling:

- Endophthalmitis and retinal detachments [*see Warnings and Precautions (5.1)*]
- Increased intraocular pressure [*see Warnings and Precautions (5.2)*]
- Thromboembolic events [*see Warnings and Precautions (5.3)*]

The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and increased intraocular pressure.

6.1 Injection Procedure

Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis, traumatic cataract, and increased intraocular pressure.

6.2 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described below reflect exposure to EYLEA in 1824 patients with wet AMD, including 1223 patients treated with the 2-mg dose, in 2 double-masked, active-controlled clinical studies (VIEW1 and VIEW2) for 12 months [*see Clinical Studies (14)*].

Table 1: Most Common Adverse Reactions (≥1%) in Phase 3 wet AMD studies

Adverse Reactions	**EYLEA (N=1824)**	**Active Control (ranibizumab) (N=595)**
Conjunctival hemorrhage	25%	28%
Eye pain	9%	9%
Cataract	7%	7%
Vitreous detachment	6%	6%
Vitreous floaters	6%	7%

PGR2026-00039
Biocon Ex.1065
Page 163 of 595

Adverse Reactions	EYLEA (N=1824)	Active Control (ranibizumab) (N=595)
Intraocular pressure increased	5%	7%
Conjunctival hyperemia	4%	8%
Corneal erosion	4%	5%
Detachment of the retinal pigment epithelium	3%	3%
Injection site pain	3%	3%
Foreign body sensation in eyes	3%	4%
Lacrimation increased	3%	1%
Vision blurred	2%	2%
Retinal pigment epithelium tear	2%	1%
Injection site hemorrhage	1%	2%
Eyelid edema	1%	2%
Corneal edema	1%	1%

Less common serious adverse reactions reported in <1% of the patients treated with EYLEA were retinal detachment, retinal tear, and endophthalmitis. Hypersensitivity has also been reported in less than 1% of the patients treated with EYLEA.

6.3 Immunogenicity

As with all therapeutic proteins, there is a potential for an immune response in patients treated with EYLEA. The immunogenicity of EYLEA was evaluated in serum samples. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to EYLEA in immunoassays. The detection of an immune response is highly dependent on the sensitivity and specificity of the assays used, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to EYLEA with the incidence of antibodies to other products may be misleading.

In the phase 3 studies, the pre-treatment incidence of immunoreactivity to EYLEA was 1% to 3% across treatment groups. After dosing with EYLEA for 52 weeks, antibodies to EYLEA were detected in a similar percentage range of patients. There were no differences in efficacy or safety between patients with or without immunoreactivity.

PGR2026-00039
Biocon Ex.1065
Page 164 of 595

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. Aflibercept produced embryo-fetal toxicity when administered during organogenesis in pregnant rabbits at intravenous doses of 3 to 60 mg/kg. A series of external, visceral, and skeletal malformations were observed in the fetuses. The maternal No Observed Adverse Effect Level (NOAEL) was 3 mg/kg, whereas the fetal NOAEL was below 3 mg/kg. At this dose, the systemic exposures based on C_{max} and AUC for free aflibercept were approximately 2900 times and 600 times higher, respectively, when compared to corresponding values observed in humans after an intravitreal dose of 2 mg.

There are no adequate and well-controlled studies in pregnant women. EYLEA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.3 Nursing Mothers

It is unknown whether aflibercept is excreted in human milk. Because many drugs are excreted in human milk, a risk to the breastfed child cannot be excluded. EYLEA is not recommended during breastfeeding. A decision must be made whether to discontinue nursing or to discontinue treatment with EYLEA, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and effectiveness of EYLEA in pediatric patients have not been established.

8.5 Geriatric Use

In the clinical studies, approximately 89% (1616/1817) of patients randomized to treatment with EYLEA were ≥65 years of age and approximately 63% (1139/1817) were ≥75 years of age. No significant differences in efficacy or safety were seen with increasing age in these studies.

11 DESCRIPTION

EYLEA (aflibercept) is a recombinant fusion protein consisting of portions of human VEGF receptors 1 and 2 extracellular domains fused to the Fc portion of human IgG1 formulated as an iso-osmotic solution for intravitreal administration. Aflibercept is a dimeric glycoprotein with a protein molecular weight of 97 kilodaltons (kDa) and contains glycosylation, constituting an additional 15% of the total molecular mass, resulting in a total molecular weight of 115 kDa. Aflibercept is produced in recombinant Chinese hamster ovary (CHO) cells.

EYLEA is a sterile, clear, and colorless to pale yellow solution. EYLEA is supplied as a preservative-free, sterile, aqueous solution in a single-use, glass vial designed to deliver 0.05 mL (50 microliters) of EYLEA (40 mg/mL in 10 mM sodium phosphate, 40 mM sodium chloride, 0.03% polysorbate 20, and 5% sucrose, pH 6.2).

PGR2026-00039
Biocon Ex.1065
Page 165 of 595

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Vascular endothelial growth factor-A (VEGF-A) and placental growth factor (PlGF) are members of the VEGF family of angiogenic factors that can act as mitogenic, chemotactic, and vascular permeability factors for endothelial cells. VEGF acts via two receptor tyrosine kinases, VEGFR-1 and VEGFR-2, present on the surface of endothelial cells. PlGF binds only to VEGFR-1, which is also present on the surface of leucocytes. Activation of these receptors by VEGF-A can result in neovascularization and vascular permeability.

Aflibercept acts as a soluble decoy receptor that binds VEGF-A and PlGF, and thereby can inhibit the binding and activation of these cognate VEGF receptors.

12.2 Pharmacodynamics

In the phase 3 studies anatomic measures of disease activity improved similarly in all treatment groups from baseline to week 52. Anatomic data were not used to influence treatment decisions.

12.3 Pharmacokinetics

EYLEA is administered intravitreally to exert local effects in the eye. In patients with wet AMD, following intravitreal administration of EYLEA, a fraction of the administered dose is expected to bind with endogenous VEGF in the eye to form an inactive aflibercept: VEGF complex. Once absorbed into the systemic circulation, aflibercept presents in the plasma as free aflibercept (unbound to VEGF) and a more predominant stable inactive form with circulating endogenous VEGF (i.e., aflibercept: VEGF complex).

Absorption/Distribution

Following intravitreal administration of 2 mg per eye of EYLEA to patients with wet AMD, the mean C_{max} of free aflibercept in the plasma was 0.02 mcg/mL (range: 0 to 0.054 mcg/mL) and was attained in 1 to 3 days. The free aflibercept plasma concentrations were undetectable two weeks post-dosing in all patients. Aflibercept did not accumulate in plasma when administered as repeated doses intravitreally every 4 weeks. It is estimated that after intravitreal administration of 2 mg to patients, the mean maximum plasma concentration of free aflibercept is more than 100 fold lower than the concentration of aflibercept required to half-maximally bind systemic VEGF.

The volume of distribution of free aflibercept following intravenous (I.V.) administration of aflibercept has been determined to be approximately 6L.

Metabolism/Elimination

Aflibercept is a therapeutic protein and no drug metabolism studies have been conducted. Aflibercept is expected to undergo elimination through both target-mediated disposition via binding to free endogenous VEGF and metabolism via proteolysis. The terminal elimination

PGR2026-00039
Biocon Ex.1065
Page 166 of 595

half-life (t1/2) of free aflibercept in plasma was approximately 5 to 6 days after I.V. administration of doses of 2 to 4 mg/kg aflibercept.

Specific Populations

Renal Impairment

Pharmacokinetic analysis of a subgroup of patients (n=492) in one Phase 3 study, of which 43% had renal impairment (mild n=120, moderate n=74, and severe n=16), revealed no differences with respect to plasma concentrations of free aflibercept after intravitreal administration every 4 or 8 weeks. No dose adjustment based on renal impairment status is needed.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been conducted on the mutagenic or carcinogenic potential of aflibercept. Effects on male and female fertility were assessed as part of a 6-month study in monkeys with intravenous administration of aflibercept at doses ranging from 3 to 30 mg/kg. Absent or irregular menses associated with alterations in female reproductive hormone levels and changes in sperm morphology and motility were observed at all dose levels. In addition, females showed decreased ovarian and uterine weight accompanied by compromised luteal development and reduction of maturing follicles. These changes correlated with uterine and vaginal atrophy. A No Observed Adverse Effect Level (NOAEL) was not identified. Based on C_{max} and AUC for free aflibercept observed at the lowest dose used of 3 mg/kg, the systemic exposures were approximately 4900 times and 1500 times higher, respectively, than the exposure observed in humans after an intravitreal dose of 2 mg. All changes were reversible.

13.2 Animal Toxicology and/or Pharmacology

Erosions and ulcerations of the respiratory epithelium in nasal turbinates in monkeys treated with aflibercept intravitreally were observed at intravitreal doses of 2 or 4 mg/eye. At the NOAEL of 0.5 mg/eye in monkeys, the systemic exposure was 42 times and 56 times higher based on C_{max} and AUC, respectively, than the exposure observed in humans after an intravitreal dose of 2 mg. Similar effects were not seen in clinical studies [*see Clinical Studies (14)*].

14 CLINICAL STUDIES

The safety and efficacy of EYLEA were assessed in two randomized, multi-center, double-masked, active-controlled studies in patients with wet AMD. A total of 2412 patients were treated and evaluable for efficacy (1817 with EYLEA) in the two studies (VIEW1 and VIEW2). In each study, patients were randomly assigned in a 1:1:1:1 ratio to 1 of 4 dosing regimens: 1) EYLEA administered 2 mg every 8 weeks following 3 initial monthly doses (EYLEA 2Q8); 2) EYLEA administered 2 mg every 4 weeks (EYLEA 2Q4); 3) EYLEA 0.5 mg administered every 4 weeks (EYLEA 0.5Q4); and 4) ranibizumab administered 0.5 mg every 4 weeks (ranibizumab 0.5 mg Q4). Patient ages ranged from 49 to 99 years with a mean of 76 years.

PGR2026-00039
Biocon Ex.1065
Page 167 of 595

In both studies, the primary efficacy endpoint was the proportion of patients who maintained vision, defined as losing fewer than 15 letters of visual acuity at week 52 compared to baseline. Data are available through week 52. Both EYLEA 2Q8 and EYLEA 2Q4 groups were shown to have efficacy that was clinically equivalent to the ranibizumab 0.5 mg Q4 group.

Detailed results from the analysis of the VIEW1 and VIEW2 studies are shown in Table 2 and Figure 9 below.

Table 2: Efficacy Outcomes at Week 52 (Full Analysis Set with LOCF) in VIEW1 and VIEW2 Studies

	VIEW1			VIEW2		
	EYLEA 2 mg Q8 weeks [a]	EYLEA 2 mg Q4 weeks	ranibizumab 0.5 mg Q4 weeks	EYLEA 2 mg Q8 weeks [a]	EYLEA 2 mg Q4 weeks	ranibizumab 0.5 mg Q4 weeks
Full Analysis Set	N=301	N=304	N=304	N=306	N=309	N=291
Efficacy Outcomes						
Proportion of patients who maintained visual acuity (%) (<15 letters of BCVA loss)	94%	95%	94%	95%	95%	95%
Difference[b] (%) (95.1% CI)	0.6 (-3.2, 4.4)	1.3 (-2.4, 5.0)		0.6 (-2.9, 4.0)	-0.3 (-4.0, 3.3)	
Mean change in BCVA as measured by ETDRS letter score from Baseline	7.9	10.9	8.1	8.9	7.6	9.4
Difference[b] in LS mean (95.1% CI)	0.3 (-2.0, 2.5)	3.2 (0.9, 5.4)		-0.9 (-3.1, 1.3)	-2.0 (-4.1, 0.2)	
Number of patients who gained at least 15 letters of vision from Baseline (%)	92 (31%)	114 (38%)	94 (31%)	96 (31%)	91 (29%)	99 (34%)
Difference[b] (%) (95.1% CI)	-0.4 (-7.7, 7.0)	6.6 (-1.0, 14.1)		-2.6 (-10.2, 4.9)	-4.6 (-12.1, 2.9)	

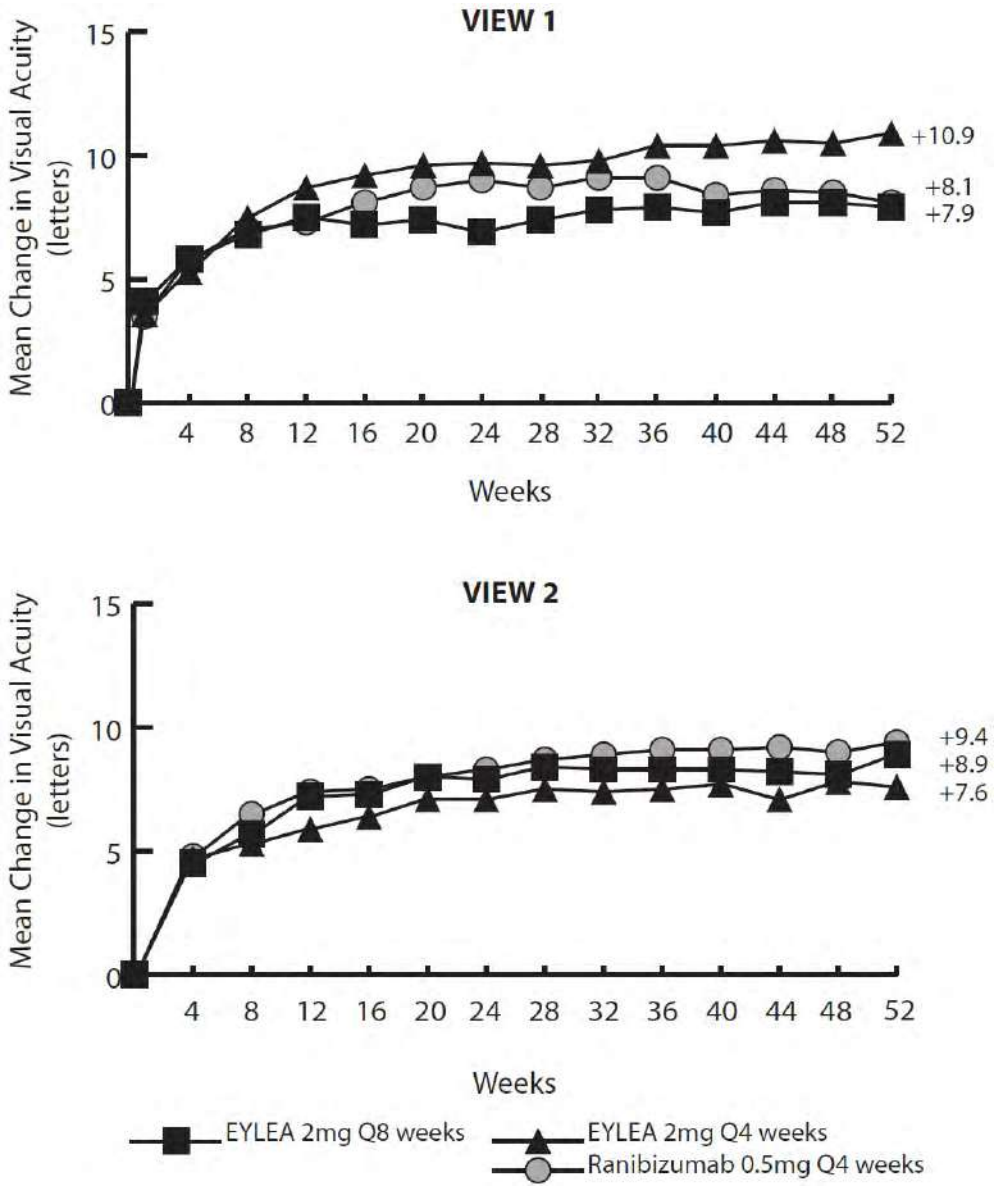
BCVA = Best Corrected Visual Acuity; CI = Confidence Interval; ETDRS = Early Treatment Diabetic Retinopathy Study; LOCF = Last Observation Carried Forward (baseline values are not carried forward); 95.1% confidence intervals were presented to adjust for safety assessment conducted during the study.

[a] After treatment initiation with 3 monthly doses

[b] EYLEA group minus the ranibizumab group

PGR2026-00039
Biocon Ex.1065
Page 168 of 595

Figure 9: Mean Change in Visual Acuity from Baseline to Week 52 in VIEW1 and VIEW2 Studies



16 HOW SUPPLIED/STORAGE AND HANDLING

Each Vial is for single eye use only. EYLEA is supplied in the following presentation [*see Dosage and Administration (2.3) and (2.4)*].

PGR2026-00039
Biocon Ex.1065
Page 169 of 595

NDC NUMBER	CARTON TYPE	CARTON CONTENTS
61755-005-02	Vial	one single-use, sterile, 3-mL, glass vial containing a 0.278 mL fill of 40 mg/mL EYLEA one 19-gauge x 1½-inch, 5-micron, filter needle for withdrawal of the vial contents one 30-gauge x ½-inch injection needle for intravitreal injection one 1-mL syringe for administration one package insert

Storage

EYLEA should be refrigerated at 2°C to 8ºC (36°F to 46ºF). Do Not Freeze. Do not use beyond the date stamped on the carton and container label. Protect from light. Store in the original carton until time of use.

17 PATIENT COUNSELING INFORMATION

Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA and the associated eye examinations [*see Adverse Reactions (6)*]. Patients should be advised not to drive or use machinery until visual function has recovered sufficiently.

In the days following EYLEA administration, patients are at risk of developing endophthalmitis or retinal detachment. If the eye becomes red, sensitive to light, painful, or develops a change in vision, the patient should seek immediate care from an ophthalmologist [*see Warnings and Precautions (5.1)*].

PGR2026-00039
Biocon Ex.1065
Page 170 of 595

REGENERON

Manufactured by:

Regeneron Pharmaceuticals, Inc.

777 Old Saw Mill River Road

Tarrytown, NY 10591-6707

U.S. License Number 1760

EYLEA™ is a trademark of Regeneron Pharmaceuticals, Inc.

© 2011, Regeneron Pharmaceuticals, Inc.

All rights reserved.

V1.0

Issue Date: November /2011

Initial U.S. Approval: 2011

Regeneron U.S. Patents 7,306,799; 7,531,173; 7,608,261; 7,070,959; 7,374,757; 7,374,758, and other pending patents

PGR2026-00039
Biocon Ex.1065
Page 171 of 595

APPENDIX FDA05

https://web.archive.org/web/20170201000000*/http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/125387s004lbl.pdf September 17, 2025

INTERNET ARCHIVE WEB TEXTS VIDEO AUDIO SOFTWARE IMAGES SIGN UP | LOG IN UPLOAD Search

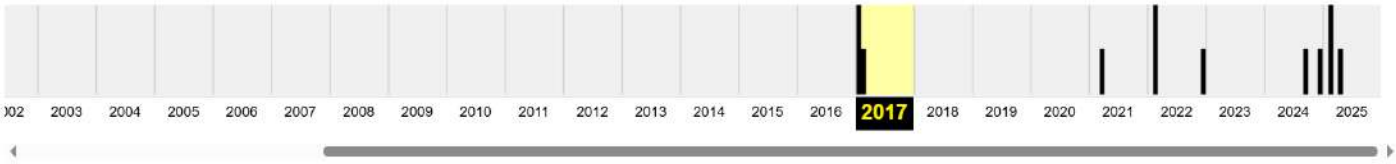
ABOUT BLOG PROJECTS HELP DONATE CONTACT JOBS VOLUNTEER PEOPLE

DONATE INTERNET ARCHIVE WayBackMachine Explore more than 946 billion web pages saved over time

http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/1253

Calendar · Collections · Changes · Summary · Site Map · URLs

Saved **12 times** between January 18, 2017 and April 1, 2025.



JAN

1	2	3	4	5	6	7
8	9	10	11	12	13	14
15	16	17	18	19	20	21
22	23	24	25	26	27	28
29	30	31				

FEB

			1	2	3	4
5	6	7	8	9	10	11
12	13	14	15	16	17	18
19	20	21	22	23	24	25
26	27	28				

MAR

			1	2	3	4
5	6	7	8	9	10	11
12	13	14	15	16	17	18
19	20	21	22	23	24	25
26	27	28	29	30	31	

APR

						1
2	3	4	5	6	7	8
9	10	11	12	13	14	15
16	17	18	19	20	21	22
23	24	25	26	27	28	29
30						

MAY

	1	2	3	4	5	6
7	8	9	10	11	12	13
14	15	16	17	18	19	20
21	22	23	24	25	26	27
28	29	30	31			

JUN

				1	2	3
4	5	6	7	8	9	10
11	12	13	14	15	16	17
18	19	20	21	22	23	24
25	26	27	28	29	30	

JUL

						1
2	3	4	5	6	7	8
9	10	11	12	13	14	15
16	17	18	19	20	21	22
23	24	25	26	27	28	29
30	31					

AUG

		1	2	3	4	5
6	7	8	9	10	11	12
13	14	15	16	17	18	19
20	21	22	23	24	25	26
27	28	29	30	31		

SEP

				1	2	
3	4	5	6	7	8	9
10	11	12	13	14	15	16
17	18	19	20	21	22	23
24	25	26	27	28	29	30

OCT

1	2	3	4	5	6	7
8	9	10	11	12	13	14
15	16	17	18	19	20	21
22	23	24	25	26	27	28
29	30	31				

NOV

			1	2	3	4
5	6	7	8	9	10	11
12	13	14	15	16	17	18
19	20	21	22	23	24	25
26	27	28	29	30		

DEC

					1	2
3	4	5	6	7	8	9
10	11	12	13	14	15	16
17	18	19	20	21	22	23
24	25	26	27	28	29	30
31						

Note

This calendar view maps the number of times **http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/125387s004lbl.pdf** was crawled by the Wayback Machine, *not* how many times the site was actually updated. More info in the FAQ.

FAQ | Contact Us | Terms of Service (Dec 31, 2014)

The Wayback Machine is an initiative of the Internet Archive, a 501(c)(3) non-profit, building a digital library of Internet sites and other cultural artifacts in digital form. Other projects include Open Library & archive-it.org.

Your use of the Wayback Machine is subject to the Internet Archive's Terms of Use.

https://web.archive.org/web/20170120063346/http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/125387s004lbl.pdf September 17, 2025
INTERNET ARCHIVE Wayback Machine http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/125387s004lbl.pdf Go DEC JAN MAR
12 captures 18 Jan 2017 - 1 Apr 2025 2016 20 2017 2021 About this capture
label 1 / 19 100% + − 1 2

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use EYLEA safely and effectively. See full prescribing information for EYLEA.

EYLEA™ (aflibercept) Injection
For Intravitreal Injection
Initial U.S. Approval: 2011

RECENT MAJOR CHANGES
- Indications and Usage, Macular Edema Following Central Retinal Vein Occlusion (CRVO) (1.2) 9/2012
- Dosage and Administration, Macular Edema Following Central Retinal Vein Occlusion (CRVO) (2.3) 9/2012
- Dosage and Administration, Preparation for Administration (2.4) 9/2012
- Contraindications, Hypersensitivity (4.3) 9/2012
- Warnings and Precautions, Thromboembolic Events (5.3) 9/2012

INDICATIONS AND USAGE
EYLEA is indicated for the treatment of patients with:
- Neovascular (Wet) Age-Related Macular Degeneration (AMD) (1.1)
- Macular Edema Following Central Retinal Vein Occlusion (CRVO) (1.2)

DOSAGE AND ADMINISTRATION
For ophthalmic intravitreal injection only. (2.1)

Neovascular (Wet) Age-Related Macular Degeneration (AMD)
- The recommended dose for EYLEA is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (monthly) for the first 3 months,

Macular Edema Following Central Retinal Vein Occlusion (CRVO)
- The recommended dose for EYLEA is 2 mg (0.05 mL) administered by intravitreal injection once every 4 weeks (monthly). (2.3)

DOSAGE FORMS AND STRENGTHS
40 mg/mL solution for intravitreal injection in a single-use vial (3)

CONTRAINDICATIONS
- Ocular or periocular infection (4.1)
- Active intraocular inflammation (4.2)
- Hypersensitivity (4.3)

WARNINGS AND PRECAUTIONS
- Endophthalmitis and retinal detachments may occur following intravitreal injections. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately. (5.1)
- Increases in intraocular pressure have been seen within 60 minutes of an intravitreal injection. (5.2)
- There is a potential risk of arterial thromboembolic events following intravitreal use of VEGF inhibitors. (5.3)

ADVERSE REACTIONS
The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and increased intraocular pressure. (6.2)

To report SUSPECTED ADVERSE REACTIONS, contact Regeneron at 1-855-395-3248 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use EYLEA safely and effectively. See full prescribing information for EYLEA.

EYLEA™ (aflibercept) Injection
For Intravitreal Injection
Initial U.S. Approval: 2011

RECENT MAJOR CHANGES

- Indications and Usage, Macular Edema Following Central Retinal Vein Occlusion (CRVO) (1.2) 9/2012
- Dosage and Administration, Macular Edema Following Central Retinal Vein Occlusion (CRVO) (2.3) 9/2012
- Dosage and Administration, Preparation for Administration (2.4) 9/2012
- Contraindications, Hypersensitivity (4.3) 9/2012
- Warnings and Precautions, Thromboembolic Events (5.3) 9/2012

INDICATIONS AND USAGE

EYLEA is indicated for the treatment of patients with:

- Neovascular (Wet) Age-Related Macular Degeneration (AMD) (1.1)
- Macular Edema Following Central Retinal Vein Occlusion (CRVO) (1.2)

DOSAGE AND ADMINISTRATION

For ophthalmic intravitreal injection only. (2.1)

Neovascular (Wet) Age-Related Macular Degeneration (AMD)

- The recommended dose for EYLEA is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (monthly) for the first 3 months, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). (2.2)
- Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated when EYLEA was dosed every 4 weeks compared to every 8 weeks. (2.2)

Macular Edema Following Central Retinal Vein Occlusion (CRVO)

- The recommended dose for EYLEA is 2 mg (0.05 mL) administered by intravitreal injection once every 4 weeks (monthly). (2.3)

DOSAGE FORMS AND STRENGTHS

40 mg/mL solution for intravitreal injection in a single-use vial (3)

CONTRAINDICATIONS

- Ocular or periocular infection (4.1)
- Active intraocular inflammation (4.2)
- Hypersensitivity (4.3)

WARNINGS AND PRECAUTIONS

- Endophthalmitis and retinal detachments may occur following intravitreal injections. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately. (5.1)
- Increases in intraocular pressure have been seen within 60 minutes of an intravitreal injection. (5.2)
- There is a potential risk of arterial thromboembolic events following intravitreal use of VEGF inhibitors. (5.3)

ADVERSE REACTIONS

The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and increased intraocular pressure. (6.2)

To report SUSPECTED ADVERSE REACTIONS, contact Regeneron at 1-855-395-3248 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

See 17 for PATIENT COUNSELING INFORMATION

Revised: 9/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
1.1 Neovascular (Wet) Age-Related Macular Degeneration (AMD)
1.2 Macular Edema Following Central Retinal Vein Occlusion (CRVO)
2 DOSAGE AND ADMINISTRATION
2.1 General Dosing Information
2.2 Neovascular (Wet) Age-Related Macular Degeneration (AMD)
2.3 Macular Edema Following Central Retinal Vein Occlusion (CRVO)
2.4 Preparation for Administration
2.5 Administration
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
4.1 Ocular or Periocular Infections
4.2 Active Intraocular Inflammation
4.3 Hypersensitivity
5 WARNINGS AND PRECAUTIONS
5.1 Endophthalmitis and Retinal Detachments
5.2 Increase in Intraocular Pressure
5.3 Thromboembolic Events
6 ADVERSE REACTIONS
6.1 Injection Procedure
6.2 Clinical Studies Experience
6.3 Immunogenicity
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
14.1 Neovascular (Wet) Age-Related Macular Degeneration (AMD)
14.2 Macular Edema Following Central Retinal Vein Occlusion (CRVO)
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

***Sections or subsections omitted from the full prescribing information are not listed**

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

EYLEA is indicated for the treatment of patients with:

1.1 Neovascular (Wet) Age-Related Macular Degeneration (AMD)

1.2 Macular Edema Following Central Retinal Vein Occlusion (CRVO)

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

FOR OPHTHALMIC INTRAVITREAL INJECTION ONLY. EYLEA must only be administered by a qualified physician.

2.2 Neovascular (Wet) Age-Related Macular Degeneration (AMD)

The recommended dose for EYLEA is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (monthly) for the first 12 weeks (3 months), followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated when EYLEA was dosed every 4 weeks compared to every 8 weeks [*see Clinical Studies (14.1)*].

2.3 Macular Edema Following Central Retinal Vein Occlusion (CRVO)

The recommended dose for EYLEA is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection once every 4 weeks (monthly) [*see Clinical Studies (14.2)*].

2.4 Preparation for Administration

EYLEA should be inspected visually prior to administration. If particulates, cloudiness, or discoloration are visible, the vial must not be used.

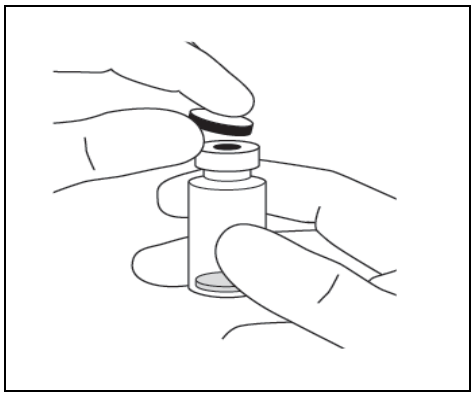
Using aseptic technique, the intravitreal injection should be performed with a 30-gauge x ½-inch injection needle.

Vial

The glass vial is for single use only.

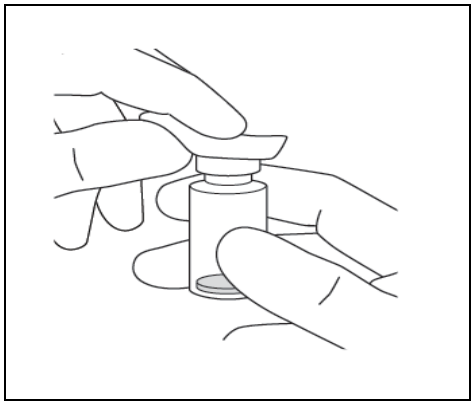
1. Remove the protective plastic cap from the vial (see Figure 1).

Figure 1:



2. Clean the top of the vial with an alcohol wipe (see Figure 2).

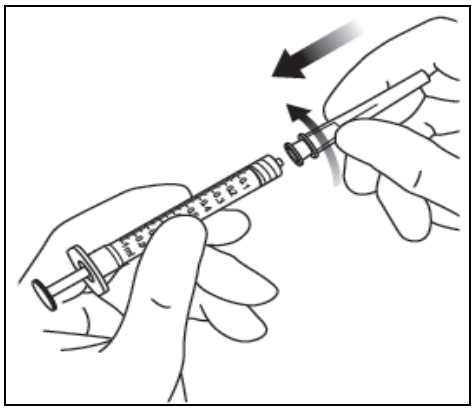
Figure 2:



3. Remove the 19-gauge x 1½-inch, 5-micron, filter needle from its pouch and remove the 1-mL syringe supplied in the carton from its pouch. Attach the filter needle to the syringe by twisting it onto the Luer lock syringe tip (see Figure 3).

PGR2026-00039
Biocon Ex.1065
Page 177 of 595

Figure 3:



4. Push the filter needle into the center of the vial stopper until the needle is completely inserted into the vial and the tip touches the bottom or bottom edge of the vial.

5. Using aseptic technique withdraw all of the EYLEA vial contents into the syringe, keeping the vial in an upright position, slightly inclined to ease complete withdrawal. To deter the introduction of air, ensure the bevel of the filter needle is submerged into the liquid. Continue to tilt the vial during withdrawal keeping the bevel of the filter needle submerged in the liquid (see Figures 4a and 4b).

Figure 4a:

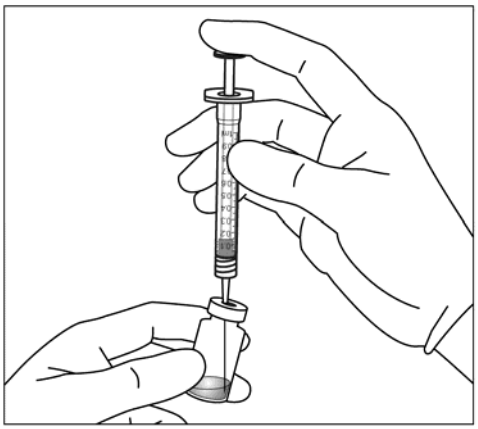
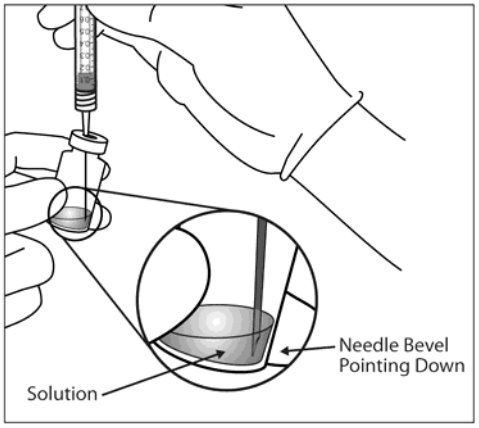


Figure 4b:



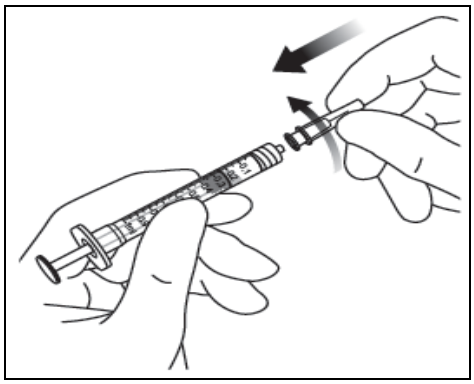
6. Ensure that the plunger rod is drawn sufficiently back when emptying the vial in order to completely empty the filter needle.

7. Remove the filter needle from the syringe and properly dispose of the filter needle.
Note: Filter needle is **not** to be used for intravitreal injection.

PGR2026-00039
Biocon Ex.1065
Page 178 of 595

8. Remove the 30-gauge x ½-inch injection needle from the plastic pouch and attach the injection needle to the syringe by firmly twisting the injection needle onto the Luer lock syringe tip (see Figure 5).

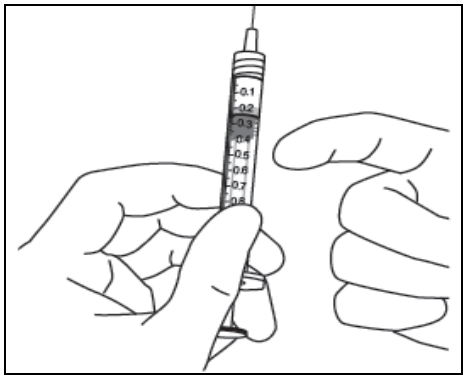
Figure 5:



9. When ready to administer EYLEA, remove the plastic needle shield from the needle.

10. Holding the syringe with the needle pointing up, check the syringe for bubbles. If there are bubbles, gently tap the syringe with your finger until the bubbles rise to the top (see Figure 6).

Figure 6:



11. To eliminate all of the bubbles and to expel excess drug, SLOWLY depress the plunger so that the plunger tip aligns with the line that marks 0.05 mL on the syringe (see Figures 7a and 7b).

Figure 7a:

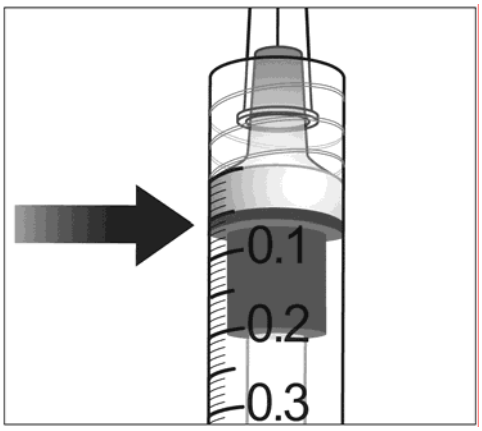
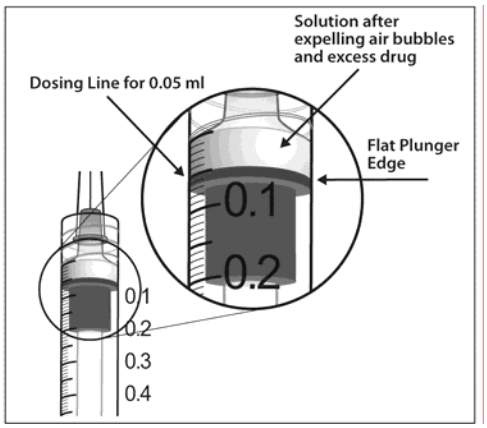


Figure 7b:



2.5 Administration

The intravitreal injection procedure should be carried out under controlled aseptic conditions, which include surgical hand disinfection and the use of sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent). Adequate anesthesia and a topical broad–spectrum microbicide should be given prior to the injection.

Immediately following the intravitreal injection, patients should be monitored for elevation in intraocular pressure. Appropriate monitoring may consist of a check for perfusion of the optic nerve head or tonometry. If required, a sterile paracentesis needle should be available.

Following intravitreal injection, patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment (e.g., eye pain, redness of the eye, photophobia, blurring of vision) without delay [*see Patient Counseling Information (17)*].

Each vial should only be used for the treatment of a single eye. If the contralateral eye requires treatment, a new vial should be used and the sterile field, syringe, gloves, drapes, eyelid speculum, filter, and injection needles should be changed before EYLEA is administered to the other eye.

After injection, any unused product must be discarded.

No special dosage modification is required for any of the populations that have been studied (e.g., gender, elderly).

3 DOSAGE FORMS AND STRENGTHS

Single-use, glass vial designed to provide 0.05 mL of 40 mg/mL solution for intravitreal injection.

4 CONTRAINDICATIONS

4.1 Ocular or Periocular Infections

EYLEA is contraindicated in patients with ocular or periocular infections.

4.2 Active Intraocular Inflammation

EYLEA is contraindicated in patients with active intraocular inflammation.

4.3 Hypersensitivity

EYLEA is contraindicated in patients with known hypersensitivity to aflibercept or any of the excipients in EYLEA. Hypersensitivity reactions may manifest as severe intraocular inflammation.

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis and Retinal Detachments

Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments [*see Adverse Reactions (6.1)*]. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately [*see Dosage and Administration (2.5) and Patient Counseling Information (17)*].

5.2 Increase in Intraocular Pressure

Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA [*see Adverse Reactions (6.1)*]. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with VEGF inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately [*see Dosage and Administration (2.5)*].

5.3 Thromboembolic Events

There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence in the VIEW1 and VIEW2 wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA [*see Clinical Studies (14.1)*]. The incidence in the COPERNICUS and GALILEO CRVO studies during the first 6 months was 0% (0/218) in patients treated with EYLEA 2 mg every 4 weeks compared with 1.4% (2/142) in patients receiving sham treatment [*see Clinical Studies (14.2)*].

PGR2026-00039
Biocon Ex.1065
Page 181 of 595

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in the *Warnings and Precautions (5)* section of the labeling:

- Endophthalmitis and retinal detachments
- Increased intraocular pressure
- Thromboembolic events

The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and increased intraocular pressure.

6.1 Injection Procedure

Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis, traumatic cataract, increased intraocular pressure, and vitreous detachment.

6.2 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in other clinical trials of the same or another drug and may not reflect the rates observed in practice.

A total of 2042 patients treated with EYLEA constituted the safety population in four phase 3 studies. Among those, 1441 patients were treated with the recommended dose of 2 mg.

Neovascular (Wet) Age-Related Macular Degeneration (AMD)

The data described below reflect exposure to EYLEA in 1824 patients with wet AMD, including 1223 patients treated with the 2-mg dose, in 2 double-masked, active-controlled clinical studies (VIEW1 and VIEW2) for 12 months [*see Clinical Studies (14.1)*].

Table 1: Most Common Adverse Reactions (≥1%) in Wet AMD Studies

Adverse Reactions	**EYLEA (N=1824)**	**Active Control (ranibizumab) (N=595)**
Conjunctival hemorrhage	25%	28%
Eye pain	9%	9%
Cataract	7%	7%

Adverse Reactions	EYLEA (N=1824)	Active Control (ranibizumab) (N=595)
Vitreous detachment	6%	6%
Vitreous floaters	6%	7%
Intraocular pressure increased	5%	7%
Conjunctival hyperemia	4%	8%
Corneal erosion	4%	5%
Detachment of the retinal pigment epithelium	3%	3%
Injection site pain	3%	3%
Foreign body sensation in eyes	3%	4%
Lacrimation increased	3%	1%
Vision blurred	2%	2%
Retinal pigment epithelium tear	2%	1%
Injection site hemorrhage	1%	2%
Eyelid edema	1%	2%
Corneal edema	1%	1%

Less common serious adverse reactions reported in <1% of the patients treated with EYLEA were retinal detachment, retinal tear, and endophthalmitis. Hypersensitivity has also been reported in less than 1% of the patients treated with EYLEA.

Macular Edema Following Central Retinal Vein Occlusion (CRVO)

The data described below reflect exposure to EYLEA in 218 patients with macular edema following CRVO treated with 2 mg dose in 2 double-masked, controlled clinical studies (COPERNICUS and GALILEO) for 6 months [*see Clinical Studies (14.2)*].

Table 2: Most Common Adverse Reactions (≥1%) in CRVO Studies

Adverse Reactions	EYLEA (N=218)	Control (N=142)
Eye pain	13%	5%
Conjunctival hemorrhage	12%	11%
Intraocular pressure increased	8%	6%
Corneal erosion	5%	4%
Vitreous floaters	5%	1%

Adverse Reactions	EYLEA (N=218)	Control (N=142)
Conjunctival hyperemia	5%	3%
Foreign body sensation in eyes	3%	5%
Vitreous detachment	3%	4%
Lacrimation increased	3%	4%
Injection site pain	3%	1%
Vision blurred	1%	<1%

Less common adverse reactions reported in <1% of the patients treated with EYLEA were cataract, eyelid edema, corneal edema, retinal tear, hypersensitivity, and endophthalmitis.

6.3 Immunogenicity

As with all therapeutic proteins, there is a potential for an immune response in patients treated with EYLEA. The immunogenicity of EYLEA was evaluated in serum samples. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to EYLEA in immunoassays. The detection of an immune response is highly dependent on the sensitivity and specificity of the assays used, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to EYLEA with the incidence of antibodies to other products may be misleading.

In the wet AMD and CRVO studies, the pre-treatment incidence of immunoreactivity to EYLEA was 1% to 3% across treatment groups. After dosing with EYLEA for 52 weeks (wet AMD), or 24 weeks (CRVO), antibodies to EYLEA were detected in a similar percentage range of patients. Both in the wet AMD and in the CRVO studies, there were no differences in efficacy or safety between patients with or without immunoreactivity.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. Aflibercept produced embryo-fetal toxicity when administered during organogenesis in pregnant rabbits at intravenous doses of 3 to 60 mg/kg. A series of external, visceral, and skeletal malformations were observed in the fetuses. The maternal No Observed Adverse Effect Level (NOAEL) was 3 mg/kg, whereas the fetal NOAEL was below 3 mg/kg. At this dose, the systemic exposures based on C_{max} and AUC for free aflibercept were approximately 2900 times and 600 times higher, respectively, when compared to corresponding values observed in humans after an intravitreal dose of 2 mg.

There are no adequate and well-controlled studies in pregnant women. EYLEA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.3 Nursing Mothers

It is unknown whether aflibercept is excreted in human milk. Because many drugs are excreted in human milk, a risk to the breastfed child cannot be excluded. EYLEA is not recommended during breastfeeding. A decision must be made whether to discontinue nursing or to discontinue treatment with EYLEA, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and effectiveness of EYLEA in pediatric patients have not been established.

8.5 Geriatric Use

In the clinical studies, approximately 85% (1728/2034) of patients randomized to treatment with EYLEA were ≥65 years of age and approximately 58% (1177/2034) were ≥75 years of age. No significant differences in efficacy or safety were seen with increasing age in these studies.

11 DESCRIPTION

EYLEA (aflibercept) is a recombinant fusion protein consisting of portions of human VEGF receptors 1 and 2 extracellular domains fused to the Fc portion of human IgG1 formulated as an iso-osmotic solution for intravitreal administration. Aflibercept is a dimeric glycoprotein with a protein molecular weight of 97 kilodaltons (kDa) and contains glycosylation, constituting an additional 15% of the total molecular mass, resulting in a total molecular weight of 115 kDa. Aflibercept is produced in recombinant Chinese hamster ovary (CHO) cells.

EYLEA is a sterile, clear, and colorless to pale yellow solution. EYLEA is supplied as a preservative-free, sterile, aqueous solution in a single-use, glass vial designed to deliver 0.05 mL (50 microliters) of EYLEA (40 mg/mL in 10 mM sodium phosphate, 40 mM sodium chloride, 0.03% polysorbate 20, and 5% sucrose, pH 6.2).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Vascular endothelial growth factor-A (VEGF-A) and placental growth factor (PlGF) are members of the VEGF family of angiogenic factors that can act as mitogenic, chemotactic, and vascular permeability factors for endothelial cells. VEGF acts via two receptor tyrosine kinases, VEGFR-1 and VEGFR-2, present on the surface of endothelial cells. PlGF binds only to VEGFR-1, which is also present on the surface of leucocytes. Activation of these receptors by VEGF-A can result in neovascularization and vascular permeability.

Aflibercept acts as a soluble decoy receptor that binds VEGF-A and PlGF, and thereby can inhibit the binding and activation of these cognate VEGF receptors.

12.2 Pharmacodynamics

Neovascular (Wet) Age-Related Macular Degeneration (AMD)

In the clinical studies anatomic measures of disease activity improved similarly in all treatment groups from baseline to week 52. Anatomic data were not used to influence treatment decisions. [*see Clinical Studies (14.1)*].

Macular Edema Following Central Retinal Vein Occlusion (CRVO)

Reductions in mean retinal thickness were observed in COPERNICUS and GALILEO at Week 24 compared to baseline. Anatomic data were not used to influence treatment decisions. [*see Clinical Studies (14.2)*].

12.3 Pharmacokinetics

EYLEA is administered intravitreally to exert local effects in the eye. In patients with wet AMD or CRVO, following intravitreal administration of EYLEA, a fraction of the administered dose is expected to bind with endogenous VEGF in the eye to form an inactive aflibercept: VEGF complex. Once absorbed into the systemic circulation, aflibercept presents in the plasma as free aflibercept (unbound to VEGF) and a more predominant stable inactive form with circulating endogenous VEGF (i.e., aflibercept: VEGF complex).

Absorption/Distribution

Following intravitreal administration of 2 mg per eye of EYLEA to patients with wet AMD and CRVO, the mean C_{max} of free aflibercept in the plasma was 0.02 mcg/mL (range: 0 to 0.054 mcg/mL) and 0.05 mcg/mL (range 0 to 0.081 mcg/mL), respectively and was attained in 1 to 3 days. The free aflibercept plasma concentrations were undetectable two weeks post-dosing in all patients. Aflibercept did not accumulate in plasma when administered as repeated doses intravitreally every 4 weeks. It is estimated that after intravitreal administration of 2 mg to patients, the mean maximum plasma concentration of free aflibercept is more than 100 fold lower than the concentration of aflibercept required to half-maximally bind systemic VEGF.

The volume of distribution of free aflibercept following intravenous (I.V.) administration of aflibercept has been determined to be approximately 6L.

Metabolism/Elimination

Aflibercept is a therapeutic protein and no drug metabolism studies have been conducted. Aflibercept is expected to undergo elimination through both target-mediated disposition via binding to free endogenous VEGF and metabolism via proteolysis. The terminal elimination half-life (t1/2) of free aflibercept in plasma was approximately 5 to 6 days after I.V. administration of doses of 2 to 4 mg/kg aflibercept.

Specific Populations

Renal Impairment

Pharmacokinetic analysis of a subgroup of patients (n=492) in one wet AMD study, of which 43% had renal impairment (mild n=120, moderate n=74, and severe n=16), revealed no differences with respect to plasma concentrations of free aflibercept after intravitreal administration every 4 or 8 weeks. Similar results were seen in patients in a CRVO study. No dose adjustment based on renal impairment status is needed for either wet AMD or CRVO patients.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been conducted on the mutagenic or carcinogenic potential of aflibercept. Effects on male and female fertility were assessed as part of a 6-month study in monkeys with intravenous administration of aflibercept at doses ranging from 3 to 30 mg/kg. Absent or irregular menses associated with alterations in female reproductive hormone levels and changes in sperm morphology and motility were observed at all dose levels. In addition, females showed decreased ovarian and uterine weight accompanied by compromised luteal development and reduction of maturing follicles. These changes correlated with uterine and vaginal atrophy. A No Observed Adverse Effect Level (NOAEL) was not identified. Based on C_{max} and AUC for free aflibercept observed at the lowest dose used of 3 mg/kg, the systemic exposures were approximately 4900 times and 1500 times higher, respectively, than the exposure observed in humans after an intravitreal dose of 2 mg. All changes were reversible.

13.2 Animal Toxicology and/or Pharmacology

Erosions and ulcerations of the respiratory epithelium in nasal turbinates in monkeys treated with aflibercept intravitreally were observed at intravitreal doses of 2 or 4 mg/eye. At the NOAEL of 0.5 mg/eye in monkeys, the systemic exposure was 42 times and 56 times higher based on C_{max} and AUC, respectively, than the exposure observed in humans after an intravitreal dose of 2 mg. Similar effects were not seen in clinical studies [*see Clinical Studies (14)*].

14 CLINICAL STUDIES

14.1 Neovascular (Wet) Age-Related Macular Degeneration (AMD)

The safety and efficacy of EYLEA were assessed in two randomized, multi-center, double-masked, active-controlled studies in patients with wet AMD. A total of 2412 patients were treated and evaluable for efficacy (1817 with EYLEA) in the two studies (VIEW1 and VIEW2). In each study, patients were randomly assigned in a 1:1:1:1 ratio to 1 of 4 dosing regimens: 1) EYLEA administered 2 mg every 8 weeks following 3 initial monthly doses (EYLEA 2Q8);

2) EYLEA administered 2 mg every 4 weeks (EYLEA 2Q4); 3) EYLEA 0.5 mg administered every 4 weeks (EYLEA 0.5Q4); and 4) ranibizumab administered 0.5 mg every 4 weeks (ranibizumab 0.5 mg Q4). Patient ages ranged from 49 to 99 years with a mean of 76 years.

In both studies, the primary efficacy endpoint was the proportion of patients who maintained vision, defined as losing fewer than 15 letters of visual acuity at week 52 compared to baseline. Data are available through week 52. Both EYLEA 2Q8 and EYLEA 2Q4 groups were shown to have efficacy that was clinically equivalent to the ranibizumab 0.5 mg Q4 group.

Detailed results from the analysis of the VIEW1 and VIEW2 studies are shown in Table 3 and Figure 8 below.

Table 3: Efficacy Outcomes at Week 52 (Full Analysis Set with LOCF) in VIEW1 and VIEW2 Studies

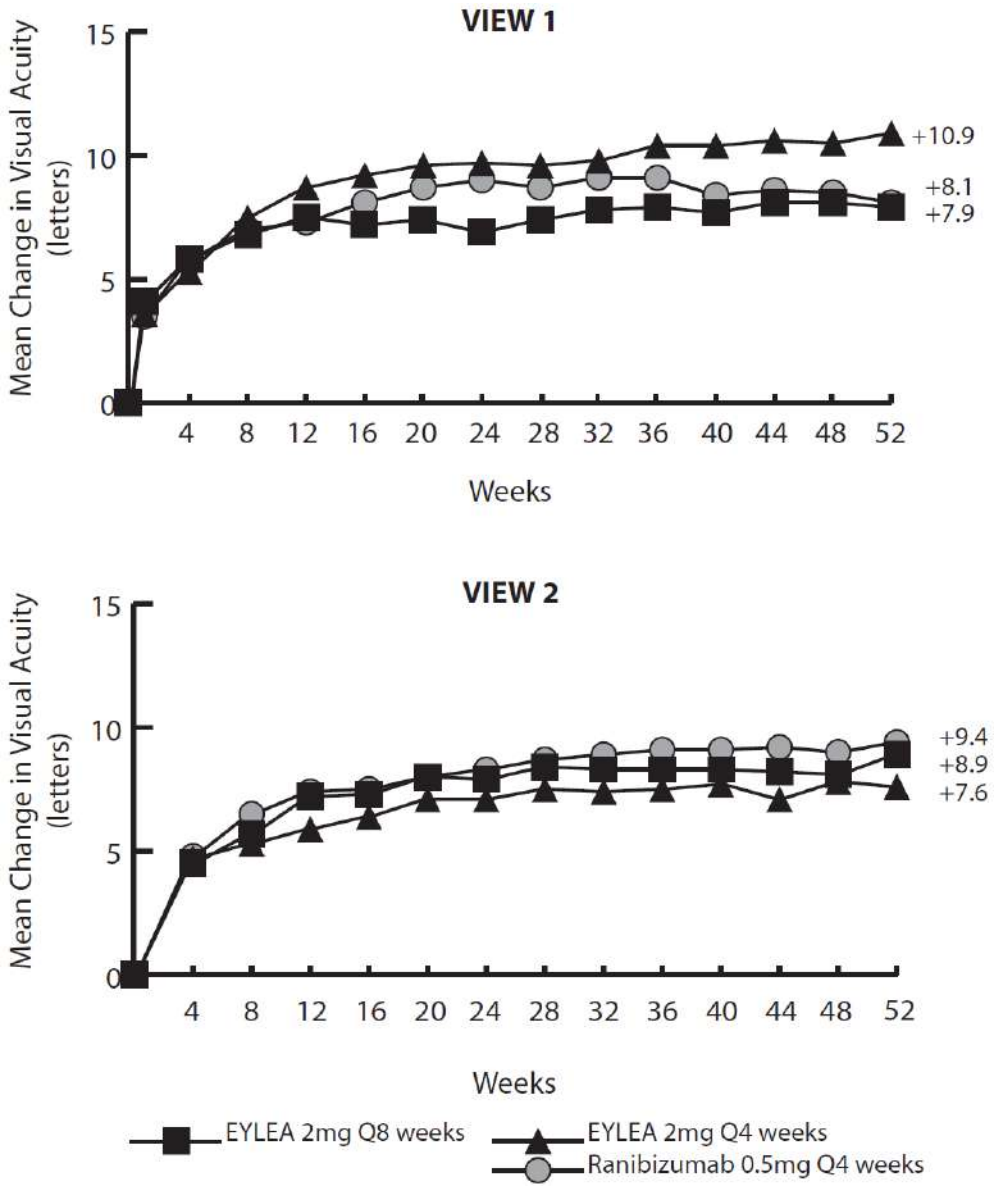
	VIEW1			VIEW2		
	EYLEA 2 mg Q8 weeks [a]	EYLEA 2 mg Q4 weeks	ranibizumab 0.5 mg Q4 weeks	EYLEA 2 mg Q8 weeks [a]	EYLEA 2 mg Q4 weeks	ranibizumab 0.5 mg Q4 weeks
Full Analysis Set	N=301	N=304	N=304	N=306	N=309	N=291
Efficacy Outcomes						
Proportion of patients who maintained visual acuity (%) (<15 letters of BCVA loss)	94%	95%	94%	95%	95%	95%
Difference[b] (%) (95.1% CI)	0.6 (-3.2, 4.4)	1.3 (-2.4, 5.0)		0.6 (-2.9, 4.0)	-0.3 (-4.0, 3.3)	
Mean change in BCVA as measured by ETDRS letter score from Baseline	7.9	10.9	8.1	8.9	7.6	9.4
Difference[b] in LS mean (95.1% CI)	0.3 (-2.0, 2.5)	3.2 (0.9, 5.4)		-0.9 (-3.1, 1.3)	-2.0 (-4.1, 0.2)	
Number of patients who gained at least 15 letters of vision from Baseline (%)	92 (31%)	114 (38%)	94 (31%)	96 (31%)	91 (29%)	99 (34%)
Difference[b] (%) (95.1% CI)	-0.4 (-7.7, 7.0)	6.6 (-1.0, 14.1)		-2.6 (-10.2, 4.9)	-4.6 (-12.1, 2.9)	

BCVA = Best Corrected Visual Acuity; CI = Confidence Interval; ETDRS = Early Treatment Diabetic Retinopathy Study; LOCF = Last Observation Carried Forward (baseline values are not carried forward); 95.1% confidence intervals were presented to adjust for safety assessment conducted during the study.

PGR2026-00039
Biocon Ex.1065
Page 188 of 595

[a] After treatment initiation with 3 monthly doses
[b] EYLEA group minus the ranibizumab group

Figure 8: Mean Change in Visual Acuity from Baseline to Week 52 in VIEW1 and VIEW2 Studies



14.2 Macular Edema Following Central Retinal Vein Occlusion (CRVO)

The safety and efficacy of EYLEA were assessed in two randomized, multi-center, double-masked, sham-controlled studies in patients with macular edema following CRVO. A total of 358 patients were treated and evaluable for efficacy (217 with EYLEA) in the two studies

(COPERNICUS and GALILEO). In both studies, patients were randomly assigned in a 3:2 ratio to either 2 mg EYLEA administered every 4 weeks (2Q4), or sham injections (control group) administered every 4 weeks for a total of 6 injections. Patient ages ranged from 22 to 89 years with a mean of 64 years.

In both studies, the primary efficacy endpoint was the proportion of patients who gained at least 15 letters in BCVA compared to baseline. At week 24, the EYLEA 2 mg Q4 group was superior to the control group for the primary endpoint.

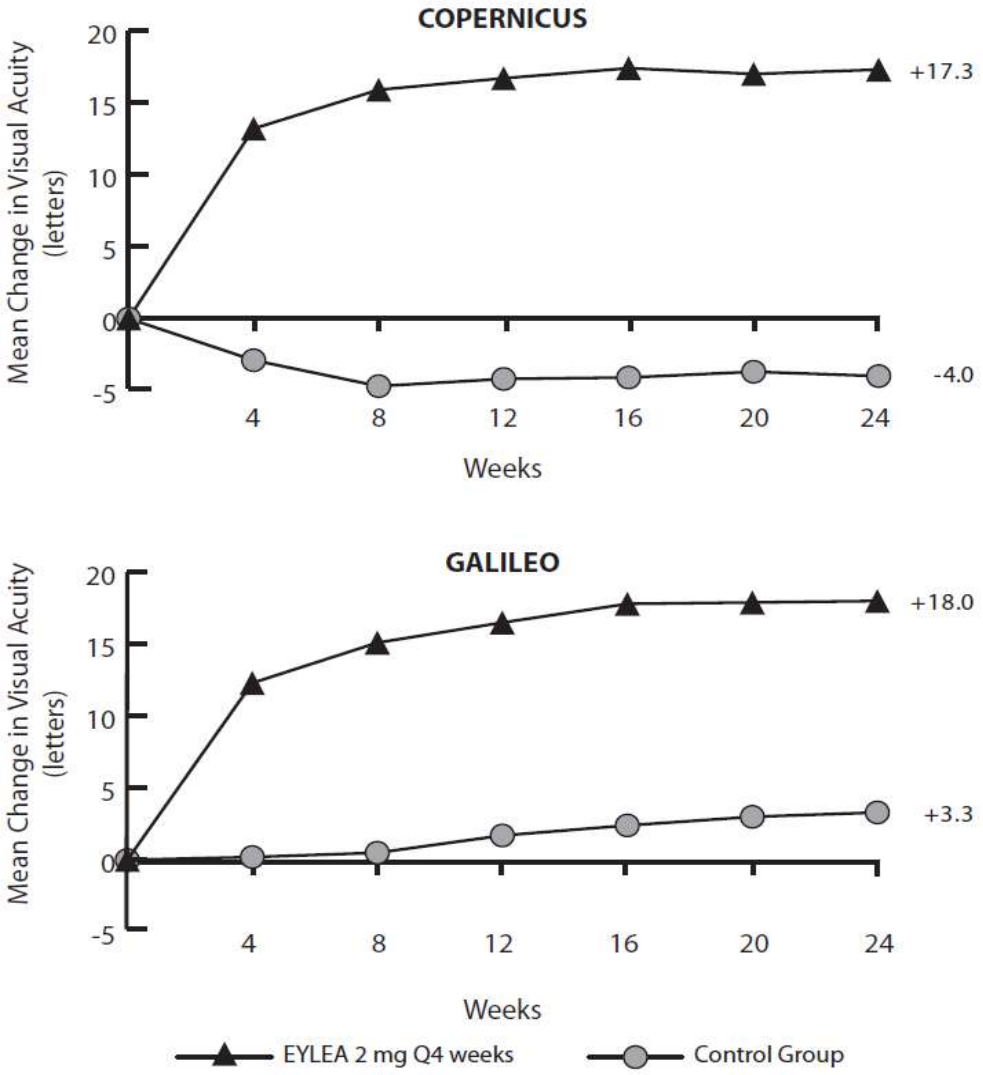
Results from the analysis of the COPERNICUS and GALILEO studies are shown in Table 4 and Figure 9 below.

Table 4: Efficacy Outcomes at Week 24 (Full Analysis Set with LOCF) in COPERNICUS and GALILEO Studies

	COPERNICUS		GALILEO	
	Control	EYLEA 2 mg Q4 weeks	Control	EYLEA 2 mg Q4 weeks
	N=73	N=114	N=68	N=103
Efficacy Outcomes				
Proportion of patients who gained at least 15 letters in BCVA from Baseline (%)	12%	56%	22%	60%
Weighted Difference [a,b] (%) (95.1% CI)		44.8%[c] (32.9, 56.6)		38.3%[c] (24.4, 52.1)
Mean change in BCVA as measured by ETDRS letter score from Baseline (SD)	-4.0 (18.0)	17.3 (12.8)	3.3 (14.1)	18.0 (12.2)
Difference in LS mean [a,d] (95.1% CI)		21.7[c] (17.3, 26.1)		14.7[c] (10.7, 18.7)

[a] Difference is EYLEA 2 mg Q4 weeks minus Control
[b] Difference and CI are calculated using Cochran-Mantel-Haenszel (CMH) test adjusted for baseline factors; 95.1% confidence intervals were presented to adjust for the multiple assessments conducted during the study.
[c] $p<0.01$ compared with control
[d] LS mean and CI based on an ANCOVA model

Figure 9: Mean Change in BCVA as Measured by ETDRS Letter Score from Baseline to Week 24 in COPERNICUS and GALILEO Studies



Treatment effects in evaluable subgroups (e.g., age, gender, race, baseline visual acuity, retinal perfusion status, and CRVO duration) in each study and in the combined analysis were in general consistent with the results in the overall populations.

16 HOW SUPPLIED/STORAGE AND HANDLING

Each Vial is for single eye use only. EYLEA is supplied in the following presentation [*see Dosage and Administration (2.4) and (2.5)*].

NDC NUMBER	CARTON TYPE	CARTON CONTENTS
61755-005-02	Vial	one single-use, sterile, 3-mL, glass vial containing a 0.278 mL fill of 40 mg/mL EYLEA one 19-gauge x 1½-inch, 5-micron, filter needle for withdrawal of the vial contents one 30-gauge x ½-inch injection needle for intravitreal injection one 1-mL syringe for administration one package insert

Storage

EYLEA should be refrigerated at 2°C to 8ºC (36°F to 46ºF). Do Not Freeze. Do not use beyond the date stamped on the carton and container label. Protect from light. Store in the original carton until time of use.

17 PATIENT COUNSELING INFORMATION

In the days following EYLEA administration, patients are at risk of developing endophthalmitis or retinal detachment. If the eye becomes red, sensitive to light, painful, or develops a change in vision, the patient should seek immediate care from an ophthalmologist [*see Warnings and Precautions (5.1)*].

Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA and the associated eye examinations [*see Adverse Reactions (6)*]. Patients should be advised not to drive or use machinery until visual function has recovered sufficiently.

REGENERON

Manufactured by:

Regeneron Pharmaceuticals, Inc.

777 Old Saw Mill River Road

Tarrytown, NY 10591-6707

U.S. License Number 1760

EYLEA™ is a trademark of Regeneron Pharmaceuticals, Inc.

© 2012, Regeneron Pharmaceuticals, Inc.

All rights reserved.

V X.0

Issue Date: 9/2012

Initial U.S. Approval: 2011

Regeneron U.S. Patents 7,306,799; 7,531,173; 7,608,261; 7,070,959; 7,374,757; 7,374,758, and other pending patents

APPENDIX FDA06

https://web.archive.org/web/20170615000000*/http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/125387s043lbl.pdf September 13, 2025

INTERNET ARCHIVE WEB TEXTS VIDEO AUDIO SOFTWARE IMAGES SIGN UP | LOG IN UPLOAD Search

ABOUT BLOG PROJECTS HELP DONATE CONTACT JOBS VOLUNTEER PEOPLE

DONATE

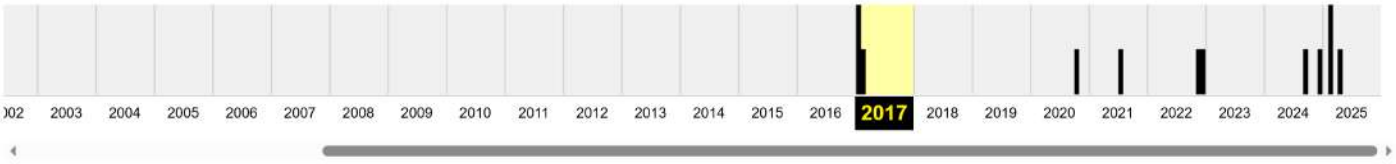
INTERNET ARCHIVE WaybackMachine

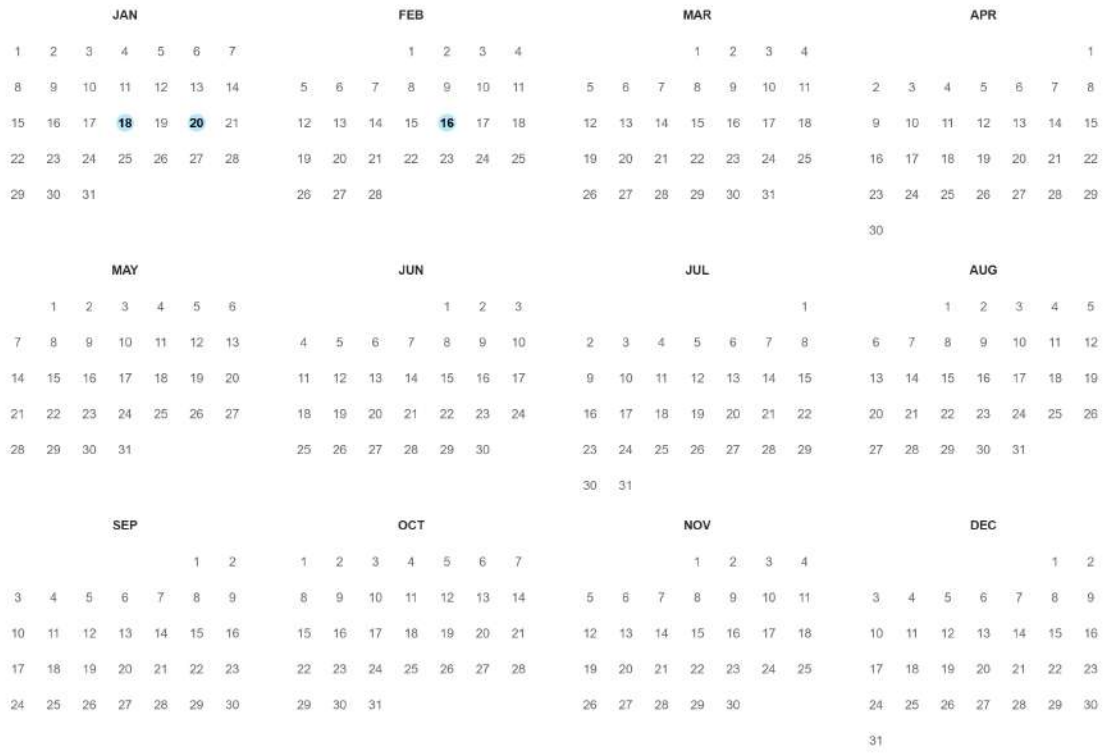
Explore more than 946 billion web pages saved over time

http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/1253

Calendar · Collections · Changes · Summary · Site Map · URLs

Saved **12 times** between January 18, 2017 and April 1, 2025.





Note

This calendar view maps the number of times **http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/125387s043lbl.pdf** was crawled by the Wayback Machine, *not* how many times the site was actually updated. More info in the FAQ.

FAQ | Contact Us | Terms of Service (Dec 31, 2014)

The Wayback Machine is an initiative of the Internet Archive, a 501(c)(3) non-profit, building a digital library of Internet sites and other cultural artifacts in digital form. Other projects include Open Library & archive-it.org.

Your use of the Wayback Machine is subject to the Internet Archive's Terms of Use.

https://web.archive.org/web/20170216202634/http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/125387s043lbl.pdf September 13, 2025

INTERNET ARCHIVE WayBack Machine http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/125387s043lbl.pdf Go JAN FEB OCT 16 2016 2017 2020 About this capture
12 captures 18 Jan 2017 - 1 Apr 2025

LABEL 1 / 25 100%



1



2



3

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use EYLEA safely and effectively. See full prescribing information for EYLEA.

EYLEA® (aflibercept) Injection
For Intravitreal Injection
Initial U.S. Approval: 2011

RECENT MAJOR CHANGES

- Indications and Usage, Macular Edema Following Retinal Vein Occlusion (RVO) (1.2) 10/2014
- Indications and Usage, Diabetic Macular Edema (DME) (1.3) 7/2014
- Dosage and Administration, Macular Edema Following Retinal Vein Occlusion (RVO) (2.3) 10/2014
- Dosage and Administration, Diabetic Macular Edema (DME) (2.4) 7/2014
- Dosage and Administration, Preparation for Administration (2.5) 1/2014
- Warnings and Precautions, Thromboembolic Events (5.3) 10/2014

INDICATIONS AND USAGE

EYLEA is indicated for the treatment of patients with:

- Neovascular (Wet) Age-Related Macular Degeneration (AMD) (1.1)
- Macular Edema Following Retinal Vein Occlusion (RVO) (1.2)
- Diabetic Macular Edema (DME) (1.3)

DOSAGE AND ADMINISTRATION

Neovascular (Wet) Age-Related Macular Degeneration (AMD)

- The recommended dose for EYLEA is 2 mg (0.05 mL) administered by

Diabetic Macular Edema (DME)

- The recommended dose for EYLEA is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). (2.4)
- Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated when EYLEA was dosed every 4 weeks compared to every 8 weeks. (2.4)

DOSAGE FORMS AND STRENGTHS

40 mg/mL solution for intravitreal injection in a single-use vial (3)

CONTRAINDICATIONS

- Ocular or periocular infection (4.1)
- Active intraocular inflammation (4.2)
- Hypersensitivity (4.3)

WARNINGS AND PRECAUTIONS

- Endophthalmitis and retinal detachments may occur following intravitreal injections. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately. (5.1)
- Increases in intraocular pressure have been seen within 60 minutes of an intravitreal injection. (5.2)
- There is a potential risk of arterial thromboembolic events following intravitreal use of VEGF inhibitors. (5.3)

ADVERSE REACTIONS

The most common adverse reactions (≥5%) reported in patients receiving

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use EYLEA safely and effectively. See full prescribing information for EYLEA.

EYLEA® (aflibercept) Injection
For Intravitreal Injection
Initial U.S. Approval: 2011

RECENT MAJOR CHANGES

- Indications and Usage, Macular Edema Following Retinal Vein Occlusion (RVO) (1.2) 10/2014
- Indications and Usage, Diabetic Macular Edema (DME) (1.3) 7/2014
- Dosage and Administration, Macular Edema Following Retinal Vein Occlusion (RVO) (2.3) 10/2014
- Dosage and Administration, Diabetic Macular Edema (DME) (2.4) 7/2014
- Dosage and Administration, Preparation for Administration (2.5) 1/2014
- Warnings and Precautions, Thromboembolic Events (5.3) 10/2014

INDICATIONS AND USAGE

EYLEA is indicated for the treatment of patients with:

- Neovascular (Wet) Age-Related Macular Degeneration (AMD) (1.1)
- Macular Edema Following Retinal Vein Occlusion (RVO) (1.2)
- Diabetic Macular Edema (DME) (1.3)

DOSAGE AND ADMINISTRATION

Neovascular (Wet) Age-Related Macular Degeneration (AMD)

- The recommended dose for EYLEA is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (monthly) for the first 3 months, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). (2.2)
- Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated when EYLEA was dosed every 4 weeks compared to every 8 weeks. (2.2)

Macular Edema Following Retinal Vein Occlusion (RVO)

- The recommended dose for EYLEA is 2 mg (0.05 mL) administered by intravitreal injection once every 4 weeks (monthly). (2.3)

Diabetic Macular Edema (DME)

- The recommended dose for EYLEA is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). (2.4)
- Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated when EYLEA was dosed every 4 weeks compared to every 8 weeks. (2.4)

DOSAGE FORMS AND STRENGTHS

40 mg/mL solution for intravitreal injection in a single-use vial (3)

CONTRAINDICATIONS

- Ocular or periocular infection (4.1)
- Active intraocular inflammation (4.2)
- Hypersensitivity (4.3)

WARNINGS AND PRECAUTIONS

- Endophthalmitis and retinal detachments may occur following intravitreal injections. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately. (5.1)
- Increases in intraocular pressure have been seen within 60 minutes of an intravitreal injection. (5.2)
- There is a potential risk of arterial thromboembolic events following intravitreal use of VEGF inhibitors. (5.3)

ADVERSE REACTIONS

The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous floaters, intraocular pressure increased, and vitreous detachment. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Regeneron at 1-855-395-3248 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

See 17 for PATIENT COUNSELING INFORMATION

Revised: 10/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
1.1 Neovascular (Wet) Age-Related Macular Degeneration (AMD)
1.2 Macular Edema Following Retinal Vein Occlusion (RVO)
1.3 Diabetic Macular Edema (DME)
2 DOSAGE AND ADMINISTRATION
2.1 Important Injection Instructions
2.2 Neovascular (Wet) Age-Related Macular Degeneration (AMD)
2.3 Macular Edema Following Retinal Vein Occlusion (RVO)
2.4 Diabetic Macular Edema (DME)
2.5 Preparation for Administration
2.6 Injection Procedure
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
4.1 Ocular or Periocular Infections
4.2 Active Intraocular Inflammation
4.3 Hypersensitivity
5 WARNINGS AND PRECAUTIONS
5.1 Endophthalmitis and Retinal Detachments
5.2 Increase in Intraocular Pressure
5.3 Thromboembolic Events
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Immunogenicity
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
14.1 Neovascular (Wet) Age-Related Macular Degeneration (AMD)
14.2 Macular Edema Following Central Retinal Vein Occlusion (CRVO)
14.3 Macular Edema Following Branch Retinal Vein Occlusion (BRVO)
14.4 Diabetic Macular Edema (DME)
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

***Sections or subsections omitted from the full prescribing information are not listed**

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

EYLEA is indicated for the treatment of patients with:

1.1 Neovascular (Wet) Age-Related Macular Degeneration (AMD)

1.2 Macular Edema Following Retinal Vein Occlusion (RVO)

1.3 Diabetic Macular Edema (DME)

2 DOSAGE AND ADMINISTRATION

2.1 Important Injection Instructions

For ophthalmic intravitreal injection. EYLEA must only be administered by a qualified physician.

2.2 Neovascular (Wet) Age-Related Macular Degeneration (AMD)

The recommended dose for EYLEA is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (monthly) for the first 12 weeks (3 months), followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated when EYLEA was dosed every 4 weeks compared to every 8 weeks [*see Clinical Studies (14.1)*].

2.3 Macular Edema Following Retinal Vein Occlusion (RVO)

The recommended dose for EYLEA is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection once every 4 weeks (monthly) [*see Clinical Studies (14.2), (14.3)*].

2.4 Diabetic Macular Edema (DME)

The recommended dose for EYLEA is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (monthly) for the first 5 injections, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated when EYLEA was dosed every 4 weeks compared to every 8 weeks [*see Clinical Studies (14.4)*].

2.5 Preparation for Administration

EYLEA should be inspected visually prior to administration. If particulates, cloudiness, or discoloration are visible, the vial must not be used.

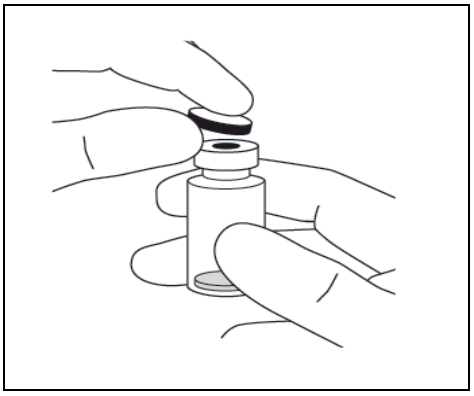
Using aseptic technique, the intravitreal injection should be performed with a 30-gauge x ½-inch injection needle.

Vial

The glass vial is for single use only.

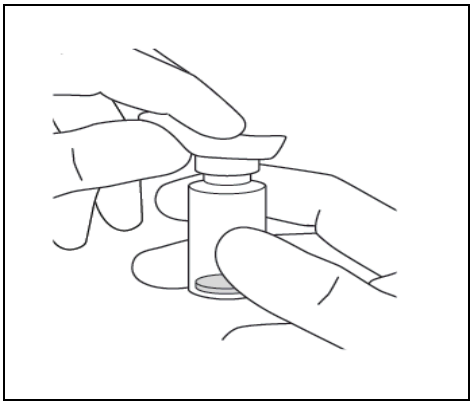
1. Remove the protective plastic cap from the vial (see Figure 1).

Figure 1:



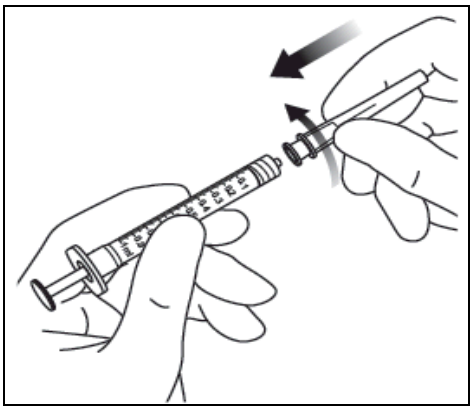
2. Clean the top of the vial with an alcohol wipe (see Figure 2).

Figure 2:



3. Remove the 19-gauge x 1½-inch, 5-micron, filter needle from its pouch and remove the 1-mL syringe supplied in the carton from its pouch. Attach the filter needle to the syringe by twisting it onto the Luer lock syringe tip (see Figure 3).

Figure 3:



4. Push the filter needle into the center of the vial stopper until the needle is completely inserted into the vial and the tip touches the bottom or bottom edge of the vial.

5. Using aseptic technique withdraw all of the EYLEA vial contents into the syringe, keeping the vial in an upright position, slightly inclined to ease complete withdrawal. To deter the introduction of air, ensure the bevel of the filter needle is submerged into the liquid. Continue to tilt the vial during withdrawal keeping the bevel of the filter needle submerged in the liquid (see Figures 4a and 4b).

Figure 4a:

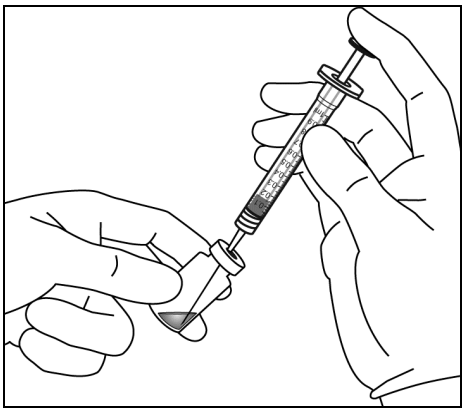
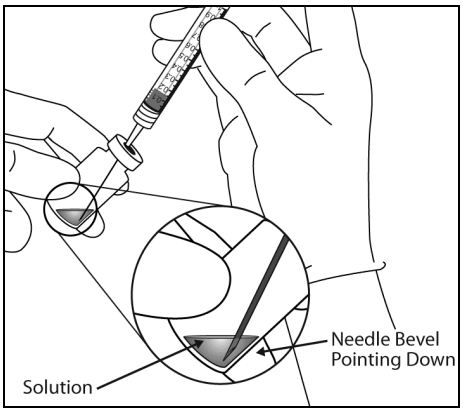


Figure 4b:



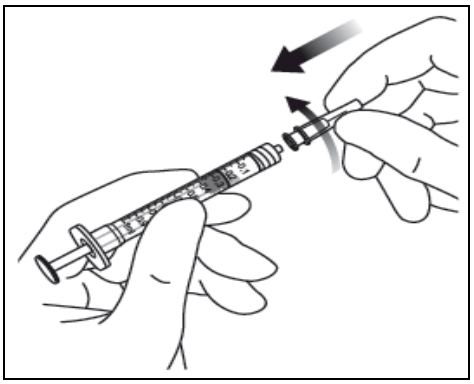
6. Ensure that the plunger rod is drawn sufficiently back when emptying the vial in order to completely empty the filter needle.

7. Remove the filter needle from the syringe and properly dispose of the filter needle.
Note: Filter needle is **not** to be used for intravitreal injection.

PGR2026-00039
Biocon Ex.1065
Page 200 of 595

8. Remove the 30-gauge x ½-inch injection needle from the plastic pouch and attach the injection needle to the syringe by firmly twisting the injection needle onto the Luer lock syringe tip (see Figure 5).

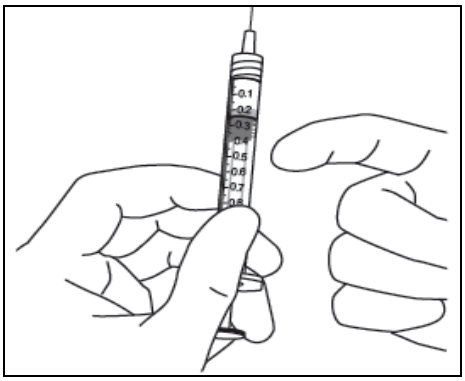
Figure 5:



9. When ready to administer EYLEA, remove the plastic needle shield from the needle.

10. Holding the syringe with the needle pointing up, check the syringe for bubbles. If there are bubbles, gently tap the syringe with your finger until the bubbles rise to the top (see Figure 6).

Figure 6:



11. To eliminate all of the bubbles and to expel excess drug, SLOWLY depress the plunger so that the plunger tip aligns with the line that marks 0.05 mL on the syringe (see Figures 7a and 7b).

Figure 7a:

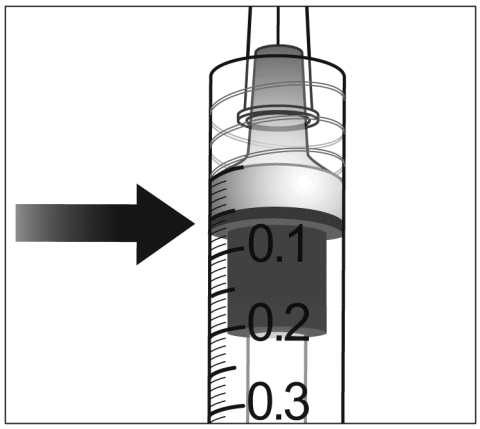
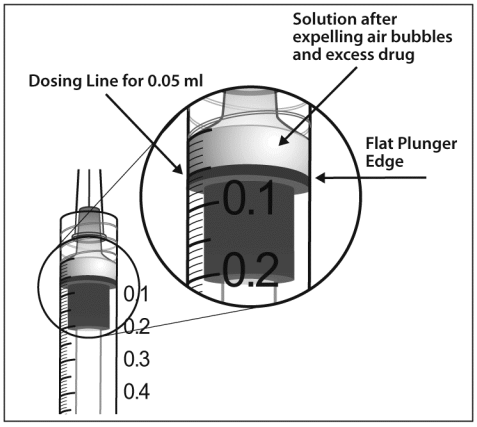


Figure 7b:



2.6 Injection Procedure

The intravitreal injection procedure should be carried out under controlled aseptic conditions, which include surgical hand disinfection and the use of sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent). Adequate anesthesia and a topical broad–spectrum microbicide should be given prior to the injection.

Immediately following the intravitreal injection, patients should be monitored for elevation in intraocular pressure. Appropriate monitoring may consist of a check for perfusion of the optic nerve head or tonometry. If required, a sterile paracentesis needle should be available.

Following intravitreal injection, patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment (e.g., eye pain, redness of the eye, photophobia, blurring of vision) without delay [*see Patient Counseling Information (17)*].

Each vial should only be used for the treatment of a single eye. If the contralateral eye requires treatment, a new vial should be used and the sterile field, syringe, gloves, drapes, eyelid speculum, filter, and injection needles should be changed before EYLEA is administered to the other eye.

After injection, any unused product must be discarded.

3 DOSAGE FORMS AND STRENGTHS

Single-use, glass vial designed to provide 0.05 mL of 40 mg/mL solution (2 mg) for intravitreal injection.

4 CONTRAINDICATIONS

4.1 Ocular or Periocular Infections

EYLEA is contraindicated in patients with ocular or periocular infections.

4.2 Active Intraocular Inflammation

EYLEA is contraindicated in patients with active intraocular inflammation.

4.3 Hypersensitivity

EYLEA is contraindicated in patients with known hypersensitivity to aflibercept or any of the excipients in EYLEA. Hypersensitivity reactions may manifest as severe intraocular inflammation.

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis and Retinal Detachments

Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments [*see Adverse Reactions (6.1)*]. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately [*see Dosage and Administration (2.6) and Patient Counseling Information (17)*].

5.2 Increase in Intraocular Pressure

Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA [*see Adverse Reactions (6.1)*]. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with vascular endothelial growth factor (VEGF) inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately [*see Dosage and Administration (2.6)*].

5.3 Thromboembolic Events

There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA. The incidence in the DME studies during the first year was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in the *Warnings and Precautions (5)* section of the labeling:

- Endophthalmitis and retinal detachments
- Increased intraocular pressure
- Thromboembolic events

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in other clinical trials of the same or another drug and may not reflect the rates observed in practice.

A total of 2711 patients treated with EYLEA constituted the safety population in seven phase 3 studies. Among those, 2110 patients were treated with the recommended dose of 2 mg. Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment. The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous floaters, intraocular pressure increased, and vitreous detachment.

Neovascular (Wet) Age-Related Macular Degeneration (AMD)

The data described below reflect exposure to EYLEA in 1824 patients with wet AMD, including 1223 patients treated with the 2-mg dose, in 2 double-masked, active-controlled clinical studies (VIEW1 and VIEW2) for 12 months [*see Clinical Studies (14.1)*].

Table 1: Most Common Adverse Reactions (≥1%) in Wet AMD Studies

Adverse Reactions	**EYLEA (N=1824)**	**Active Control (ranibizumab) (N=595)**
Conjunctival hemorrhage	25%	28%
Eye pain	9%	9%
Cataract	7%	7%
Vitreous detachment	6%	6%
Vitreous floaters	6%	7%
Intraocular pressure increased	5%	7%
Conjunctival hyperemia	4%	8%
Corneal erosion	4%	5%

Adverse Reactions	EYLEA (N=1824)	Active Control (ranibizumab) (N=595)
Detachment of the retinal pigment epithelium	3%	3%
Injection site pain	3%	3%
Foreign body sensation in eyes	3%	4%
Lacrimation increased	3%	1%
Vision blurred	2%	2%
Intraocular inflammation	2%	3%
Retinal pigment epithelium tear	2%	1%
Injection site hemorrhage	1%	2%
Eyelid edema	1%	2%
Corneal edema	1%	1%

Less common serious adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, retinal detachment, retinal tear, and endophthalmitis.

Macular Edema Following Retinal Vein Occlusion (RVO)

The data described below reflect 6 months exposure to EYLEA with a monthly 2 mg dose in 218 patients following CRVO in 2 clinical studies (COPERNICUS and GALILEO) and 91 patients following BRVO in one clinical study (VIBRANT) [*see Clinical Studies (14.2), (14.3)*].

Table 2: Most Common Adverse Reactions (≥1%) in RVO Studies

Adverse Reactions	CRVO		BRVO	
	EYLEA (N=218)	Control (N=142)	EYLEA (N=91)	Control (N=92)
Eye pain	13%	5%	4%	5%
Conjunctival hemorrhage	12%	11%	20%	4%
Intraocular pressure increased	8%	6%	2%	0%
Corneal epithelium defect	5%	4%	2%	0%
Vitreous floaters	5%	1%	1%	0%
Ocular hyperemia	5%	3%	2%	2%
Foreign body sensation in eyes	3%	5%	3%	0%
Vitreous detachment	3%	4%	2%	0%
Lacrimation increased	3%	4%	3%	0%

Adverse Reactions	CRVO		BRVO	
	EYLEA (N=218)	Control (N=142)	EYLEA (N=91)	Control (N=92)
Injection site pain	3%	1%	1%	0%
Vision blurred	1%	<1%	1%	1%
Intraocular inflammation	1%	1%	0%	0%
Cataract	<1%	1%	5%	0%
Eyelid edema	<1%	1%	1%	0%

Less common adverse reactions reported in <1% of the patients treated with EYLEA in the CRVO studies were corneal edema, retinal tear, hypersensitivity, and endophthalmitis.

Diabetic Macular Edema (DME)

The data described below reflect exposure to EYLEA in 578 patients with DME treated with the 2-mg dose in 2 double-masked, controlled clinical studies (VIVID and VISTA) for 52 weeks [*see Clinical Studies (14.4)*].

Table 3: Most Common Adverse Reactions (≥1%) in DME Studies

Adverse Reactions	EYLEA (N=578)	Control (N=287)
Conjunctival hemorrhage	28%	17%
Eye pain	9%	6%
Cataract	8%	9%
Vitreous floaters	6%	3%
Corneal erosion	5%	3%
Intraocular pressure increased	5%	3%
Conjunctival hyperemia	5%	6%
Vitreous detachment	3%	3%
Foreign body sensation in eyes	3%	3%
Lacrimation increased	3%	2%
Vision blurred	2%	2%
Intraocular inflammation	2%	<1%
Injection site pain	2%	<1%

Less common adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, eyelid edema, corneal edema, retinal detachment, injection site hemorrhage, and retinal tear.

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for an immune response in patients treated with EYLEA. The immunogenicity of EYLEA was evaluated in serum samples. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to EYLEA in immunoassays. The detection of an immune response is highly dependent on the sensitivity and specificity of the assays used, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to EYLEA with the incidence of antibodies to other products may be misleading.

In the wet AMD, RVO, and DME studies, the pre-treatment incidence of immunoreactivity to EYLEA was approximately 1% to 3% across treatment groups. After dosing with EYLEA for 24-52 weeks, antibodies to EYLEA were detected in a similar percentage range of patients. There were no differences in efficacy or safety between patients with or without immunoreactivity.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. Aflibercept produced embryo-fetal toxicity when administered every three days during organogenesis to pregnant rabbits at intravenous doses ≥3 mg per kg, or every six days at subcutaneous doses ≥0.1 mg per kg. Adverse embryo-fetal effects included increased incidences of postimplantation loss and fetal malformations, including anasarca, umbilical hernia, diaphragmatic hernia, gastroschisis, cleft palate, ectrodactyly, intestinal atresia, spina bifida, encephalomeningocele, heart and major vessel defects, and skeletal malformations (fused vertebrae, sternebrae, and ribs; supernumerary vertebral arches and ribs; and incomplete ossification). The maternal No Observed Adverse Effect Level (NOAEL) in these studies was 3 mg per kg. Aflibercept produced fetal malformations at all doses assessed in rabbits and the fetal NOAEL was less than 0.1 mg per kg. Administration of the lowest dose assessed in rabbits (0.1 mg per kg) resulted in systemic exposure (AUC) that was approximately 10 times the systemic exposure observed in humans after an intravitreal dose of 2 mg.

There are no adequate and well-controlled studies in pregnant women. EYLEA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.3 Nursing Mothers

It is unknown whether aflibercept is excreted in human milk. Because many drugs are excreted in human milk, a risk to the breastfed child cannot be excluded. EYLEA is not recommended

during breastfeeding. A decision must be made whether to discontinue nursing or to discontinue treatment with EYLEA, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and effectiveness of EYLEA in pediatric patients have not been established.

8.5 Geriatric Use

In the clinical studies, approximately 76% (2049/2701) of patients randomized to treatment with EYLEA were ≥65 years of age and approximately 46% (1250/2701) were ≥75 years of age. No significant differences in efficacy or safety were seen with increasing age in these studies.

11 DESCRIPTION

EYLEA (aflibercept) is a recombinant fusion protein consisting of portions of human VEGF receptors 1 and 2 extracellular domains fused to the Fc portion of human IgG1 formulated as an iso-osmotic solution for intravitreal administration. Aflibercept is a dimeric glycoprotein with a protein molecular weight of 97 kilodaltons (kDa) and contains glycosylation, constituting an additional 15% of the total molecular mass, resulting in a total molecular weight of 115 kDa. Aflibercept is produced in recombinant Chinese hamster ovary (CHO) cells.

EYLEA is a sterile, clear, and colorless to pale yellow solution. EYLEA is supplied as a preservative-free, sterile, aqueous solution in a single-use, glass vial designed to deliver 0.05 mL (50 microliters) of EYLEA (40 mg/mL in 10 mM sodium phosphate, 40 mM sodium chloride, 0.03% polysorbate 20, and 5% sucrose, pH 6.2).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Vascular endothelial growth factor-A (VEGF-A) and placental growth factor (PlGF) are members of the VEGF family of angiogenic factors that can act as mitogenic, chemotactic, and vascular permeability factors for endothelial cells. VEGF acts via two receptor tyrosine kinases, VEGFR-1 and VEGFR-2, present on the surface of endothelial cells. PlGF binds only to VEGFR-1, which is also present on the surface of leucocytes. Activation of these receptors by VEGF-A can result in neovascularization and vascular permeability.

Aflibercept acts as a soluble decoy receptor that binds VEGF-A and PlGF, and thereby can inhibit the binding and activation of these cognate VEGF receptors.

12.2 Pharmacodynamics

Neovascular (Wet) Age-Related Macular Degeneration (AMD)

In the clinical studies anatomic measures of disease activity improved similarly in all treatment groups from baseline to week 52. Anatomic data were not used to influence treatment decisions [*see Clinical Studies (14.1)*].

Macular Edema Following Retinal Vein Occlusion (RVO)

Reductions in mean retinal thickness were observed in COPERNICUS, GALILEO, and VIBRANT at week 24 compared to baseline. Anatomic data were not used to influence treatment decisions [*see Clinical Studies (14.2), (14.3)*].

Diabetic Macular Edema (DME)

Reductions in mean retinal thickness were observed in VIVID and VISTA at week 52 compared to baseline. Anatomic data were not used to influence EYLEA treatment decisions [*see Clinical Studies (14.4)*].

12.3 Pharmacokinetics

EYLEA is administered intravitreally to exert local effects in the eye. In patients with wet AMD, RVO, or DME, following intravitreal administration of EYLEA, a fraction of the administered dose is expected to bind with endogenous VEGF in the eye to form an inactive aflibercept: VEGF complex. Once absorbed into the systemic circulation, aflibercept presents in the plasma as free aflibercept (unbound to VEGF) and a more predominant stable inactive form with circulating endogenous VEGF (i.e., aflibercept: VEGF complex).

Absorption/Distribution

Following intravitreal administration of 2 mg per eye of EYLEA to patients with wet AMD, RVO, and DME, the mean C_{max} of free aflibercept in the plasma was 0.02 mcg/mL (range: 0 to 0.054 mcg/mL), 0.05 mcg/mL (range: 0 to 0.081 mcg/mL), and 0.03 mcg/mL (range: 0 to 0.076 mcg/mL), respectively and was attained in 1 to 3 days. The free aflibercept plasma concentrations were undetectable two weeks post-dosing in all patients. Aflibercept did not accumulate in plasma when administered as repeated doses intravitreally every 4 weeks. It is estimated that after intravitreal administration of 2 mg to patients, the mean maximum plasma concentration of free aflibercept is more than 100 fold lower than the concentration of aflibercept required to half-maximally bind systemic VEGF.

The volume of distribution of free aflibercept following intravenous (I.V.) administration of aflibercept has been determined to be approximately 6L.

Metabolism/Elimination

Aflibercept is a therapeutic protein and no drug metabolism studies have been conducted. Aflibercept is expected to undergo elimination through both target-mediated disposition via

binding to free endogenous VEGF and metabolism via proteolysis. The terminal elimination half-life (t1/2) of free aflibercept in plasma was approximately 5 to 6 days after I.V. administration of doses of 2 to 4 mg/kg aflibercept.

Specific Populations

Renal Impairment

Pharmacokinetic analysis of a subgroup of patients (n=492) in one wet AMD study, of which 43% had renal impairment (mild n=120, moderate n=74, and severe n=16), revealed no differences with respect to plasma concentrations of free aflibercept after intravitreal administration every 4 or 8 weeks. Similar results were seen in patients in a RVO study and in patients in a DME study. No dose adjustment based on renal impairment status is needed for either wet AMD, RVO, or DME patients.

Other

No special dosage modification is required for any of the populations that have been studied (e.g., gender, elderly).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been conducted on the mutagenic or carcinogenic potential of aflibercept. Effects on male and female fertility were assessed as part of a 6-month study in monkeys with intravenous administration of aflibercept at weekly doses ranging from 3 to 30 mg per kg. Absent or irregular menses associated with alterations in female reproductive hormone levels and changes in sperm morphology and motility were observed at all dose levels. In addition, females showed decreased ovarian and uterine weight accompanied by compromised luteal development and reduction of maturing follicles. These changes correlated with uterine and vaginal atrophy. A No Observed Adverse Effect Level (NOAEL) was not identified. Intravenous administration of the lowest dose of aflibercept assessed in monkeys (3 mg per kg) resulted in systemic exposure (AUC) that was approximately 1500 times higher than the systemic exposure observed in humans after an intravitreal dose of 2 mg. All changes were reversible within 20 weeks after cessation of treatment.

13.2 Animal Toxicology and/or Pharmacology

Erosions and ulcerations of the respiratory epithelium in nasal turbinates in monkeys treated with aflibercept intravitreally were observed at intravitreal doses of 2 or 4 mg per eye. At the NOAEL of 0.5 mg per eye in monkeys, the systemic exposure (AUC) was 56 times higher than the exposure observed in humans after an intravitreal dose of 2 mg. Similar effects were not seen in clinical studies [*see Clinical Studies (14)*].

14 CLINICAL STUDIES

14.1 Neovascular (Wet) Age-Related Macular Degeneration (AMD)

The safety and efficacy of EYLEA were assessed in two randomized, multi-center, double-masked, active-controlled studies in patients with wet AMD. A total of 2412 patients were treated and evaluable for efficacy (1817 with EYLEA) in the two studies (VIEW1 and VIEW2). In each study, patients were randomly assigned in a 1:1:1:1 ratio to 1 of 4 dosing regimens: 1) EYLEA administered 2 mg every 8 weeks following 3 initial monthly doses (EYLEA 2Q8); 2) EYLEA administered 2 mg every 4 weeks (EYLEA 2Q4); 3) EYLEA 0.5 mg administered every 4 weeks (EYLEA 0.5Q4); and 4) ranibizumab administered 0.5 mg every 4 weeks (ranibizumab 0.5 mg Q4). Patient ages ranged from 49 to 99 years with a mean of 76 years.

In both studies, the primary efficacy endpoint was the proportion of patients who maintained vision, defined as losing fewer than 15 letters of visual acuity at week 52 compared to baseline. Data are available through week 52. Both EYLEA 2Q8 and EYLEA 2Q4 groups were shown to have efficacy that was clinically equivalent to the ranibizumab 0.5 mg Q4 group.

Detailed results from the analysis of the VIEW1 and VIEW2 studies are shown in Table 4 and Figure 8 below.

Table 4: Efficacy Outcomes at Week 52 (Full Analysis Set with LOCF) in VIEW1 and VIEW2 Studies

	VIEW1			VIEW2		
	EYLEA 2 mg Q8 weeks [a]	EYLEA 2 mg Q4 weeks	ranibizumab 0.5 mg Q4 weeks	EYLEA 2 mg Q8 weeks [a]	EYLEA 2 mg Q4 weeks	ranibizumab 0.5 mg Q4 weeks
Full Analysis Set	N=301	N=304	N=304	N=306	N=309	N=291
Efficacy Outcomes						
Proportion of patients who maintained visual acuity (%) (<15 letters of BCVA loss)	94%	95%	94%	95%	95%	95%
Difference[b] (%) (95.1% CI)	0.6 (-3.2, 4.4)	1.3 (-2.4, 5.0)		0.6 (-2.9, 4.0)	-0.3 (-4.0, 3.3)	
Mean change in BCVA as measured by ETDRS letter score from Baseline	7.9	10.9	8.1	8.9	7.6	9.4
Difference[b] in LS mean (95.1% CI)	0.3 (-2.0, 2.5)	3.2 (0.9, 5.4)		-0.9 (-3.1, 1.3)	-2.0 (-4.1, 0.2)	
Number of patients who gained at least 15 letters of vision from Baseline (%)	92 (31%)	114 (38%)	94 (31%)	96 (31%)	91 (29%)	99 (34%)
Difference[b] (%) (95.1% CI)	-0.4 (-7.7, 7.0)	6.6 (-1.0, 14.1)		-2.6 (-10.2, 4.9)	-4.6 (-12.1, 2.9)	

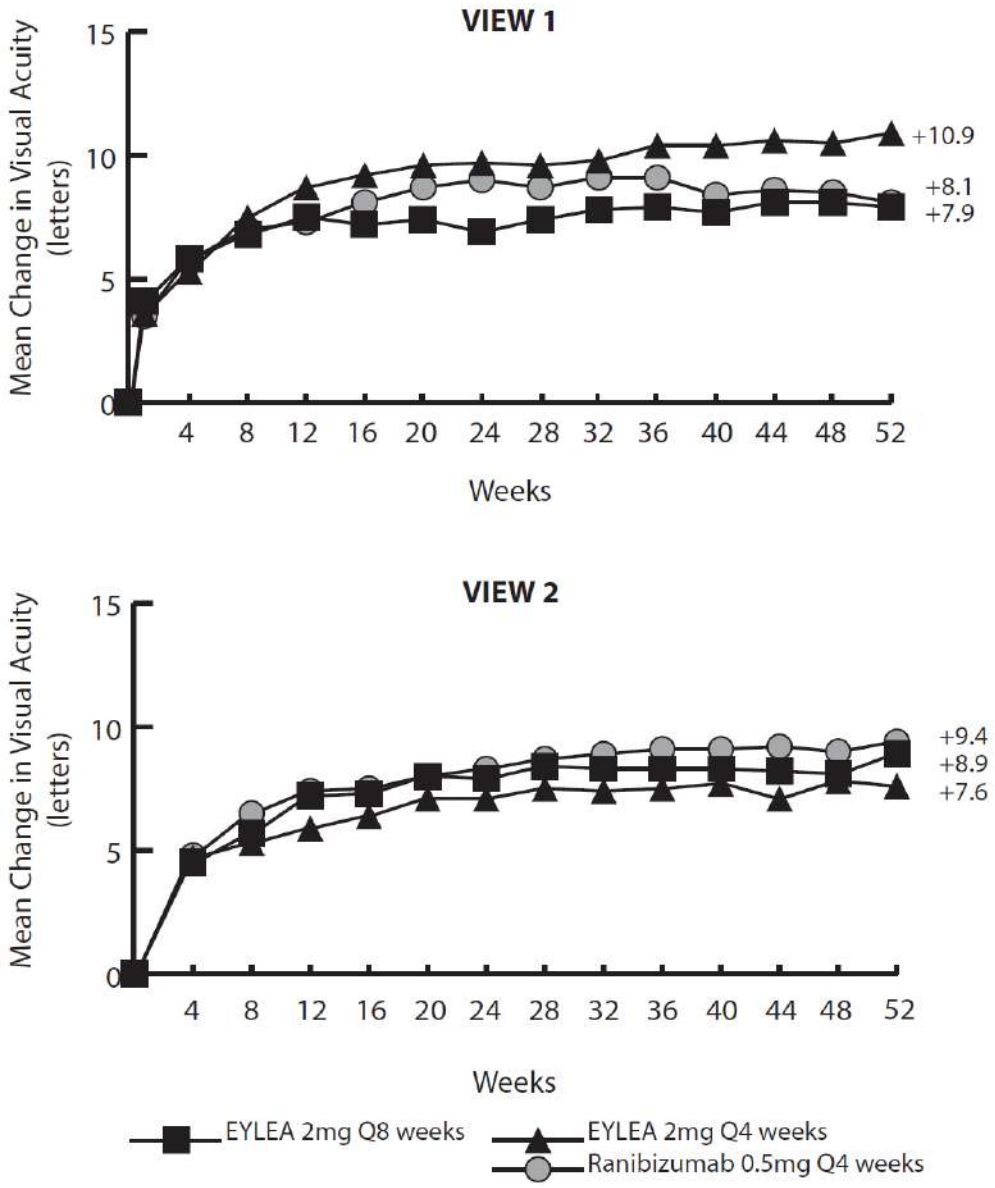
BCVA = Best Corrected Visual Acuity; CI = Confidence Interval; ETDRS = Early Treatment Diabetic Retinopathy Study; LOCF = Last Observation Carried Forward (baseline values are not carried forward); 95.1% confidence intervals were presented to adjust for safety assessment conducted during the study.

[a] After treatment initiation with 3 monthly doses

[b] EYLEA group minus the ranibizumab group

PGR2026-00039
Biocon Ex.1065
Page 212 of 595

Figure 8: Mean Change in Visual Acuity from Baseline to Week 52 in VIEW1 and VIEW2 Studies



14.2 Macular Edema Following Central Retinal Vein Occlusion (CRVO)

The safety and efficacy of EYLEA were assessed in two randomized, multi-center, double-masked, sham-controlled studies in patients with macular edema following CRVO. A total of 358 patients were treated and evaluable for efficacy (217 with EYLEA) in the two studies (COPERNICUS and GALILEO). In both studies, patients were randomly assigned in a 3:2 ratio to either 2 mg EYLEA administered every 4 weeks (2Q4), or sham injections (control group) administered every 4 weeks for a total of 6 injections. Patient ages ranged from 22 to 89 years with a mean of 64 years.

In both studies, the primary efficacy endpoint was the proportion of patients who gained at least 15 letters in BCVA compared to baseline. At week 24, the EYLEA 2 mg Q4 group was superior to the control group for the primary endpoint.

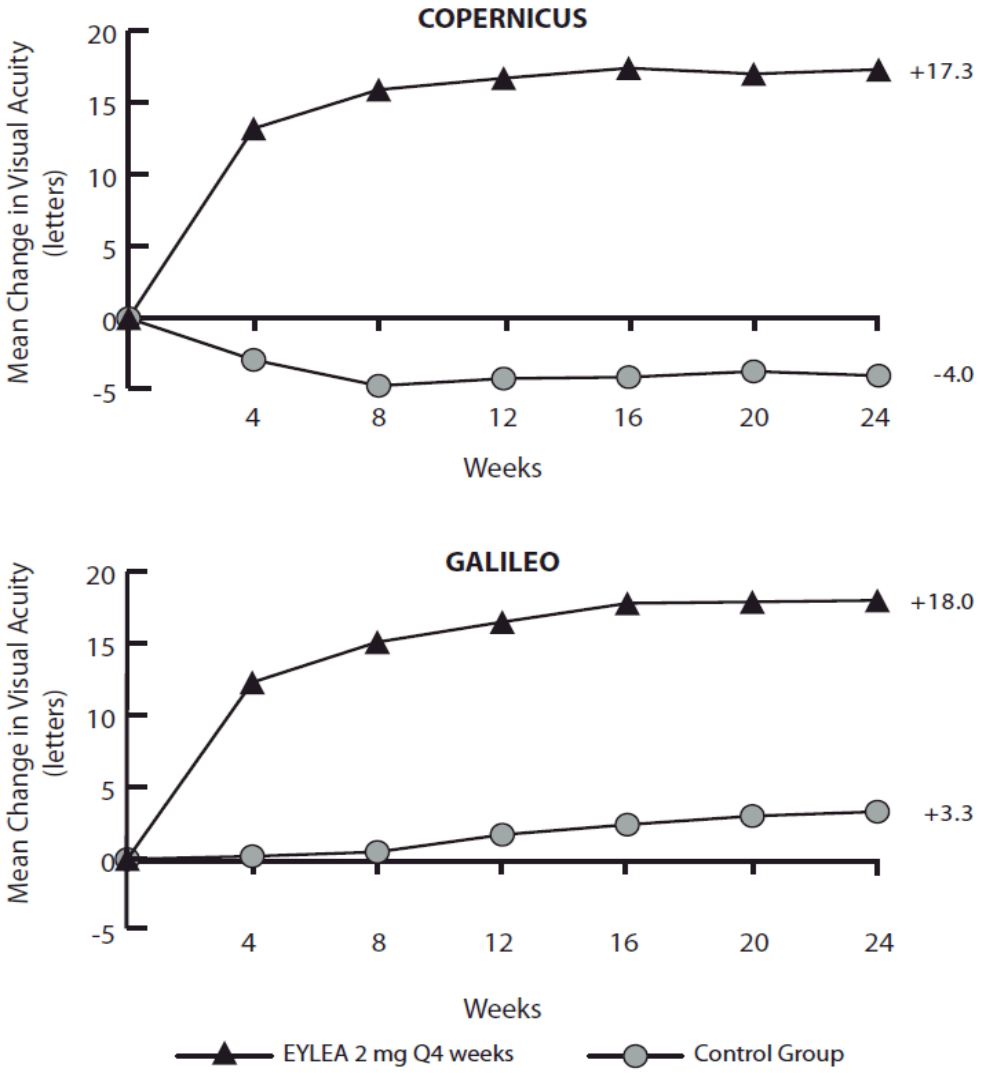
Results from the analysis of the COPERNICUS and GALILEO studies are shown in Table 5 and Figure 9 below.

Table 5: Efficacy Outcomes at Week 24 (Full Analysis Set with LOCF) in COPERNICUS and GALILEO Studies

	COPERNICUS		GALILEO	
	Control	EYLEA 2 mg Q4 weeks	Control	EYLEA 2 mg Q4 weeks
	N=73	N=114	N=68	N=103
Efficacy Outcomes				
Proportion of patients who gained at least 15 letters in BCVA from Baseline (%)	12%	56%	22%	60%
Weighted Difference [a,b] (%) (95.1% CI)		44.8%[c] (32.9, 56.6)		38.3%[c] (24.4, 52.1)
Mean change in BCVA as measured by ETDRS letter score from Baseline (SD)	-4.0 (18.0)	17.3 (12.8)	3.3 (14.1)	18.0 (12.2)
Difference in LS mean [a,d] (95.1% CI)		21.7[c] (17.3, 26.1)		14.7[c] (10.7, 18.7)

[a] Difference is EYLEA 2 mg Q4 weeks minus Control
[b] Difference and CI are calculated using Cochran-Mantel-Haenszel (CMH) test adjusted for baseline factors; 95.1% confidence intervals were presented to adjust for the multiple assessments conducted during the study.
[c] $p<0.01$ compared with control
[d] LS mean and CI based on an ANCOVA model

Figure 9: Mean Change in BCVA as Measured by ETDRS Letter Score from Baseline to Week 24 in COPERNICUS and GALILEO Studies



Treatment effects in evaluable subgroups (e.g., age, gender, race, baseline visual acuity, retinal perfusion status, and CRVO duration) in each study and in the combined analysis were in general consistent with the results in the overall populations.

14.3 Macular Edema Following Branch Retinal Vein Occlusion (BRVO)

The safety and efficacy of EYLEA were assessed in a 24-week, randomized, multi-center, double-masked, controlled study in patients with macular edema following BRVO. A total of 181 patients were treated and evaluable for efficacy (91 with EYLEA) in the VIBRANT study. In the study, patients were randomly assigned in a 1:1 ratio to either 2 mg EYLEA administered

every 4 weeks (2Q4) or laser photocoagulation administered at baseline and subsequently as needed (control group). Patient ages ranged from 42 to 94 years with a mean of 65 years.

In the VIBRANT study, the primary efficacy endpoint was the proportion of patients who gained at least 15 letters in BCVA at week 24 compared to baseline. At week 24, the EYLEA 2 mg Q4 group was superior to the control group for the primary endpoint.

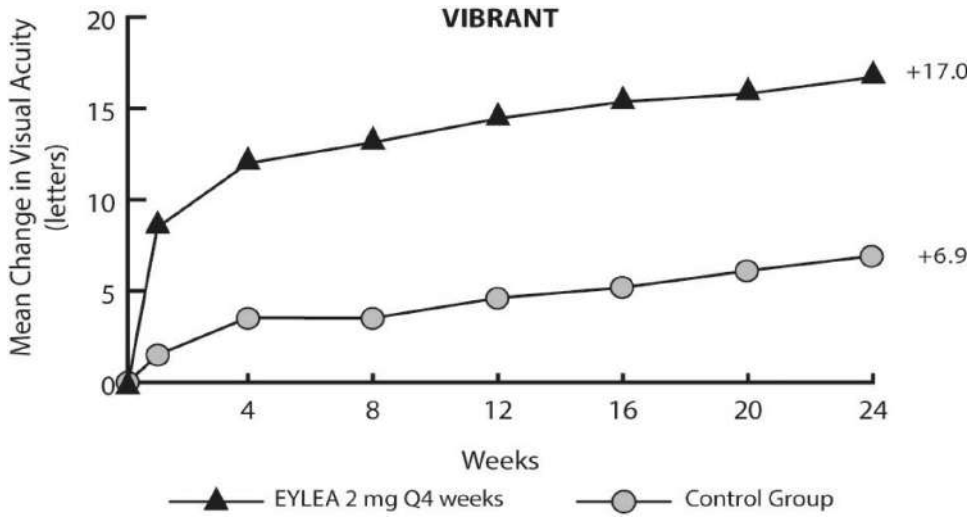
Detailed results from the analysis of the VIBRANT study are shown in Table 6 and Figure 10 below.

Table 6: Efficacy Outcomes at Week 24 (Full Analysis Set with LOCF) in VIBRANT Study

	VIBRANT	
	Control	EYLEA 2 mg Q4 weeks
	N=90	N=91
Efficacy Outcomes		
Proportion of patients who gained at least 15 letters in BCVA from Baseline (%)	26.7%	52.7%
Weighted Difference [a,b] (%) (95% CI)		26.6%[c] (13.0, 40.1)
Mean change in BCVA as measured by ETDRS letter score from Baseline (SD)	6.9 (12.9)	17.0 (11.9)
Difference in LS mean [a,d] (95% CI)		10.5[c] (7.1, 14.0)

[a] Difference is EYLEA 2 mg Q4 weeks minus Control
[b] Difference and CI are calculated using Mantel-Haenszel weighting scheme adjusted for region (North America vs. Japan) and baseline BCVA category (> 20/200 and ≤ 20/200)
[c] $p<0.01$ compared with Control
[d] LS mean and CI based on an ANCOVA model

Figure 10: Mean Change in BCVA as Measured by ETDRS Letter Score from Baseline to Week 24 in VIBRANT Study



Treatment effects in evaluable subgroups (e.g., age, gender, and baseline retinal perfusion status) in the study were in general consistent with the results in the overall populations.

14.4 Diabetic Macular Edema (DME)

The safety and efficacy of EYLEA were assessed in two randomized, multi-center, double-masked, controlled studies in patients with DME. A total of 862 randomized and treated patients were evaluable for efficacy. Patient ages ranged from 23 to 87 years with a mean of 63 years.

Of those, 576 were randomized to EYLEA groups in the two studies (VIVID and VISTA). In each study, patients were randomly assigned in a 1:1:1 ratio to 1 of 3 dosing regimens: 1) EYLEA administered 2 mg every 8 weeks following 5 initial monthly injections (EYLEA 2Q8); 2) EYLEA administered 2 mg every 4 weeks (EYLEA 2Q4); and 3) macular laser photocoagulation (at baseline and then as needed). Beginning at week 24, patients meeting a pre-specified threshold of vision loss were eligible to receive additional treatment: patients in the EYLEA groups could receive laser and patients in the laser group could receive EYLEA.

In both studies, the primary efficacy endpoint was the mean change from baseline in BCVA at week 52 as measured by ETDRS letter score. Efficacy of both EYLEA 2Q8 and EYLEA 2Q4 groups was statistically superior to the control group.

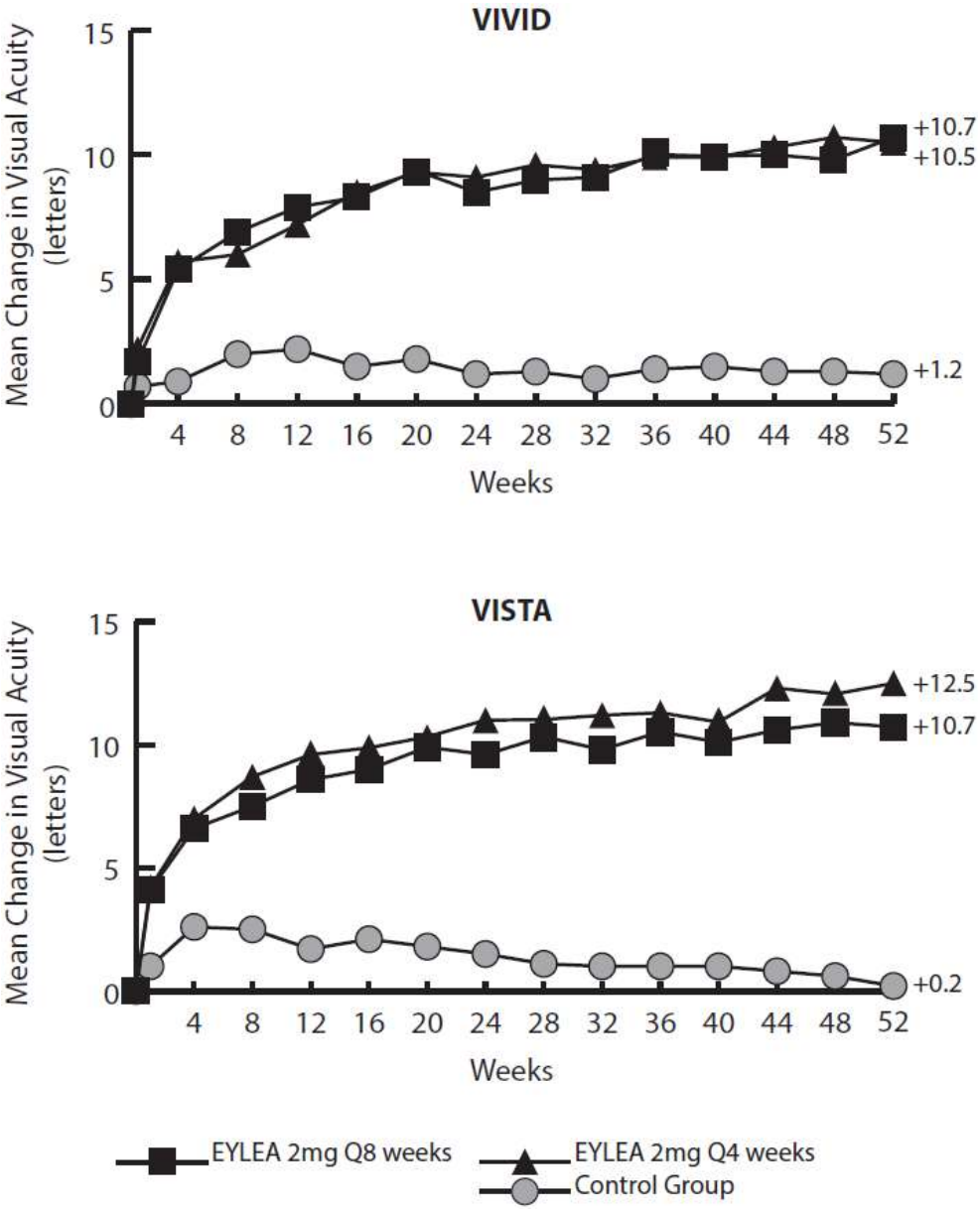
Results from the analysis of the VIVID and VISTA studies are shown in Table 7 and Figure 11 below.

Table 7: Efficacy Outcomes at Week 52 (Full Analysis Set with LOCF) in VIVID and VISTA Studies

	VIVID			VISTA		
	EYLEA 2 mg Q8 weeks [a]	EYLEA 2 mg Q4 weeks	Control	EYLEA 2 mg Q8 weeks [a]	EYLEA 2 mg Q4 weeks	Control
Full Analysis Set	N=135	N=136	N=132	N=151	N=154	N=154
Efficacy Outcomes						
Mean change in BCVA as measured by ETDRS letter score from Baseline (SD)	10.7 (9.3)	10.5 (9.6)	1.2 (10.6)	10.7 (8.2)	12.5 (9.5)	0.2 (12.5)
Difference[b, c] in LS mean (97.5% CI)	9.1[d] (6.3, 11.8)	9.3[d] (6.5, 12.0)		10.5[d] (7.7, 13.2)	12.2[d] (9.4, 15.0)	
Proportion of patients who gained at least 15 letters in BCVA from Baseline (%)	33.3%	32.4%	9.1%	31.1%	41.6%	7.8%
Adjusted Difference[c, e] (%) (97.5% CI)	24.2%[d] (13.5, 34.9)	23.3%[d] (12.6, 33.9)		23.3%[d] (13.5, 33.1)	34.2%[d] (24.1, 44.4)	

[a] After treatment initiation with 5 monthly injections
[b] LS mean and CI based on an ANCOVA model with baseline BCVA measurement as a covariate and a factor for treatment group. Additionally, protocol specified stratification factors were included in the model.
[c] Difference is EYLEA group minus control group
[d] p-value <0.01 compared with control
[e] Difference with confidence interval (CI) and statistical test is calculated using Mantel-Haenszel weighting scheme adjusted by protocol specified stratification factors.

Figure 11: Mean Change in BCVA as Measured by ETDRS Letter Score from Baseline to Week 52 in VIVID and VISTA Studies



Treatment effects in the subgroup of patients who had previously been treated with a VEGF inhibitor prior to study participation were similar to those seen in patients who were VEGF inhibitor naïve prior to study participation.

Treatment effects in evaluable subgroups (e.g., age, gender, race, baseline HbA1c, baseline visual acuity, prior anti-VEGF therapy) in each study were in general consistent with the results in the overall populations.

16 HOW SUPPLIED/STORAGE AND HANDLING

Each Vial is for single eye use only. EYLEA is supplied in the following presentation [*see Dosage and Administration (2.5) and (2.6)*].

NDC NUMBER	CARTON TYPE	CARTON CONTENTS
61755-005-02	Vial	one single-use, sterile, 3-mL, glass vial designed to deliver 0.05 mL of 40 mg/mL EYLEA one 19-gauge x 1½-inch, 5-micron, filter needle for withdrawal of the vial contents one 30-gauge x ½-inch injection needle for intravitreal injection one 1-mL syringe for administration one package insert

Storage

EYLEA should be refrigerated at 2°C to 8ºC (36°F to 46ºF). Do Not Freeze. Do not use beyond the date stamped on the carton and container label. Protect from light. Store in the original carton until time of use.

17 PATIENT COUNSELING INFORMATION

In the days following EYLEA administration, patients are at risk of developing endophthalmitis or retinal detachment. If the eye becomes red, sensitive to light, painful, or develops a change in vision, advise patients to seek immediate care from an ophthalmologist [*see Warnings and Precautions (5.1)*].

Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA and the associated eye examinations [*see Adverse Reactions (6)*]. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

REGENERON

Manufactured by:

Regeneron Pharmaceuticals, Inc.

777 Old Saw Mill River Road

Tarrytown, NY 10591-6707

U.S. License Number 1760

EYLEA is a registered trademark of Regeneron Pharmaceuticals, Inc.

© 2014, Regeneron Pharmaceuticals, Inc.

All rights reserved.

Issue Date: October 2014

Initial U.S. Approval: 2011

Regeneron U.S. Patents 7,306,799; 7,531,173; 7,608,261; 7,070,959; 7,374,757; 7,374,758, and other pending patents

APPENDIX FDA07

https://web.archive.org/web/20170501000000*/http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/125387s052lbl.pdf September 13, 2025

INTERNET ARCHIVE WEB TEXTS VIDEO AUDIO SOFTWARE IMAGES SIGN UP | LOG IN UPLOAD Search

ABOUT BLOG PROJECTS HELP DONATE CONTACT JOBS VOLUNTEER PEOPLE

DONATE

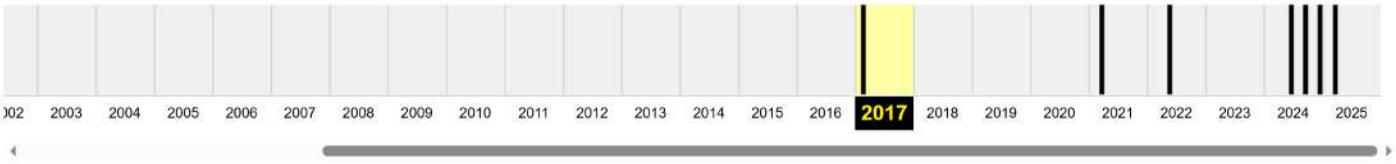
INTERNET ARCHIVE WaybackMachine

Explore more than 946 billion web pages saved over time

http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/1253

Calendar · Collections · Changes · Summary · Site Map · URLs

Saved **7 times** between February 28, 2017 and March 31, 2025.



JAN

1	2	3	4	5	6	7
8	9	10	11	12	13	14
15	16	17	18	19	20	21
22	23	24	25	26	27	28
29	30	31				

FEB

			1	2	3	4
5	6	7	8	9	10	11
12	13	14	15	16	17	18
19	20	21	22	23	24	25
26	27	28				

MAR

			1	2	3	4
5	6	7	8	9	10	11
12	13	14	15	16	17	18
19	20	21	22	23	24	25
26	27	28	29	30	31	

APR

						1
2	3	4	5	6	7	8
9	10	11	12	13	14	15
16	17	18	19	20	21	22
23	24	25	26	27	28	29
30						

MAY

	1	2	3	4	5	6
7	8	9	10	11	12	13
14	15	16	17	18	19	20
21	22	23	24	25	26	27
28	29	30	31			

JUN

				1	2	3
4	5	6	7	8	9	10
11	12	13	14	15	16	17
18	19	20	21	22	23	24
25	26	27	28	29	30	

JUL

						1
2	3	4	5	6	7	8
9	10	11	12	13	14	15
16	17	18	19	20	21	22
23	24	25	26	27	28	29
30	31					

AUG

		1	2	3	4	5
6	7	8	9	10	11	12
13	14	15	16	17	18	19
20	21	22	23	24	25	26
27	28	29	30	31		

SEP

				1	2	
3	4	5	6	7	8	9
10	11	12	13	14	15	16
17	18	19	20	21	22	23
24	25	26	27	28	29	30

OCT

1	2	3	4	5	6	7
8	9	10	11	12	13	14
15	16	17	18	19	20	21
22	23	24	25	26	27	28
29	30	31				

NOV

			1	2	3	4
5	6	7	8	9	10	11
12	13	14	15	16	17	18
19	20	21	22	23	24	25
26	27	28	29	30		

DEC

					1	2
3	4	5	6	7	8	9
10	11	12	13	14	15	16
17	18	19	20	21	22	23
24	25	26	27	28	29	30
31						

Note

This calendar view maps the number of times **http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/125387s052lbl.pdf** was crawled by the Wayback Machine, *not* how many times the site was actually updated. More info in the FAQ.

FAQ | Contact Us | Terms of Service (Dec 31, 2014)

The Wayback Machine is an initiative of the Internet Archive, a 501(c)(3) non-profit, building a digital library of Internet sites and other cultural artifacts in digital form. Other projects include Open Library & archive-it.org.

Your use of the Wayback Machine is subject to the Internet Archive's Terms of Use.

https://web.archive.org/web/20170228032713/http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/125387s052lbl.pdf September 13, 2025

INTERNET ARCHIVE WayBack Machine http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/125387s052lbl.pdf Go JAN FEB MAR 28 2016 2017 2021 About this capture
7 captures
28 Feb 2017 - 31 Mar 2025

label 1 / 26 − 100% +



1



2



3

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use EYLEA safely and effectively. See full prescribing information for EYLEA.

EYLEA® (aflibercept) Injection
For Intravitreal Injection
Initial U.S. Approval: 2011

RECENT MAJOR CHANGES

- Dosage and Administration, Neovascular (Wet) Age-Related Macular Degeneration (AMD) (2.2) 5/2016
- Dosage and Administration, Diabetic Macular Edema (DME) (2.4) 5/2016
- Dosage and Administration, Diabetic Retinopathy (DR) in Patients with DME (2.5) 5/2016
- Contraindications, Hypersensitivity (4.3) 5/2016

INDICATIONS AND USAGE

EYLEA is indicated for the treatment of patients with:

- Neovascular (Wet) Age-Related Macular Degeneration (AMD) (1.1)
- Macular Edema Following Retinal Vein Occlusion (RVO) (1.2)
- Diabetic Macular Edema (DME) (1.3)
- Diabetic Retinopathy (DR) in Patients with DME (1.4)

DOSAGE AND ADMINISTRATION

Neovascular (Wet) Age-Related Macular Degeneration (AMD)

- The recommended dose for EYLEA is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (monthly) for the first 3 months, followed by 2 mg (0.05 mL) via intravitreal injection once every

Diabetic Macular Edema (DME) and Diabetic Retinopathy (DR) in Patients with Diabetic Macular Edema

- The recommended dose for EYLEA is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). (2.4, 2.5)
- Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4 week (monthly) dosing after the first 20 weeks (5 months). (2.4, 2.5)

DOSAGE FORMS AND STRENGTHS

40 mg/mL solution for intravitreal injection in a single-use vial (3)

CONTRAINDICATIONS

- Ocular or periocular infection (4.1)
- Active intraocular inflammation (4.2)
- Hypersensitivity (4.3)

WARNINGS AND PRECAUTIONS

- Endophthalmitis and retinal detachments may occur following intravitreal injections. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately. (5.1)
- Increases in intraocular pressure have been seen within 60 minutes of an intravitreal injection. (5.2)
- There is a potential risk of arterial thromboembolic events following intravitreal use of VEGF inhibitors. (5.3)

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use EYLEA safely and effectively. See full prescribing information for EYLEA.

EYLEA® (aflibercept) Injection
For Intravitreal Injection
Initial U.S. Approval: 2011

RECENT MAJOR CHANGES

- Dosage and Administration, Neovascular (Wet) Age-Related Macular Degeneration (AMD) (2.2) 5/2016
- Dosage and Administration, Diabetic Macular Edema (DME) (2.4) 5/2016
- Dosage and Administration, Diabetic Retinopathy (DR) in Patients with DME (2.5) 5/2016
- Contraindications, Hypersensitivity (4.3) 5/2016

INDICATIONS AND USAGE

EYLEA is indicated for the treatment of patients with:

- Neovascular (Wet) Age-Related Macular Degeneration (AMD) (1.1)
- Macular Edema Following Retinal Vein Occlusion (RVO) (1.2)
- Diabetic Macular Edema (DME) (1.3)
- Diabetic Retinopathy (DR) in Patients with DME (1.4)

DOSAGE AND ADMINISTRATION

Neovascular (Wet) Age-Related Macular Degeneration (AMD)

- The recommended dose for EYLEA is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (monthly) for the first 3 months, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). (2.2)
- Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4 week (monthly) dosing after the first 12 weeks (3 months). (2.2)

Macular Edema Following Retinal Vein Occlusion (RVO)

- The recommended dose for EYLEA is 2 mg (0.05 mL) administered by intravitreal injection once every 4 weeks (monthly). (2.3)

Diabetic Macular Edema (DME) and Diabetic Retinopathy (DR) in Patients with Diabetic Macular Edema

- The recommended dose for EYLEA is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). (2.4, 2.5)
- Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4 week (monthly) dosing after the first 20 weeks (5 months). (2.4, 2.5)

DOSAGE FORMS AND STRENGTHS

40 mg/mL solution for intravitreal injection in a single-use vial (3)

CONTRAINDICATIONS

- Ocular or periocular infection (4.1)
- Active intraocular inflammation (4.2)
- Hypersensitivity (4.3)

WARNINGS AND PRECAUTIONS

- Endophthalmitis and retinal detachments may occur following intravitreal injections. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately. (5.1)
- Increases in intraocular pressure have been seen within 60 minutes of an intravitreal injection. (5.2)
- There is a potential risk of arterial thromboembolic events following intravitreal use of VEGF inhibitors. (5.3)

ADVERSE REACTIONS

The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous floaters, intraocular pressure increased, and vitreous detachment. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Regeneron at 1-855-395-3248 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 9/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
1.1 Neovascular (Wet) Age-Related Macular Degeneration (AMD)
1.2 Macular Edema Following Retinal Vein Occlusion (RVO)
1.3 Diabetic Macular Edema (DME)
1.4 Diabetic Retinopathy (DR) in Patients with DME
2 DOSAGE AND ADMINISTRATION
2.1 Important Injection Instructions
2.2 Neovascular (Wet) Age-Related Macular Degeneration (AMD)
2.3 Macular Edema Following Retinal Vein Occlusion (RVO)
2.4 Diabetic Macular Edema (DME)
2.5 Diabetic Retinopathy (DR) in Patients with DME
2.6 Preparation for Administration
2.7 Injection Procedure
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
4.1 Ocular or Periocular Infections
4.2 Active Intraocular Inflammation
4.3 Hypersensitivity
5 WARNINGS AND PRECAUTIONS
5.1 Endophthalmitis and Retinal Detachments
5.2 Increase in Intraocular Pressure
5.3 Thromboembolic Events
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Immunogenicity
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
14.1 Neovascular (Wet) Age-Related Macular Degeneration (AMD)
14.2 Macular Edema Following Central Retinal Vein Occlusion (CRVO)
14.3 Macular Edema Following Branch Retinal Vein Occlusion (BRVO)
14.4 Diabetic Macular Edema (DME)
14.5 Diabetic Retinopathy (DR) in Patients with DME
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

***Sections or subsections omitted from the full prescribing information are not listed**

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

EYLEA is indicated for the treatment of:

1.1 Neovascular (Wet) Age-Related Macular Degeneration (AMD)

1.2 Macular Edema Following Retinal Vein Occlusion (RVO)

1.3 Diabetic Macular Edema (DME)

1.4 Diabetic Retinopathy (DR) in Patients with DME

2 DOSAGE AND ADMINISTRATION

2.1 Important Injection Instructions

For ophthalmic intravitreal injection. EYLEA must only be administered by a qualified physician.

2.2 Neovascular (Wet) Age-Related Macular Degeneration (AMD)

The recommended dose for EYLEA is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (monthly) for the first 12 weeks (3 months), followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks [*see Clinical Studies (14.1)*]. Some patients may need every 4 week (monthly) dosing after the first 12 weeks (3 months).

2.3 Macular Edema Following Retinal Vein Occlusion (RVO)

The recommended dose for EYLEA is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection once every 4 weeks (monthly) [*see Clinical Studies (14.2), (14.3)*].

2.4 Diabetic Macular Edema (DME)

The recommended dose for EYLEA is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (monthly) for the first 5 injections, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks [*see Clinical Studies (14.4)*]. Some patients may need every 4 week (monthly) dosing after the first 20 weeks (5 months).

2.5 Diabetic Retinopathy (DR) in Patients with DME

The recommended dose for EYLEA is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (monthly) for the first 5 injections, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks [*see Clinical Studies (14.5)*]. Some patients may need every 4 week (monthly) dosing after the first 20 weeks (5 months).

2.6 Preparation for Administration

EYLEA should be inspected visually prior to administration. If particulates, cloudiness, or discoloration are visible, the vial must not be used.

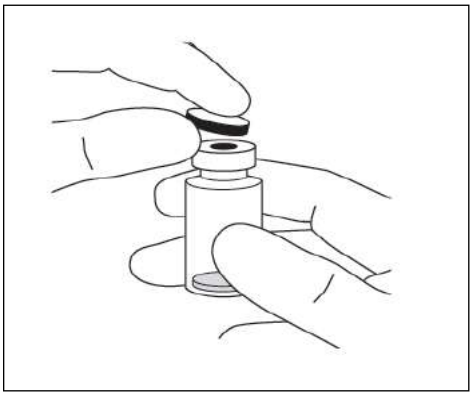
Using aseptic technique, the intravitreal injection should be performed with a 30-gauge x ½-inch injection needle.

Vial

The glass vial is for single use only.

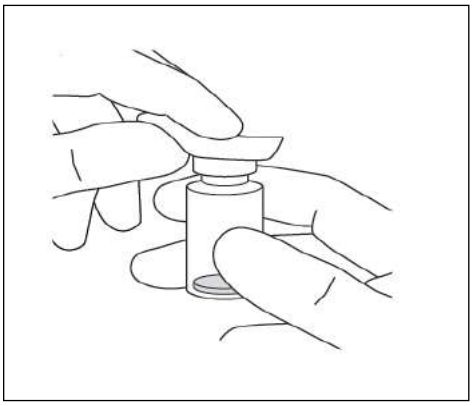
1. Remove the protective plastic cap from the vial (see Figure 1).

Figure 1:



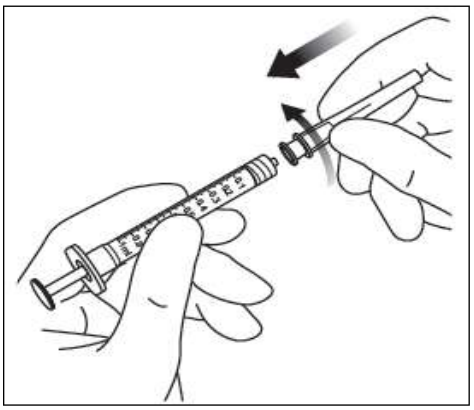
2. Clean the top of the vial with an alcohol wipe (see Figure 2).

Figure 2:



3. Remove the 19-gauge x 1½-inch, 5-micron, filter needle from its pouch and remove the 1-mL syringe supplied in the carton from its pouch. Attach the filter needle to the syringe by twisting it onto the Luer lock syringe tip (see Figure 3).

Figure 3:



4. Push the filter needle into the center of the vial stopper until the needle is completely inserted into the vial and the tip touches the bottom or bottom edge of the vial.
5. Using aseptic technique withdraw all of the EYLEA vial contents into the syringe, keeping the vial in an upright position, slightly inclined to ease complete withdrawal. To deter the introduction of air, ensure the bevel of the filter needle is submerged into the liquid. Continue to tilt the vial during withdrawal keeping the bevel of the filter needle submerged in the liquid (see Figures 4a and 4b).

Figure 4a:

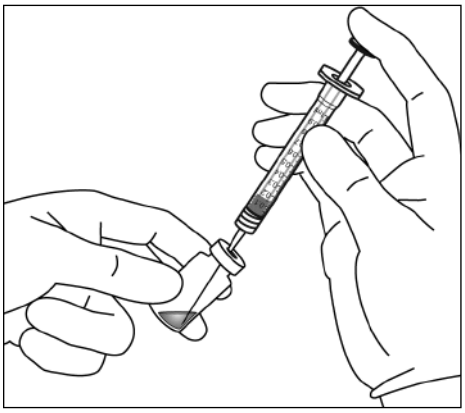
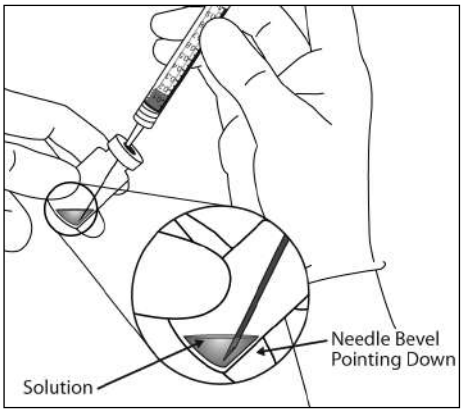
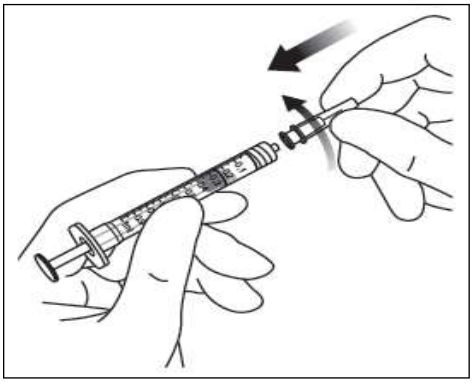


Figure 4b:



6. Ensure that the plunger rod is drawn sufficiently back when emptying the vial in order to completely empty the filter needle.
7. Remove the filter needle from the syringe and properly dispose of the filter needle. **Note**: Filter needle is **not** to be used for intravitreal injection.
8. Remove the 30-gauge x ½-inch injection needle from the plastic pouch and attach the injection needle to the syringe by firmly twisting the injection needle onto the Luer lock syringe tip (see Figure 5).

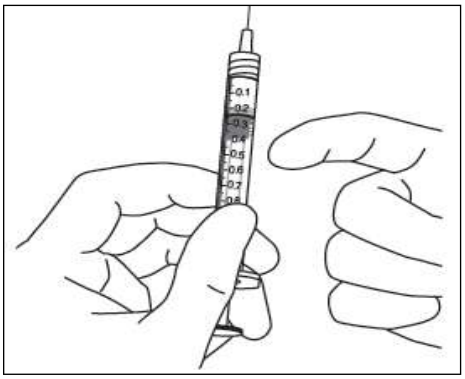
Figure 5:



9. When ready to administer EYLEA, remove the plastic needle shield from the needle.
10. Holding the syringe with the needle pointing up, check the syringe for bubbles. If there are bubbles, gently tap the syringe with your finger until the bubbles rise to the top (see Figure 6).

PGR2026-00039
Biocon Ex.1065
Page 229 of 595

Figure 6:



11. To eliminate all of the bubbles and to expel excess drug, SLOWLY depress the plunger so that the plunger tip aligns with the line that marks 0.05 mL on the syringe (see Figures 7a and 7b).

Figure 7a:

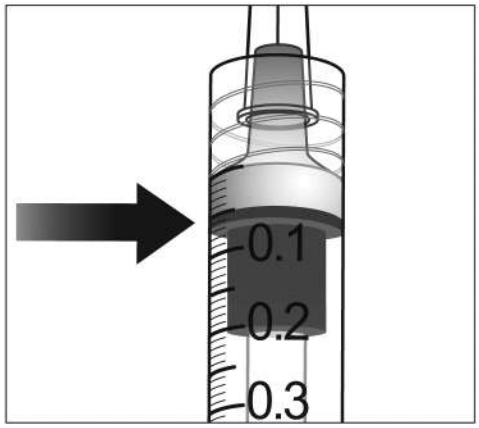
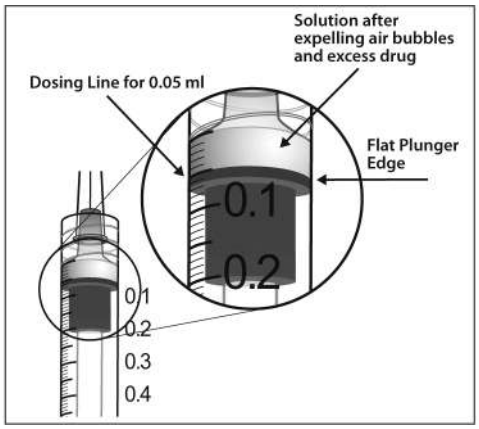


Figure 7b:



2.7 Injection Procedure

The intravitreal injection procedure should be carried out under controlled aseptic conditions, which include surgical hand disinfection and the use of sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent). Adequate anesthesia and a topical broad–spectrum microbicide should be given prior to the injection.

Immediately following the intravitreal injection, patients should be monitored for elevation in intraocular pressure. Appropriate monitoring may consist of a check for perfusion of the optic nerve head or tonometry. If required, a sterile paracentesis needle should be available.

Following intravitreal injection, patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment (e.g., eye pain, redness of the eye, photophobia, blurring of vision) without delay [*see Patient Counseling Information (17)*].

Each vial should only be used for the treatment of a single eye. If the contralateral eye requires treatment, a new vial should be used and the sterile field, syringe, gloves, drapes, eyelid

speculum, filter, and injection needles should be changed before EYLEA is administered to the other eye.

After injection, any unused product must be discarded.

3 DOSAGE FORMS AND STRENGTHS

Single-use, glass vial designed to provide 0.05 mL of 40 mg/mL solution (2 mg) for intravitreal injection.

4 CONTRAINDICATIONS

4.1 Ocular or Periocular Infections

EYLEA is contraindicated in patients with ocular or periocular infections.

4.2 Active Intraocular Inflammation

EYLEA is contraindicated in patients with active intraocular inflammation.

4.3 Hypersensitivity

EYLEA is contraindicated in patients with known hypersensitivity to aflibercept or any of the excipients in EYLEA. Hypersensitivity reactions may manifest as rash, pruritus, urticaria, severe anaphylactic/anaphylactoid reactions, or severe intraocular inflammation.

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis and Retinal Detachments

Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments [*see Adverse Reactions (6.1)*]. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately [*see Dosage and Administration (2.7) and Patient Counseling Information (17)*].

5.2 Increase in Intraocular Pressure

Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA [*see Adverse Reactions (6.1)*]. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with vascular endothelial growth factor (VEGF) inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately [*see Dosage and Administration (2.7)*].

5.3 Thromboembolic Events

There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

6 ADVERSE REACTIONS

The following potentially serious adverse reactions are described elsewhere in the labeling:

- Hypersensitivity [*see Contraindications (4.3)*]
- Endophthalmitis and retinal detachments [*see Warnings and Precautions (5.1)*]
- Increase in intraocular pressure [*see Warnings and Precautions (5.2)*]
- Thromboembolic events [*see Warnings and Precautions (5.3)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in other clinical trials of the same or another drug and may not reflect the rates observed in practice.

A total of 2711 patients treated with EYLEA constituted the safety population in seven phase 3 studies. Among those, 2110 patients were treated with the recommended dose of 2 mg. Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment. The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous floaters, intraocular pressure increased, and vitreous detachment.

Neovascular (Wet) Age-Related Macular Degeneration (AMD)

The data described below reflect exposure to EYLEA in 1824 patients with wet AMD, including 1223 patients treated with the 2-mg dose, in 2 double-masked, active-controlled clinical studies (VIEW1 and VIEW2) for 12 months [*see Clinical Studies (14.1)*].

Table 1: Most Common Adverse Reactions (≥1%) in Wet AMD Studies

Adverse Reactions	EYLEA (N=1824)	Active Control (ranibizumab) (N=595)
Conjunctival hemorrhage	25%	28%
Eye pain	9%	9%
Cataract	7%	7%
Vitreous detachment	6%	6%
Vitreous floaters	6%	7%
Intraocular pressure increased	5%	7%
Ocular hyperemia	4%	8%
Corneal epithelium defect	4%	5%
Detachment of the retinal pigment epithelium	3%	3%
Injection site pain	3%	3%
Foreign body sensation in eyes	3%	4%
Lacrimation increased	3%	1%
Vision blurred	2%	2%
Intraocular inflammation	2%	3%
Retinal pigment epithelium tear	2%	1%
Injection site hemorrhage	1%	2%
Eyelid edema	1%	2%
Corneal edema	1%	1%

Less common serious adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, retinal detachment, retinal tear, and endophthalmitis.

PGR2026-00039
Biocon Ex.1065
Page 233 of 595

Macular Edema Following Retinal Vein Occlusion (RVO)

The data described below reflect 6 months exposure to EYLEA with a monthly 2 mg dose in 218 patients following CRVO in 2 clinical studies (COPERNICUS and GALILEO) and 91 patients following BRVO in one clinical study (VIBRANT) [*see Clinical Studies (14.2), (14.3)*].

Table 2: Most Common Adverse Reactions (≥1%) in RVO Studies

Adverse Reactions	CRVO		BRVO	
	EYLEA (N=218)	Control (N=142)	EYLEA (N=91)	Control (N=92)
Eye pain	13%	5%	4%	5%
Conjunctival hemorrhage	12%	11%	20%	4%
Intraocular pressure increased	8%	6%	2%	0%
Corneal epithelium defect	5%	4%	2%	0%
Vitreous floaters	5%	1%	1%	0%
Ocular hyperemia	5%	3%	2%	2%
Foreign body sensation in eyes	3%	5%	3%	0%
Vitreous detachment	3%	4%	2%	0%
Lacrimation increased	3%	4%	3%	0%
Injection site pain	3%	1%	1%	0%
Vision blurred	1%	<1%	1%	1%
Intraocular inflammation	1%	1%	0%	0%
Cataract	<1%	1%	5%	0%
Eyelid edema	<1%	1%	1%	0%

Less common adverse reactions reported in <1% of the patients treated with EYLEA in the CRVO studies were corneal edema, retinal tear, hypersensitivity, and endophthalmitis.

Diabetic Macular Edema (DME)

The data described below reflect exposure to EYLEA in 578 patients with DME treated with the 2-mg dose in 2 double-masked, controlled clinical studies (VIVID and VISTA) from baseline to week 52 and from baseline to week 100 [*see Clinical Studies (14.4)*].

Table 3: Most Common Adverse Reactions (≥1%) in DME Studies

Adverse Reactions	Baseline to Week 52		Baseline to Week 100	
	EYLEA (N=578)	Control (N=287)	EYLEA (N=578)	Control (N=287)
Conjunctival hemorrhage	28%	17%	31%	21%
Eye pain	9%	6%	11%	9%
Cataract	8%	9%	19%	17%
Vitreous floaters	6%	3%	8%	6%
Corneal epithelium defect	5%	3%	7%	5%
Intraocular pressure increased	5%	3%	9%	5%
Ocular hyperemia	5%	6%	5%	6%
Vitreous detachment	3%	3%	8%	6%
Foreign body sensation in eyes	3%	3%	3%	3%
Lacrimation increased	3%	2%	4%	2%
Vision blurred	2%	2%	3%	4%
Intraocular inflammation	2%	<1%	3%	1%
Injection site pain	2%	<1%	2%	<1%
Eyelid edema	<1%	1%	2%	1%

Less common adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, retinal detachment, retinal tear, corneal edema, and injection site hemorrhage.

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for an immune response in patients treated with EYLEA. The immunogenicity of EYLEA was evaluated in serum samples. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to EYLEA in immunoassays. The detection of an immune response is highly dependent on the sensitivity and specificity of the assays used, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to EYLEA with the incidence of antibodies to other products may be misleading.

In the wet AMD, RVO, and DME studies, the pre-treatment incidence of immunoreactivity to EYLEA was approximately 1% to 3% across treatment groups. After dosing with EYLEA for

24-100 weeks, antibodies to EYLEA were detected in a similar percentage range of patients. There were no differences in efficacy or safety between patients with or without immunoreactivity.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. Aflibercept produced embryo-fetal toxicity when administered every three days during organogenesis to pregnant rabbits at intravenous doses ≥3 mg per kg, or every six days at subcutaneous doses ≥0.1 mg per kg. Adverse embryo-fetal effects included increased incidences of postimplantation loss and fetal malformations, including anasarca, umbilical hernia, diaphragmatic hernia, gastroschisis, cleft palate, ectrodactyly, intestinal atresia, spina bifida, encephalomeningocele, heart and major vessel defects, and skeletal malformations (fused vertebrae, sternebrae, and ribs; supernumerary vertebral arches and ribs; and incomplete ossification). The maternal No Observed Adverse Effect Level (NOAEL) in these studies was 3 mg per kg. Aflibercept produced fetal malformations at all doses assessed in rabbits and the fetal NOAEL was less than 0.1 mg per kg. Administration of the lowest dose assessed in rabbits (0.1 mg per kg) resulted in systemic exposure (AUC) that was approximately 10 times the systemic exposure observed in humans after an intravitreal dose of 2 mg.

There are no adequate and well-controlled studies in pregnant women. EYLEA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Females of reproductive potential should use effective contraception prior to the initial dose, during treatment, and for at least 3 months after the last intravitreal injection of EYLEA.

8.3 Nursing Mothers

It is unknown whether aflibercept is excreted in human milk. Because many drugs are excreted in human milk, a risk to the breastfed child cannot be excluded. EYLEA is not recommended during breastfeeding. A decision must be made whether to discontinue nursing or to discontinue treatment with EYLEA, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and effectiveness of EYLEA in pediatric patients have not been established.

8.5 Geriatric Use

In the clinical studies, approximately 76% (2049/2701) of patients randomized to treatment with EYLEA were ≥65 years of age and approximately 46% (1250/2701) were ≥75 years of age. No significant differences in efficacy or safety were seen with increasing age in these studies.

11 DESCRIPTION

EYLEA (aflibercept) is a recombinant fusion protein consisting of portions of human VEGF receptors 1 and 2 extracellular domains fused to the Fc portion of human IgG1 formulated as an

iso-osmotic solution for intravitreal administration. Aflibercept is a dimeric glycoprotein with a protein molecular weight of 97 kilodaltons (kDa) and contains glycosylation, constituting an additional 15% of the total molecular mass, resulting in a total molecular weight of 115 kDa. Aflibercept is produced in recombinant Chinese hamster ovary (CHO) cells.

EYLEA is a sterile, clear, and colorless to pale yellow solution. EYLEA is supplied as a preservative-free, sterile, aqueous solution in a single-use, glass vial designed to deliver 0.05 mL (50 microliters) of EYLEA (40 mg/mL in 10 mM sodium phosphate, 40 mM sodium chloride, 0.03% polysorbate 20, and 5% sucrose, pH 6.2).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Vascular endothelial growth factor-A (VEGF-A) and placental growth factor (PlGF) are members of the VEGF family of angiogenic factors that can act as mitogenic, chemotactic, and vascular permeability factors for endothelial cells. VEGF acts via two receptor tyrosine kinases, VEGFR-1 and VEGFR-2, present on the surface of endothelial cells. PlGF binds only to VEGFR-1, which is also present on the surface of leucocytes. Activation of these receptors by VEGF-A can result in neovascularization and vascular permeability.

Aflibercept acts as a soluble decoy receptor that binds VEGF-A and PlGF, and thereby can inhibit the binding and activation of these cognate VEGF receptors.

12.2 Pharmacodynamics

Neovascular (Wet) Age-Related Macular Degeneration (AMD)

In the clinical studies anatomic measures of disease activity improved similarly in all treatment groups from baseline to week 52. Anatomic data were not used to influence treatment decisions [*see Clinical Studies (14.1)*].

Macular Edema Following Retinal Vein Occlusion (RVO)

Reductions in mean retinal thickness were observed in COPERNICUS, GALILEO, and VIBRANT at week 24 compared to baseline. Anatomic data were not used to influence treatment decisions [*see Clinical Studies (14.2), (14.3)*].

Diabetic Macular Edema (DME)

Reductions in mean retinal thickness were observed in VIVID and VISTA at weeks 52 and 100 compared to baseline. Anatomic data were not used to influence EYLEA treatment decisions [*see Clinical Studies (14.4)*].

12.3 Pharmacokinetics

EYLEA is administered intravitreally to exert local effects in the eye. In patients with wet AMD, RVO, or DME, following intravitreal administration of EYLEA, a fraction of the administered dose is expected to bind with endogenous VEGF in the eye to form an inactive aflibercept: VEGF complex. Once absorbed into the systemic circulation, aflibercept presents in the plasma

as free aflibercept (unbound to VEGF) and a more predominant stable inactive form with circulating endogenous VEGF (i.e., aflibercept: VEGF complex).

Absorption/Distribution

Following intravitreal administration of 2 mg per eye of EYLEA to patients with wet AMD, RVO, and DME, the mean C_{max} of free aflibercept in the plasma was 0.02 mcg/mL (range: 0 to 0.054 mcg/mL), 0.05 mcg/mL (range: 0 to 0.081 mcg/mL), and 0.03 mcg/mL (range: 0 to 0.076 mcg/mL), respectively and was attained in 1 to 3 days. The free aflibercept plasma concentrations were undetectable two weeks post-dosing in all patients. Aflibercept did not accumulate in plasma when administered as repeated doses intravitreally every 4 weeks. It is estimated that after intravitreal administration of 2 mg to patients, the mean maximum plasma concentration of free aflibercept is more than 100 fold lower than the concentration of aflibercept required to half-maximally bind systemic VEGF.

The volume of distribution of free aflibercept following intravenous (I.V.) administration of aflibercept has been determined to be approximately 6L.

Metabolism/Elimination

Aflibercept is a therapeutic protein and no drug metabolism studies have been conducted. Aflibercept is expected to undergo elimination through both target-mediated disposition via binding to free endogenous VEGF and metabolism via proteolysis. The terminal elimination half-life (t1/2) of free aflibercept in plasma was approximately 5 to 6 days after I.V. administration of doses of 2 to 4 mg/kg aflibercept.

Specific Populations

Renal Impairment

Pharmacokinetic analysis of a subgroup of patients (n=492) in one wet AMD study, of which 43% had renal impairment (mild n=120, moderate n=74, and severe n=16), revealed no differences with respect to plasma concentrations of free aflibercept after intravitreal administration every 4 or 8 weeks. Similar results were seen in patients in a RVO study and in patients in a DME study. No dose adjustment based on renal impairment status is needed for either wet AMD, RVO, or DME patients.

Other

No special dosage modification is required for any of the populations that have been studied (e.g., gender, elderly).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been conducted on the mutagenic or carcinogenic potential of aflibercept. Effects on male and female fertility were assessed as part of a 6-month study in monkeys with intravenous administration of aflibercept at weekly doses ranging from 3 to 30 mg per kg. Absent or irregular menses associated with alterations in female reproductive hormone levels and changes in sperm morphology and motility were observed at all dose levels. In addition, females

showed decreased ovarian and uterine weight accompanied by compromised luteal development and reduction of maturing follicles. These changes correlated with uterine and vaginal atrophy. A No Observed Adverse Effect Level (NOAEL) was not identified. Intravenous administration of the lowest dose of aflibercept assessed in monkeys (3 mg per kg) resulted in systemic exposure (AUC) that was approximately 1500 times higher than the systemic exposure observed in humans after an intravitreal dose of 2 mg. All changes were reversible within 20 weeks after cessation of treatment.

13.2 Animal Toxicology and/or Pharmacology

Erosions and ulcerations of the respiratory epithelium in nasal turbinates in monkeys treated with aflibercept intravitreally were observed at intravitreal doses of 2 or 4 mg per eye. At the NOAEL of 0.5 mg per eye in monkeys, the systemic exposure (AUC) was 56 times higher than the exposure observed in humans after an intravitreal dose of 2 mg. Similar effects were not seen in clinical studies [*see Clinical Studies (14)*].

14 CLINICAL STUDIES

14.1 Neovascular (Wet) Age-Related Macular Degeneration (AMD)

The safety and efficacy of EYLEA were assessed in two randomized, multi-center, double-masked, active-controlled studies in patients with wet AMD. A total of 2412 patients were treated and evaluable for efficacy (1817 with EYLEA) in the two studies (VIEW1 and VIEW2). In each study, patients were randomly assigned in a 1:1:1:1 ratio to 1 of 4 dosing regimens: 1) EYLEA administered 2 mg every 8 weeks following 3 initial monthly doses (EYLEA 2Q8); 2) EYLEA administered 2 mg every 4 weeks (EYLEA 2Q4); 3) EYLEA 0.5 mg administered every 4 weeks (EYLEA 0.5Q4); and 4) ranibizumab administered 0.5 mg every 4 weeks (ranibizumab 0.5 mg Q4). Patient ages ranged from 49 to 99 years with a mean of 76 years.

In both studies, the primary efficacy endpoint was the proportion of patients who maintained vision, defined as losing fewer than 15 letters of visual acuity at week 52 compared to baseline. Data are available through week 52. Both EYLEA 2Q8 and EYLEA 2Q4 groups were shown to have efficacy that was clinically equivalent to the ranibizumab 0.5 mg Q4 group.

Detailed results from the analysis of the VIEW1 and VIEW2 studies are shown in Table 4 and Figure 8 below.

Table 4: Efficacy Outcomes at Week 52 (Full Analysis Set with LOCF) in VIEW1 and VIEW2 Studies

	VIEW1			VIEW2		
	EYLEA 2 mg Q8 weeks [a]	EYLEA 2 mg Q4 weeks	ranibizumab 0.5 mg Q4 weeks	EYLEA 2 mg Q8 weeks [a]	EYLEA 2 mg Q4 weeks	ranibizumab 0.5 mg Q4 weeks
Full Analysis Set	N=301	N=304	N=304	N=306	N=309	N=291
Efficacy Outcomes						
Proportion of patients who maintained visual acuity (%) (<15 letters of BCVA loss)	94%	95%	94%	95%	95%	95%
Difference[b] (%) (95.1% CI)	0.6 (-3.2, 4.4)	1.3 (-2.4, 5.0)		0.6 (-2.9, 4.0)	-0.3 (-4.0, 3.3)	
Mean change in BCVA as measured by ETDRS letter score from Baseline	7.9	10.9	8.1	8.9	7.6	9.4
Difference[b] in LS mean (95.1% CI)	0.3 (-2.0, 2.5)	3.2 (0.9, 5.4)		-0.9 (-3.1, 1.3)	-2.0 (-4.1, 0.2)	
Number of patients who gained at least 15 letters of vision from Baseline (%)	92 (31%)	114 (38%)	94 (31%)	96 (31%)	91 (29%)	99 (34%)
Difference[b] (%) (95.1% CI)	-0.4 (-7.7, 7.0)	6.6 (-1.0, 14.1)		-2.6 (-10.2, 4.9)	-4.6 (-12.1, 2.9)	

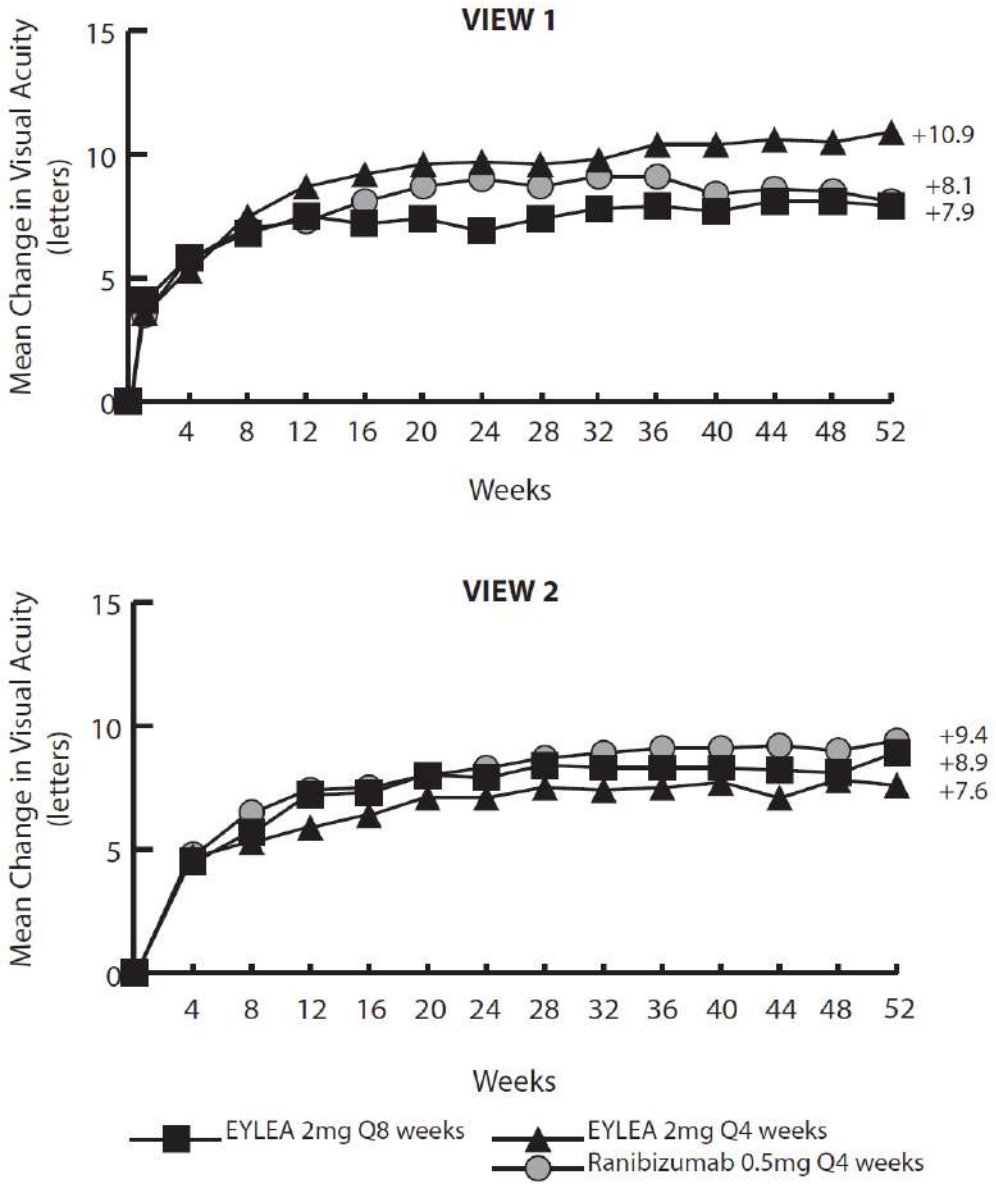
BCVA = Best Corrected Visual Acuity; CI = Confidence Interval; ETDRS = Early Treatment Diabetic Retinopathy Study; LOCF = Last Observation Carried Forward (baseline values are not carried forward); 95.1% confidence intervals were presented to adjust for safety assessment conducted during the study.

[a] After treatment initiation with 3 monthly doses

[b] EYLEA group minus the ranibizumab group

PGR2026-00039
Biocon Ex.1065
Page 240 of 595

Figure 8: Mean Change in Visual Acuity from Baseline to Week 52 in VIEW1 and VIEW2 Studies



14.2 Macular Edema Following Central Retinal Vein Occlusion (CRVO)

The safety and efficacy of EYLEA were assessed in two randomized, multi-center, double-masked, sham-controlled studies in patients with macular edema following CRVO. A total of 358 patients were treated and evaluable for efficacy (217 with EYLEA) in the two studies (COPERNICUS and GALILEO). In both studies, patients were randomly assigned in a 3:2 ratio to either 2 mg EYLEA administered every 4 weeks (2Q4), or sham injections (control group) administered every 4 weeks for a total of 6 injections. Patient ages ranged from 22 to 89 years with a mean of 64 years.

In both studies, the primary efficacy endpoint was the proportion of patients who gained at least 15 letters in BCVA compared to baseline. At week 24, the EYLEA 2 mg Q4 group was superior to the control group for the primary endpoint.

Results from the analysis of the COPERNICUS and GALILEO studies are shown in Table 5 and Figure 9 below.

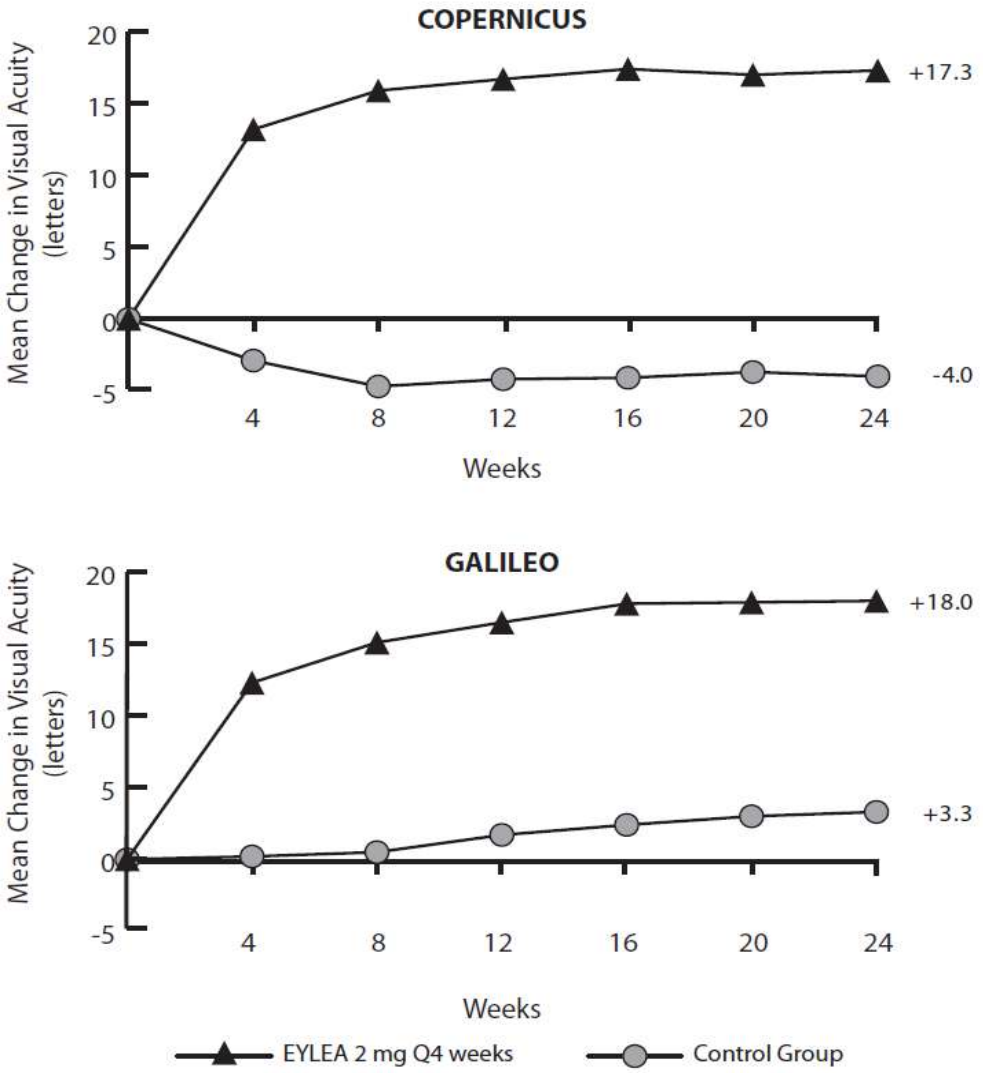
Table 5: Efficacy Outcomes at Week 24 (Full Analysis Set with LOCF) in COPERNICUS and GALILEO Studies

	COPERNICUS		GALILEO	
	Control	EYLEA 2 mg Q4 weeks	Control	EYLEA 2 mg Q4 weeks
	N=73	N=114	N=68	N=103
Efficacy Outcomes				
Proportion of patients who gained at least 15 letters in BCVA from Baseline (%)	12%	56%	22%	60%
Weighted Difference [a,b] (%) (95.1% CI)		44.8%[c] (32.9, 56.6)		38.3%[c] (24.4, 52.1)
Mean change in BCVA as measured by ETDRS letter score from Baseline (SD)	-4.0 (18.0)	17.3 (12.8)	3.3 (14.1)	18.0 (12.2)
Difference in LS mean [a,d] (95.1% CI)		21.7[c] (17.3, 26.1)		14.7[c] (10.7, 18.7)

[a] Difference is EYLEA 2 mg Q4 weeks minus Control
[b] Difference and CI are calculated using Cochran-Mantel-Haenszel (CMH) test adjusted for baseline factors; 95.1% confidence intervals were presented to adjust for the multiple assessments conducted during the study.
[c] $p<0.01$ compared with Control
[d] LS mean and CI based on an ANCOVA model

PGR2026-00039
Biocon Ex.1065
Page 242 of 595

Figure 9: Mean Change in BCVA as Measured by ETDRS Letter Score from Baseline to Week 24 in COPERNICUS and GALILEO Studies



Treatment effects in evaluable subgroups (e.g., age, gender, race, baseline visual acuity, retinal perfusion status, and CRVO duration) in each study and in the combined analysis were in general consistent with the results in the overall populations.

14.3 Macular Edema Following Branch Retinal Vein Occlusion (BRVO)

The safety and efficacy of EYLEA were assessed in a 24-week, randomized, multi-center, double-masked, controlled study in patients with macular edema following BRVO. A total of 181 patients were treated and evaluable for efficacy (91 with EYLEA) in the VIBRANT study. In the study, patients were randomly assigned in a 1:1 ratio to either 2 mg EYLEA administered every 4 weeks (2Q4) or laser photocoagulation administered at baseline and subsequently as needed (control group). Patient ages ranged from 42 to 94 years with a mean of 65 years.

In the VIBRANT study, the primary efficacy endpoint was the proportion of patients who gained at least 15 letters in BCVA at week 24 compared to baseline. At week 24, the EYLEA 2 mg Q4 group was superior to the control group for the primary endpoint.

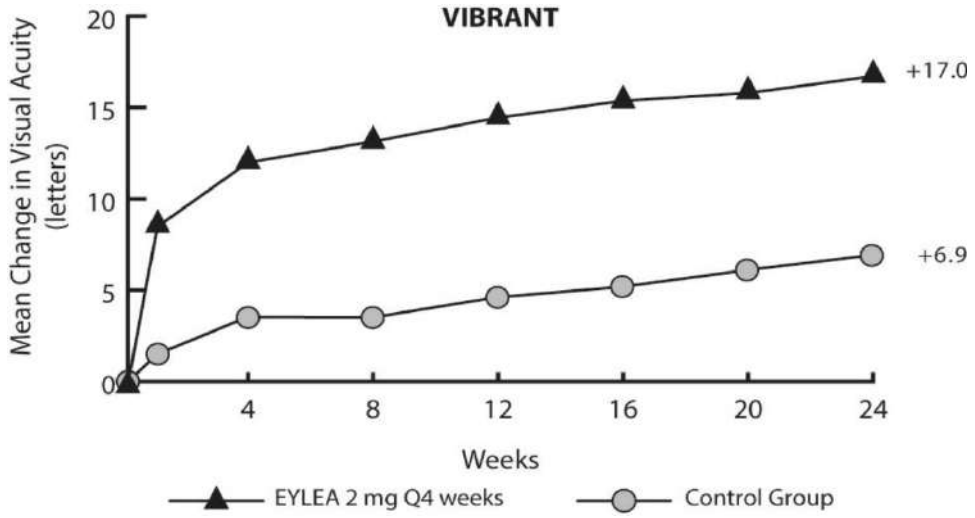
Detailed results from the analysis of the VIBRANT study are shown in Table 6 and Figure 10 below.

Table 6: Efficacy Outcomes at Week 24 (Full Analysis Set with LOCF) in VIBRANT Study

	VIBRANT	
	Control	EYLEA 2 mg Q4 weeks
	N=90	N=91
Efficacy Outcomes		
Proportion of patients who gained at least 15 letters in BCVA from Baseline (%)	26.7%	52.7%
Weighted Difference [a,b] (%) (95% CI)		26.6%[c] (13.0, 40.1)
Mean change in BCVA as measured by ETDRS letter score from Baseline (SD)	6.9 (12.9)	17.0 (11.9)
Difference in LS mean [a,d] (95% CI)		10.5[c] (7.1, 14.0)

[a] Difference is EYLEA 2 mg Q4 weeks minus Control
[b] Difference and CI are calculated using Mantel-Haenszel weighting scheme adjusted for region (North America vs. Japan) and baseline BCVA category (> 20/200 and ≤ 20/200)
[c] $p<0.01$ compared with Control
[d] LS mean and CI based on an ANCOVA model

Figure 10: Mean Change in BCVA as Measured by ETDRS Letter Score from Baseline to Week 24 in VIBRANT Study



Treatment effects in evaluable subgroups (e.g., age, gender, and baseline retinal perfusion status) in the study were in general consistent with the results in the overall populations.

14.4 Diabetic Macular Edema (DME)

The safety and efficacy of EYLEA were assessed in two randomized, multi-center, double-masked, controlled studies in patients with DME. A total of 862 randomized and treated patients were evaluable for efficacy. Patient ages ranged from 23 to 87 years with a mean of 63 years.

Of those, 576 were randomized to EYLEA groups in the two studies (VIVID and VISTA). In each study, patients were randomly assigned in a 1:1:1 ratio to 1 of 3 dosing regimens: 1) EYLEA administered 2 mg every 8 weeks following 5 initial monthly injections (EYLEA 2Q8); 2) EYLEA administered 2 mg every 4 weeks (EYLEA 2Q4); and 3) macular laser photocoagulation (at baseline and then as needed). Beginning at week 24, patients meeting a pre-specified threshold of vision loss were eligible to receive additional treatment: patients in the EYLEA groups could receive laser and patients in the laser group could receive EYLEA.

In both studies, the primary efficacy endpoint was the mean change from baseline in BCVA at week 52 as measured by ETDRS letter score. Efficacy of both EYLEA 2Q8 and EYLEA 2Q4 groups was statistically superior to the control group. This statistically superior improvement in BCVA was maintained at week 100 in both studies.

Results from the analysis of the VIVID and VISTA studies are shown in Table 7 and Figure 11 below.

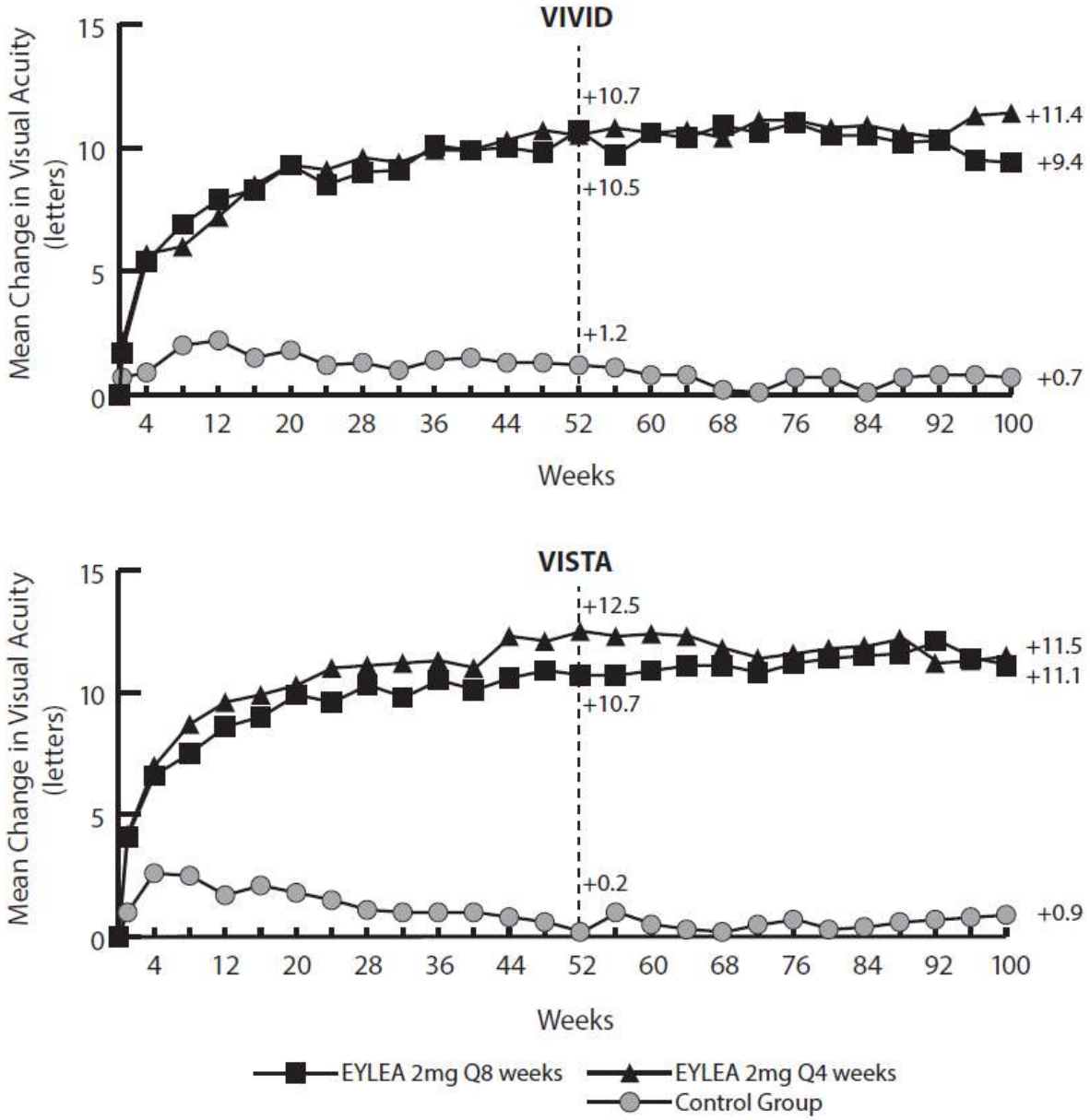
Table 7: Efficacy Outcomes at Weeks 52 and 100 (Full Analysis Set with LOCF) in VIVID and VISTA Studies

	VIVID			VISTA		
	EYLEA 2 mg Q8 weeks [a]	EYLEA 2 mg Q4 weeks	Control	EYLEA 2 mg Q8 weeks [a]	EYLEA 2 mg Q4 weeks	Control
Full Analysis Set	N=135	N=136	N=132	N=151	N=154	N=154
Efficacy Outcomes at Week 52						
Mean change in BCVA as measured by ETDRS letter score from Baseline (SD)	10.7 (9.3)	10.5 (9.6)	1.2 (10.6)	10.7 (8.2)	12.5 (9.5)	0.2 (12.5)
Difference[b, c] in LS mean (97.5% CI)	9.1[d] (6.3, 11.8)	9.3[d] (6.5, 12.0)		10.5[d] (7.7, 13.2)	12.2[d] (9.4, 15.0)	
Proportion of patients who gained at least 15 letters in BCVA from Baseline (%)	33.3%	32.4%	9.1%	31.1%	41.6%	7.8%
Adjusted Difference[c, e] (%) (97.5% CI)	24.2%[d] (13.5, 34.9)	23.3%[d] (12.6, 33.9)		23.3%[d] (13.5, 33.1)	34.2%[d] (24.1, 44.4)	
Efficacy Outcomes at Week 100						
Mean change in BCVA as measured by ETDRS letter score from Baseline (SD)	9.4 (10.5)	11.4 (11.2)	0.7 (11.8)	11.1 (10.7)	11.5 (13.8)	0.9 (13.9)
Difference[b, c] in LS mean (97.5% CI)	8.2[d] (5.2, 11.3)	10.7[d] (7.6, 13.8)		10.1[d] (7.0, 13.3)	10.6[d] (7.1, 14.2)	
Proportion of patients who gained at least 15 letters in BCVA from Baseline (%)	31.1%	38.2%	12.1%	33.1%	38.3%	13.0%
Adjusted Difference[c, e] (%) (97.5% CI)	19.0%[d] (8.0, 29.9)	26.1%[d] (14.8, 37.5)		20.1%[d] (9.6, 30.6)	25.8%[d] (15.1, 36.6)	

[a] After treatment initiation with 5 monthly injections
[b] LS mean and CI based on an ANCOVA model with baseline BCVA measurement as a covariate and a factor for treatment group. Additionally, protocol specified stratification factors were included in the model.
[c] Difference is EYLEA group minus Control group
[d] $p<0.01$ compared with Control
[e] Difference with confidence interval (CI) and statistical test is calculated using Mantel-Haenszel weighting scheme adjusted by protocol specified stratification factors.

PGR2026-00039
Biocon Ex.1065
Page 246 of 595

Figure 11: Mean Change in BCVA as Measured by ETDRS Letter Score from Baseline to Week 100 in VIVID and VISTA Studies



Treatment effects in the subgroup of patients who had previously been treated with a VEGF inhibitor prior to study participation were similar to those seen in patients who were VEGF inhibitor naïve prior to study participation.

Treatment effects in evaluable subgroups (e.g., age, gender, race, baseline HbA1c, baseline visual acuity, prior anti-VEGF therapy) in each study were in general consistent with the results in the overall populations.

14.5 Diabetic Retinopathy (DR) in Patients with DME

In the VIVID and VISTA studies, an efficacy outcome was the change in the Early Treatment Diabetic Retinopathy Study (ETDRS) Diabetic Retinopathy Severity Scale (ETDRS-DRSS). The ETDRS-DRSS score was assessed at baseline and approximately every 6 months thereafter for the duration of the studies [*see Clinical Studies (14.4)*].

All enrolled patients had DR and DME at baseline. The majority of patients enrolled in these studies (77%) had moderate-to-severe nonproliferative diabetic retinopathy (NPDR) based on the ETDRS-DRSS. At week 100, the proportion of patients improving by at least 2 steps on the ETDRS-DRSS was significantly greater in both EYLEA treatment groups (2Q4 and 2Q8) when compared to the control group.

Results from the analysis of ETDRS-DRSS at week 100 in the VIVID and VISTA studies are shown in Table 8 below.

Table 8: Proportion of Patients who Achieved a ≥2-Step Improvement from Baseline in the ETDRS-DRSS Score at Week 100 (LOCF[a]) in VIVID and VISTA Studies

	VIVID			VISTA		
	EYLEA 2 mg Q8 weeks [b]	EYLEA 2 mg Q4 weeks	Control	EYLEA 2 mg Q8 weeks [b]	EYLEA 2 mg Q4 weeks	Control
Evaluable Patients[c]	N=101	N=97	N=99	N=148	N=153	N=150
Number of patients with a ≥2-step improvement on ETDRS-DRSS from Baseline (%)	32 (32%)	27 (28%)	7 (7%)	56 (38%)	58 (38%)	24 (16%)
Difference[d,e](%) (97.5% CI)	24%[f] (12, 36)	21%[f] (9, 33)		22%[f] (11, 33)	22%[f] (11, 33)	

[a] Non-gradable post-baseline ETDRS-DRSS values were treated as missing and were imputed using the last gradable ETDRS-DRSS values (including baseline values if all post-baseline values were missing or non-gradable)
[b] After treatment initiation with 5 monthly injections
[c] The number of evaluable patients included all patients who had valid ETDRS-DRSS data at baseline
[d] Difference with confidence interval (CI) was calculated using Mantel-Haenszel weighting scheme adjusted by protocol specified stratification factors
[e] Difference is EYLEA minus Control group
[f] $p<0.01$ compared with Control

Results of the evaluable subgroups (e.g., age, gender, race, baseline HbA1c, baseline visual acuity) on the proportion of patients who achieved a ≥2-step improvement on the ETDRS-DRSS from baseline to week 100 were, in general, consistent with those in the overall population.

PGR2026-00039
Biocon Ex.1065
Page 248 of 595

16 HOW SUPPLIED/STORAGE AND HANDLING

Each Vial is for single eye use only. EYLEA is supplied in the following presentation [*see Dosage and Administration (2.6) and (2.7)*].

NDC NUMBER	CARTON TYPE	CARTON CONTENTS
61755-005-02	Vial	one single-use, sterile, 3-mL, glass vial designed to deliver 0.05 mL of 40 mg/mL EYLEA one 19-gauge x 1½-inch, 5-micron, filter needle for withdrawal of the vial contents one 30-gauge x ½-inch injection needle for intravitreal injection one 1-mL syringe for administration one package insert

Storage

EYLEA should be refrigerated at 2°C to 8ºC (36°F to 46ºF). Do Not Freeze. Do not use beyond the date stamped on the carton and container label. Protect from light. Store in the original carton until time of use.

17 PATIENT COUNSELING INFORMATION

In the days following EYLEA administration, patients are at risk of developing endophthalmitis or retinal detachment. If the eye becomes red, sensitive to light, painful, or develops a change in vision, advise patients to seek immediate care from an ophthalmologist [*see Warnings and Precautions (5.1)*].

Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA and the associated eye examinations [*see Adverse Reactions (6)*]. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

REGENERON

Manufactured by:

Regeneron Pharmaceuticals, Inc.

777 Old Saw Mill River Road

Tarrytown, NY 10591-6707

U.S. License Number 1760

EYLEA is a registered trademark of Regeneron Pharmaceuticals, Inc.

© 2016, Regeneron Pharmaceuticals, Inc.

All rights reserved.

Issue Date: September 2016

Initial U.S. Approval: 2011

PGR2026-00039
Biocon Ex.1065
Page 250 of 595

APPENDIX REGENERON02

DONATE

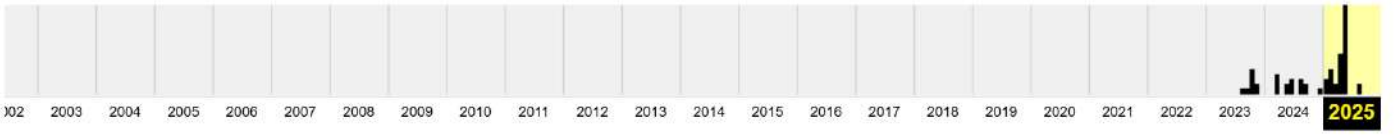
INTERNET ARCHIVE WayBackMachine

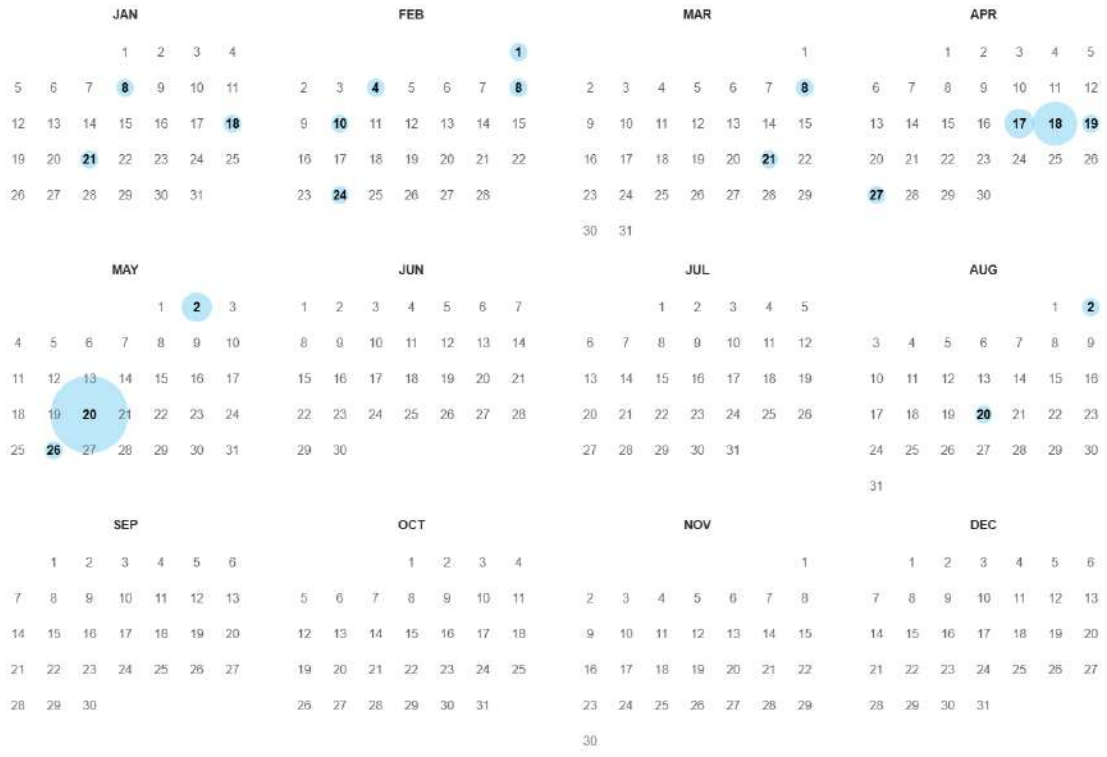
Explore more than 946 billion web pages saved over time

https://www.regeneron.com/downloads/eyleahd_fpi.pdf

Calendar · Collections · Changes · Summary · Site Map · URLs

Saved **62 times** between August 25, 2023 and August 20, 2025.





Note

This calendar view maps the number of times **https://www.regeneron.com/downloads/eyleahd_fpi.pdf** was crawled by the Wayback Machine, *not* how many times the site was actually updated. More info in the FAQ.

FAQ | Contact Us | Terms of Service (Dec 31, 2014)

The Wayback Machine is an initiative of the Internet Archive, a 501(c)(3) non-profit, building a digital library of Internet sites and other cultural artifacts in digital form. Other projects include Open Library & archive-it.org.

Your use of the Wayback Machine is subject to the Internet Archive's Terms of Use.

https://web.archive.org/web/20250820153626/https://www.regeneron.com/downloads/eyleahd_fpi.pdf September 17, 2025
INTERNET ARCHIVE Wayback Machine https://www.regeneron.com/downloads/eyleahd_fpi.pdf Go MAY AUG 20 SEP 2024 2025 2026 About this capture
62 captures 25 Aug 2023 - 20 Aug 2025







HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use EYLEA HD safely and effectively. See full prescribing information for EYLEA HD.

EYLEA HD® (aflibercept) injection, for intravitreal use
Initial U.S. Approval: 2011

RECENT MAJOR CHANGES

Warnings and Precautions (5.1) 12/2023

INDICATIONS AND USAGE

EYLEA HD is a vascular endothelial growth factor (VEGF) inhibitor indicated for the treatment of patients with:

- Neovascular (Wet) Age-Related Macular Degeneration (nAMD) (1.1)
- Diabetic Macular Edema (DME) (1.2)
- Diabetic Retinopathy (DR) (1.3)

DOSAGE AND ADMINISTRATION

- **Neovascular (Wet) Age-Related Macular Degeneration (nAMD)**
  - The recommended dose for EYLEA HD is 8 mg (0.07 mL of 114.3 mg/mL solution) administered by intravitreal injection every 4 weeks (approximately every 28 days +/- 7 days) for the first three doses, followed by 8 mg (0.07 mL of 114.3 mg/mL solution) via intravitreal injection once every 8 to 16 weeks, +/- 1 week. (2.2)
- **Diabetic Macular Edema (DME)**
  - The recommended dose for EYLEA HD is 8 mg (0.07 mL of 114.3 mg/mL solution) administered by intravitreal injection every 4 weeks (approximately every 28 days +/- 7 days) for the first three doses, followed by 8 mg (0.07 mL of 114.3 mg/mL solution) via intravitreal injection once every 8 to 16 weeks, +/- 1 week. (2.3)
- **Diabetic Retinopathy (DR)**
  - The recommended dose for EYLEA HD is 8 mg (0.07 mL of 114.3 mg/mL solution) administered by intravitreal injection every 4 weeks (approximately every 28 days +/- 7 days) for the first three doses, followed by 8 mg (0.07 mL of 114.3 mg/mL solution) via intravitreal injection once every 8 to 12 weeks, +/- 1 week. (2.4)

DOSAGE FORMS AND STRENGTHS

- Injection: 8 mg (0.07 mL of 114.3 mg/mL solution) in a single-dose vial (3)

CONTRAINDICATIONS

- Ocular or periocular infection (4.1)
- Active intraocular inflammation (4.2)
- Hypersensitivity (4.3)

WARNINGS AND PRECAUTIONS

- Endophthalmitis, retinal detachments, and retinal vasculitis with or without occlusion may occur following intravitreal injections. Patients should be instructed to report any symptoms suggestive of endophthalmitis, retinal detachment, or retinal vasculitis without delay and should be managed appropriately. (5.1)
- Increases in intraocular pressure have been seen within 60 minutes of an intravitreal injection. (5.2)
- There is a potential risk of arterial thromboembolic events following intravitreal use of VEGF inhibitors. (5.3)

ADVERSE REACTIONS

The most common adverse reactions (≥3%) reported in patients treated with EYLEA HD were cataract, conjunctival hemorrhage, intraocular pressure increased, ocular discomfort/eye pain/eye irritation, vision blurred, vitreous floaters, vitreous detachment, corneal epithelium defect, and retinal hemorrhage. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Regeneron at 1-855-395-3248 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 10/2024

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use EYLEA HD safely and effectively. See full prescribing information for EYLEA HD.

EYLEA HD® (aflibercept) injection, for intravitreal use
Initial U.S. Approval: 2011

RECENT MAJOR CHANGES

Warnings and Precautions (5.1) 12/2023

INDICATIONS AND USAGE

EYLEA HD is a vascular endothelial growth factor (VEGF) inhibitor indicated for the treatment of patients with:

- Neovascular (Wet) Age-Related Macular Degeneration (nAMD) (1.1)
- Diabetic Macular Edema (DME) (1.2)
- Diabetic Retinopathy (DR) (1.3)

DOSAGE AND ADMINISTRATION

- **Neovascular (Wet) Age-Related Macular Degeneration (nAMD)**
  - The recommended dose for EYLEA HD is 8 mg (0.07 mL of 114.3 mg/mL solution) administered by intravitreal injection every 4 weeks (approximately every 28 days +/- 7 days) for the first three doses, followed by 8 mg (0.07 mL of 114.3 mg/mL solution) via intravitreal injection once every 8 to 16 weeks, +/- 1 week. (2.2)
- **Diabetic Macular Edema (DME)**
  - The recommended dose for EYLEA HD is 8 mg (0.07 mL of 114.3 mg/mL solution) administered by intravitreal injection every 4 weeks (approximately every 28 days +/- 7 days) for the first three doses, followed by 8 mg (0.07 mL of 114.3 mg/mL solution) via intravitreal injection once every 8 to 16 weeks, +/- 1 week. (2.3)
- **Diabetic Retinopathy (DR)**
  - The recommended dose for EYLEA HD is 8 mg (0.07 mL of 114.3 mg/mL solution) administered by intravitreal injection every 4 weeks (approximately every 28 days +/- 7 days) for the first three doses, followed by 8 mg (0.07 mL of 114.3 mg/mL solution) via intravitreal injection once every 8 to 12 weeks, +/- 1 week. (2.4)

DOSAGE FORMS AND STRENGTHS

- Injection: 8 mg (0.07 mL of 114.3 mg/mL solution) in a single-dose vial (3)

CONTRAINDICATIONS

- Ocular or periocular infection (4.1)
- Active intraocular inflammation (4.2)
- Hypersensitivity (4.3)

WARNINGS AND PRECAUTIONS

- Endophthalmitis, retinal detachments, and retinal vasculitis with or without occlusion may occur following intravitreal injections. Patients should be instructed to report any symptoms suggestive of endophthalmitis, retinal detachment, or retinal vasculitis without delay and should be managed appropriately. (5.1)
- Increases in intraocular pressure have been seen within 60 minutes of an intravitreal injection. (5.2)
- There is a potential risk of arterial thromboembolic events following intravitreal use of VEGF inhibitors. (5.3)

ADVERSE REACTIONS

The most common adverse reactions (≥3%) reported in patients treated with EYLEA HD were cataract, conjunctival hemorrhage, intraocular pressure increased, ocular discomfort/eye pain/eye irritation, vision blurred, vitreous floaters, vitreous detachment, corneal epithelium defect, and retinal hemorrhage. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Regeneron at 1-855-395-3248 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 10/2024

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
1.1 Neovascular (Wet) Age-Related Macular Degeneration (nAMD)
1.2 Diabetic Macular Edema (DME)
1.3 Diabetic Retinopathy (DR)
2 DOSAGE AND ADMINISTRATION
2.1 Important Injection Instructions
2.2 Neovascular (Wet) Age-Related Macular Degeneration (nAMD)
2.3 Diabetic Macular Edema (DME)
2.4 Diabetic Retinopathy (DR)
2.5 Preparation for Administration
2.6 Injection Procedure
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
4.1 Ocular or Periocular Infections
4.2 Active Intraocular Inflammation
4.3 Hypersensitivity
5 WARNINGS AND PRECAUTIONS
5.1 Endophthalmitis, Retinal Detachments, and Retinal Vasculitis with or without Occlusion
5.2 Increase in Intraocular Pressure
5.3 Thromboembolic Events
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Postmarketing Experience
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation
8.3 Females and Males of Reproductive Potential
8.4 Pediatric Use
8.5 Geriatric Use
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.6 Immunogenicity
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
14.1 Neovascular (Wet) Age-Related Macular Degeneration (nAMD)
14.2 Diabetic Macular Edema (DME)
14.3 Diabetic Retinopathy (DR)
16 HOW SUPPLIED/STORAGE AND HANDLING
16.1 How Supplied
16.2 Storage and Handling
17 PATIENT COUNSELING INFORMATION

***Sections or subsections omitted from the full prescribing information are not listed**

PGR2026-00039
Biocon Ex.1065
Page 254 of 595

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

EYLEA HD is indicated for the treatment of:

1.1 Neovascular (Wet) Age-Related Macular Degeneration (nAMD)

1.2 Diabetic Macular Edema (DME)

1.3 Diabetic Retinopathy (DR)

2 DOSAGE AND ADMINISTRATION

2.1 Important Injection Instructions

For ophthalmic intravitreal injection. EYLEA HD must only be administered by a qualified physician.

A 5-micron sterile filter needle (18-gauge × 1½-inch), a 1-mL Luer lock syringe and a 30-gauge × ½-inch sterile injection needle are needed.

EYLEA HD is available packaged as follows:

- Vial Only
- Vial Kit with Injection Components (filter needle, syringe, injection needle)

[see How Supplied/Storage and Handling (16)].

2.2 Neovascular (Wet) Age-Related Macular Degeneration (nAMD)

The recommended dose for EYLEA HD is 8 mg (0.07 mL of 114.3 mg/mL solution) administered by intravitreal injection every 4 weeks (approximately every 28 days +/- 7 days) for the first three doses, followed by 8 mg (0.07 mL of 114.3 mg/mL solution) via intravitreal injection once every 8 to 16 weeks, +/- 1 week.

2.3 Diabetic Macular Edema (DME)

The recommended dose for EYLEA HD is 8 mg (0.07 mL of 114.3 mg/mL solution) administered by intravitreal injection every 4 weeks (approximately every 28 days +/- 7 days) for the first three doses, followed by 8 mg (0.07 mL of 114.3 mg/mL solution) via intravitreal injection once every 8 to 16 weeks, +/- 1 week.

2.4 Diabetic Retinopathy (DR)

The recommended dose for EYLEA HD is 8 mg (0.07 mL of 114.3 mg/mL solution) administered by intravitreal injection every 4 weeks (approximately every 28 days +/- 7 days) for

PGR2026-00039
Biocon Ex.1065
Page 255 of 595

the first three doses, followed by 8 mg (0.07 mL of 114.3 mg/mL solution) via intravitreal injection once every 8 to 12 weeks, +/- 1 week.

2.5 Preparation for Administration

The EYLEA HD glass vial is for one-time use in one eye only. Discard unused portion. EYLEA HD does not contain an anti-microbial preservative. Extraction of multiple doses from a single vial may increase the risk of contamination and subsequent infection.

Do not use if the package or its components are expired, damaged, or have been tampered with.

Check the label on the vial to make sure you have the correct aflibercept strength.

Prepare for intravitreal injection with the following medical devices for single use.

- a 5-micron sterile filter needle (18-gauge × 1½-inch)
- a 1-mL sterile Luer lock syringe (with marking to measure 0.07 mL)
- a sterile injection needle (30-gauge × ½-inch)

1. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. **Do not** use the vial if particulates, cloudiness, or discoloration are visible.
2. Remove the protective plastic cap from the vial (see Figure 1).

Figure 1:



PGR2026-00039
Biocon Ex.1065
Page 256 of 595

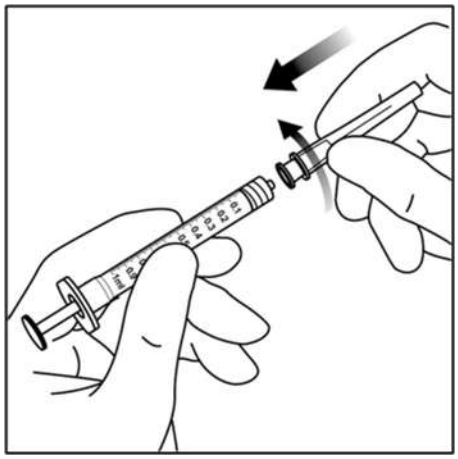
3. Clean the top of the vial with an alcohol wipe (see Figure 2).

Figure 2:



4. Use aseptic technique to carry out steps 4 – 11. Remove the 18-gauge x 1½-inch, 5-micron, filter needle and the 1-mL syringe from their packaging. Attach the filter needle to the syringe by twisting it onto the Luer lock syringe tip (see Figure 3).

Figure 3:



5. Push the filter needle into the center of the vial stopper until the needle is completely inserted into the vial and the tip touches the bottom or bottom edge of the vial.
6. Withdraw all of the EYLEA HD vial contents into the syringe, keeping the vial in an upright position, slightly inclined to ease complete withdrawal. To deter the introduction of air, ensure the bevel of the filter needle is submerged into the liquid. Continue to tilt the vial

PGR2026-00039
Biocon Ex.1065
Page 257 of 595

during withdrawal keeping the bevel of the filter needle submerged in the liquid (see Figure 4a and Figure 4b).

Figure 4a:

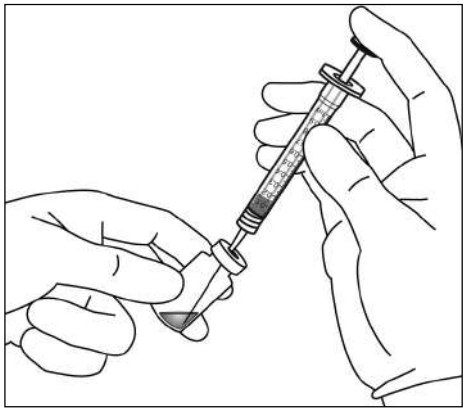
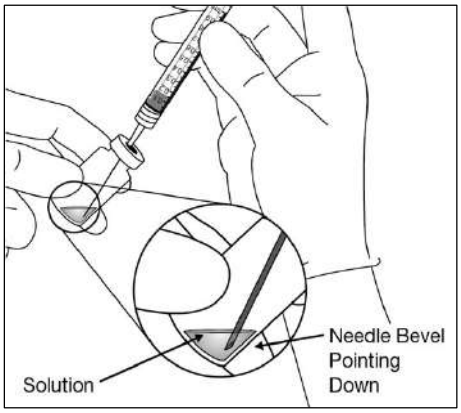
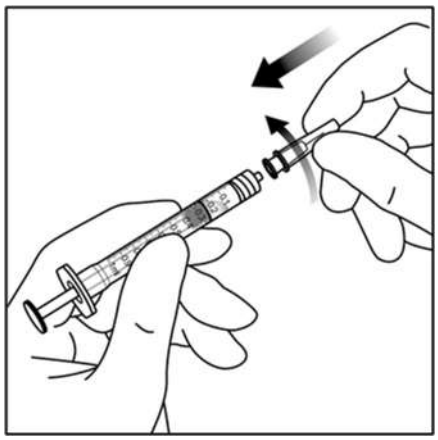


Figure 4b:



7. Ensure that the plunger rod is drawn sufficiently back when emptying the vial in order to completely empty the filter needle.
8. Remove the filter needle from the syringe and properly dispose of the filter needle.
   Note: Filter needle is **not** to be used for intravitreal injection.
9. Remove the 30-gauge x ½-inch injection needle from its packaging and attach the injection needle to the syringe by firmly twisting the injection needle onto the Luer lock syringe tip (see Figure 5).

Figure 5:



PGR2026-00039
Biocon Ex.1065
Page 258 of 595

10. Holding the syringe with the needle pointing up, check the syringe for bubbles. If there are bubbles, gently tap the syringe with your finger until the bubbles rise to the top (see Figure 6).

Figure 6:



11. To eliminate all of the bubbles and to expel excess drug, SLOWLY depress the plunger so that the plunger tip aligns with the line that marks 0.07 mL on the syringe (see Figure 7a and Figure 7b).

Figure 7a:

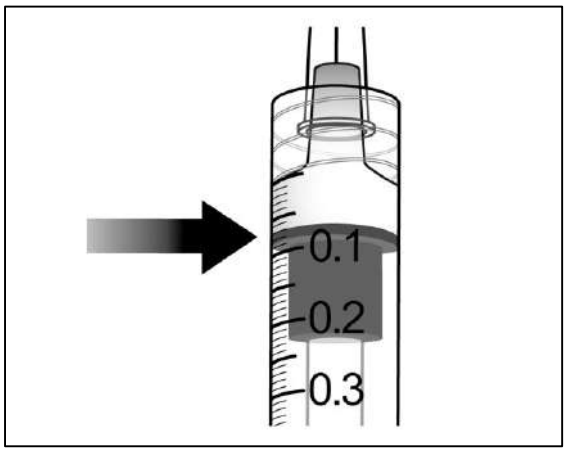
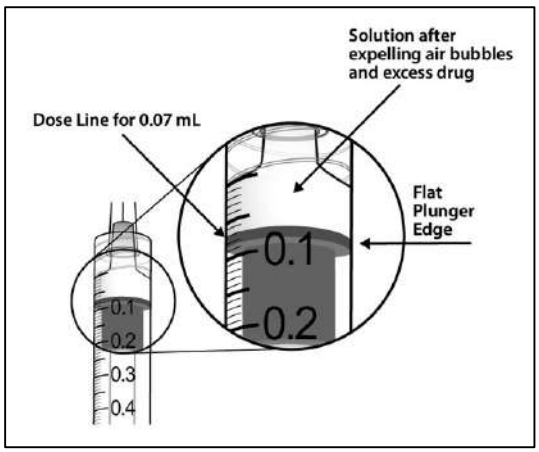


Figure 7b:



2.6 Injection Procedure

The intravitreal injection procedure should be carried out under controlled aseptic conditions, which include surgical hand disinfection and the use of sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent). Adequate anesthesia and a topical broad–spectrum microbicide should be given prior to the injection.

Immediately following the intravitreal injection, patients should be monitored for elevation in intraocular pressure. Appropriate monitoring may consist of a check for perfusion of the optic nerve head or tonometry. If required, a sterile paracentesis needle should be available.

PGR2026-00039
Biocon Ex.1065
Page 259 of 595

Following intravitreal injection, patients and/or caregivers should be instructed to report any signs and/or symptoms suggestive of endophthalmitis or retinal detachment (e.g., eye pain, redness of the eye, photophobia, blurring of vision) without delay *[see Patient Counseling Information (17)]*.

Each vial should only be used for the treatment of a single eye. If the contralateral eye requires treatment, a new vial should be used and the sterile field (including a new syringe, gloves, drapes, eyelid speculum, filter and injection needles) should be changed before EYLEA HD is administered to the other eye.

After injection, discard any unused product or waste material in accordance with local regulations.

3 DOSAGE FORMS AND STRENGTHS

EYLEA HD is a clear to slightly opalescent, colorless to pale yellow solution available as:

- Injection: 8 mg (0.07 mL of a 114.3 mg/mL solution) in a single-dose glass vial

4 CONTRAINDICATIONS

4.1 Ocular or Periocular Infections

EYLEA HD is contraindicated in patients with ocular or periocular infections.

4.2 Active Intraocular Inflammation

EYLEA HD is contraindicated in patients with active intraocular inflammation.

4.3 Hypersensitivity

EYLEA HD is contraindicated in patients with known hypersensitivity to aflibercept or any of the excipients in EYLEA HD. Hypersensitivity reactions may manifest as rash, pruritus, urticaria, severe anaphylactic/anaphylactoid reactions, or severe intraocular inflammation.

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis, Retinal Detachments, and Retinal Vasculitis with or without Occlusion

Intravitreal injections including those with aflibercept have been associated with endophthalmitis and retinal detachments *[see Adverse Reactions (6.1)]* and, more rarely, retinal vasculitis with or without occlusion *[see Adverse Reactions (6.2)]*. Proper aseptic injection technique must always be used when administering EYLEA HD. Patients and/or caregivers should be instructed to report any signs and/or symptoms suggestive of endophthalmitis, retinal detachment, or retinal vasculitis without delay and should be managed appropriately *[see Dosage and Administration (2.6) and Patient Counseling Information (17)]*.

PGR2026-00039
Biocon Ex.1065
Page 260 of 595

5.2 Increase in Intraocular Pressure

Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA HD *[see Adverse Reactions (6.1)]*. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with vascular endothelial growth factor (VEGF) inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately *[see Dosage and Administration (2.6)]*.

5.3 Thromboembolic Events

There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA HD. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in the wet AMD study (PULSAR) from baseline through week 48 was 0.4% (3 out of 673) in the combined group of patients treated with EYLEA HD compared with 1.5% (5 out of 336) in patients treated with EYLEA 2 mg. The incidence of reported thromboembolic events in the DME study (PHOTON) from baseline to week 48 was 3.1% (15 out of 491) in the combined group of patients treated with EYLEA HD compared with 3.6% (6 out of 167) in patients treated with EYLEA 2 mg.

6 ADVERSE REACTIONS

The following potentially serious adverse reactions are described elsewhere in the labeling:

- Hypersensitivity *[see Contraindications (4.3)]*
- Endophthalmitis, Retinal Detachments, and Retinal Vasculitis with or without Occlusion *[see Warnings and Precautions (5.1)]*
- Increase in intraocular pressure *[see Warnings and Precautions (5.2)]*
- Thromboembolic events *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in other clinical trials of the same or another drug and may not reflect the rates observed in practice.

A total of 1164 patients were treated with EYLEA HD and 503 patients were treated with EYLEA 2 mg in two clinical studies. The most common adverse reactions reported in ≥3% of patients treated with EYLEA HD were cataract, conjunctival hemorrhage, intraocular pressure increased, ocular discomfort/eye pain/eye irritation, vision blurred, vitreous floaters, vitreous detachment, corneal epithelium defect, and retinal hemorrhage. The data described below reflect exposure to EYLEA HD or EYLEA 2 mg in controlled clinical studies (PULSAR and PHOTON), each for 48 weeks *[see Clinical Studies (14.1, 14.2)]*.

PGR2026-00039
Biocon Ex.1065
Page 261 of 595

Table 1: Adverse Reactions (≥1%) in at least one group in the PULSAR or PHOTON studies

Adverse Reactions	PULSAR			PHOTON		
	EYLEA HD q12	EYLEA HD q16	EYLEA 2q8	EYLEA HD q12	EYLEA HD q16	EYLEA 2q8
	n=335	n=338	n=336	n=328	n=163	n=167
Cataract[a]	4%	4%	4%	3%	6%	3%
Conjunctival hemorrhage[a]	3%	2%	1%	4%	4%	4%
Intraocular pressure increased[a]	4%	4%	2%	3%	1%	4%
Ocular discomfort/eye pain/eye irritation[a]	3%	3%	2%	4%	2%	4%
Vision blurred[a]	4%	6%	7%	3%	3%	4%
Vitreous floaters[a]	1%	4%	3%	5%	2%	3%
Vitreous detachment[a]	2%	3%	2%	4%	2%	1%
Corneal epithelium defect[a]	2%	2%	3%	3%	6%	1%
Retinal hemorrhage	3%	3%	4%	0	4%	1%
Intraocular inflammation[a]	1%	1%	1%	1%	0	1%
Retinal pigment epithelial tear/epitheliopathy[a]	2%	1%	2%	<1%	0	0
Vitreous hemorrhage	<1%	1%	1%	2%	1%	1%
Retinal Detachment[a]	1%	<1%	0	<1%	1%	0
Foreign body sensation in eyes[a]	1%	1%	2%	<1%	0	0
Retinal pigment epithelial detachment[a]	1%	1%	2%	0	0	0

[a.] Represents grouping of related terms

Adverse drug reactions (ADRs) reported in <1% of participants treated with EYLEA HD were ocular hyperemia (includes adverse events of conjunctival hyperemia, conjunctival irritation, ocular hyperemia), lacrimation increased, eyelid edema, hypersensitivity (includes adverse events of rash, urticaria, pruritus), retinal tear and injection site hemorrhage.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of aflibercept. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

PGR2026-00039
Biocon Ex.1065
Page 262 of 595

Eye disorders:

- Retinal vasculitis and occlusive retinal vasculitis related to intravitreal injection with aflibercept (reported at a rate of 0.6 and 0.2 per 1 million injections, respectively, based on postmarketing experience from November 2011 until November 2023).
- Scleritis.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Adequate and well-controlled studies with EYLEA HD have not been conducted in pregnant women. Aflibercept produced adverse embryofetal effects in rabbits, including external, visceral, and skeletal malformations. A fetal No Observed Adverse Effect Level (NOAEL) was not identified. At the lowest dose shown to produce adverse embryofetal effects, systemic exposure (based on AUC for free aflibercept) was approximately 0.9 -fold of the population pharmacokinetic estimated exposure in humans after an intravitreal dose of 8 mg *(see Data)*.

Animal reproduction studies are not always predictive of human response, and it is not known whether EYLEA HD can cause fetal harm when administered to a pregnant woman. Based on the anti-VEGF mechanism of action for aflibercept *[see Clinical Pharmacology (12.1)]*, treatment with EYLEA HD may pose a risk to human embryofetal development. EYLEA HD should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

In two embryofetal development studies, aflibercept produced adverse embryofetal effects when administered every three days during organogenesis to pregnant rabbits at intravenous doses ≥3 mg per kg, or every six days during organogenesis at subcutaneous doses ≥0.1 mg per kg.

Adverse embryofetal effects included increased incidences of postimplantation loss and fetal malformations, including anasarca, umbilical hernia, diaphragmatic hernia, gastroschisis, cleft palate, ectrodactyly, intestinal atresia, spina bifida, encephalomeningocele, heart and major vessel defects, and skeletal malformations (fused vertebrae, sternebrae, and ribs; supernumerary vertebral arches and ribs; and incomplete ossification). The maternal No Observed Adverse Effect Level (NOAEL) in these studies was 3 mg per kg. Aflibercept produced fetal malformations at all doses assessed in rabbits and the fetal NOAEL was not identified. At the lowest dose shown to produce adverse embryofetal effects in rabbits (0.1 mg per kg), systemic exposure (AUC) of free aflibercept was approximately 0.9-fold of the population

PGR2026-00039
Biocon Ex.1065
Page 263 of 595

pharmacokinetic estimated systemic exposure (AUC) in humans after an intravitreal dose of 8 mg.

8.2 Lactation

Risk Summary

There is no information regarding the presence of aflibercept in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production/excretion. Because many drugs are excreted in human milk, and because the potential for absorption and harm to infant growth and development exists, EYLEA HD is not recommended during breastfeeding.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for EYLEA HD and any potential adverse effects on the breastfed child from EYLEA HD.

8.3 Females and Males of Reproductive Potential

Contraception

Females of reproductive potential are advised to use effective contraception prior to the initial dose, during treatment, and for at least 4 months after the last intravitreal injection of EYLEA HD.

Infertility

There are no data regarding the effects of EYLEA HD on human fertility. Aflibercept adversely affected female and male reproductive systems in cynomolgus monkeys when administered by intravenous injection at a dose 91 times higher (based on AUC of free aflibercept) than the corresponding systemic level estimated based on population pharmacokinetic analysis in humans following an intravitreal dose of 8 mg. A No Observed Adverse Effect Level (NOAEL) was not identified. These findings were reversible within 20 weeks after cessation of treatment *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

The safety and effectiveness of EYLEA HD in pediatric patients have not been established.

8.5 Geriatric Use

In PULSAR, approximately 90% (604/673) of the patients in the HDq12 and HDq16 groups were 65 years of age or older and approximately 51% (343/673) were 75 years of age or older.

In PHOTON, approximately 44% (214/491) of the patients in the HDq12 and HDq16 groups were 65 years of age or older and approximately 10% (50/491) were 75 years of age or older.

10 OVERDOSAGE

Overdosing with increased injection volume may increase intraocular pressure. Therefore, in case of overdosage, intraocular pressure should be monitored and if deemed necessary by the treating physician, adequate treatment should be initiated.

PGR2026-00039
Biocon Ex.1065
Page 264 of 595

11 DESCRIPTION

Aflibercept is a recombinant fusion protein consisting of portions of human VEGF receptors 1 and 2 extracellular domains fused to the Fc portion of human IgG1 formulated as an iso-osmotic solution for intravitreal administration. Aflibercept is a dimeric glycoprotein and contains glycosylation, constituting an additional 15% of the total molecular mass, resulting in a total molecular weight of 115 kDa. Aflibercept is produced in recombinant Chinese hamster ovary (CHO) cells.

EYLEA HD (aflibercept) injection is a sterile, clear to slightly opalescent, and colorless to pale yellow solution. EYLEA HD is supplied as a sterile, aqueous solution for intravitreal injection in a single-dose glass vial designed to deliver 0.07 mL (70 microliters) of solution containing 8 mg of aflibercept in a buffer containing arginine hydrochloride (0.737 mg), histidine (0.04 mg), L-histidine hydrochloride monohydrate (0.093 mg), polysorbate 20 (0.021 mg), sucrose (3.5 mg) and water for injection with a pH of 5.8. EYLEA HD does not contain an anti-microbial preservative.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Vascular endothelial growth factor-A (VEGF-A) and placental growth factor (PlGF) are members of the VEGF family of angiogenic factors that can act as mitogenic, chemotactic, and vascular permeability factors for endothelial cells. VEGF acts via two receptor tyrosine kinases, VEGFR-1 and VEGFR-2, present on the surface of endothelial cells. PlGF binds only to VEGFR-1, which is also present on the surface of leucocytes. Activation of these receptors by VEGF-A can result in neovascularization and vascular permeability.

Aflibercept acts as a soluble decoy receptor that binds VEGF-A and PlGF, and thereby can inhibit the binding and activation of these cognate VEGF receptors.

12.2 Pharmacodynamics

Increased retinal thickness, assessed by optical coherence tomography (OCT), is associated with nAMD and DME. Reductions in central subfield thickness (CST) were observed across all treatment arms throughout the two Phase 3 studies in nAMD and DME.

12.3 Pharmacokinetics

EYLEA HD is administered intravitreally to exert local effects in the eye. In patients with wet AMD, or DME, following intravitreal administration of EYLEA HD, a fraction of the administered dose is expected to bind with endogenous VEGF in the eye to form an inactive aflibercept: VEGF complex. Once absorbed into the systemic circulation, aflibercept presents in the plasma as free aflibercept (unbound to VEGF) and a more predominant stable inactive form with circulating endogenous VEGF (i.e., aflibercept: VEGF complex).

Absorption/Distribution

As no relevant differences in pharmacokinetics between the nAMD and DME populations were observed based on a population pharmacokinetic analysis of the data, population

PGR2026-00039
Biocon Ex.1065
Page 265 of 595

pharmacokinetic estimated parameters are presented for the two populations combined. Following unilateral intravitreal administration of 8 mg aflibercept, the mean (SD) C_{max} of free aflibercept in plasma was 0.30 (0.27) mg/L, and the median time to maximal concentration in plasma was 2.9 days. The accumulation of free aflibercept in plasma following three initial monthly intravitreal doses was minimal (mean accumulation ratio 1.2); subsequently, no further accumulation was observed.

The volume of distribution of free aflibercept following intravenous (I.V.) administration of aflibercept is approximately 7 L.

Metabolism/Elimination

Aflibercept is a therapeutic protein and no drug metabolism studies have been conducted. Aflibercept is expected to undergo elimination through both target-mediated disposition via binding to free endogenous VEGF and metabolism via proteolysis. The median time to reach non-quantifiable concentrations of free aflibercept in plasma for 8 mg administered intravitreally was 3.5 weeks.

Specific Populations

Renal and Hepatic Impairment

Population pharmacokinetic analysis revealed that systemic exposures to aflibercept in patients with mild to severe renal impairment (eGFR 15 to < 90 mL/min, estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation for eGFR were similar to those with normal renal function. Mild hepatic impairment had no influence on systemic exposures to aflibercept compared to patients with normal hepatic function. No data for patients with moderate and severe hepatic impairment are available. No dose adjustment based on renal or hepatic impairment status is needed.

Other

No dosage adjustment is required for any of the populations that have been studied (e.g., age and race).

12.6 Immunogenicity

The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the studies described below with the incidence of anti-drug antibodies for other products.

During the 48-week treatment with aflibercept administrated IVT, the incidence of anti-aflibercept antibody formation in the 8 mg treatment groups was 2.7% (25/937 participants with nAMD [PULSAR] or DME [PHOTON]).

PGR2026-00039
Biocon Ex.1065
Page 266 of 595

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been conducted on the mutagenic or carcinogenic potential of aflibercept. Effects on male and female fertility were assessed as part of a 6-month study in monkeys with intravenous administration of aflibercept at weekly doses ranging from 3 to 30 mg per kg. Absent or irregular menses associated with alterations in female reproductive hormone levels and changes in sperm morphology and motility were observed at all dose levels. In addition, females showed decreased ovarian and uterine weight accompanied by compromised luteal development and reduction of maturing follicles. These changes correlated with uterine and vaginal atrophy. All changes were reversible within 20 weeks after cessation of treatment. A No Observed Adverse Effect Level (NOAEL) was not identified. Intravenous administration of the lowest dose of aflibercept assessed in monkeys (3 mg per kg) resulted in systemic exposure (AUC) for free aflibercept that was 91 times higher than the population pharmacokinetic estimated systemic exposure in humans after an intravitreal dose of 8 mg.

13.2 Animal Toxicology and/or Pharmacology

Erosions and ulcerations of the respiratory epithelium in nasal turbinates in monkeys treated with aflibercept intravitreally were observed at intravitreal doses of 2, 4 or 7 mg per eye. At the NOAEL of 0.5 mg per eye in monkeys, the systemic exposure (AUC) for free aflibercept was approximately 3 times higher than the population pharmacokinetic estimated exposure observed in humans after an intravitreal dose of 8 mg. Similar effects were not seen in clinical studies *[see Clinical Studies (14)]*.

PGR2026-00039
Biocon Ex.1065
Page 267 of 595

14 CLINICAL STUDIES

14.1 Neovascular (Wet) Age-Related Macular Degeneration (nAMD)

The safety and efficacy of EYLEA HD were assessed in a randomized, multi-center, double-masked, active-controlled study (PULSAR) in treatment-naïve patients with nAMD. A total of 1009 patients were treated and analyzed for efficacy (673 with EYLEA HD). Patients were randomly assigned in a 1:1:1 ratio to 1 of 3 treatment groups: 1) EYLEA HD administered every 12 weeks following 3 initial monthly doses (HDq12); 2) EYLEA HD administered every 16 weeks following 3 initial monthly doses (HDq16); 3) EYLEA 2 mg administered every 8 weeks (2q8) following 3 initial monthly doses. In the EYLEA HD groups, patients could be treated as frequently as every 8 weeks based on protocol-defined visual and anatomic criteria, starting at week 16. Patients ranged from 50 to 96 years of age with a mean of 74.5 years. At baseline, mean visual acuity was approximately 60 letters (range: 24 to 78 letters).

The primary efficacy endpoint was the change from baseline in BCVA at week 48 as measured by the Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

Both HDq12 and HDq16 treatments were shown to be non-inferior and clinically equivalent to 2q8 treatment with respect to the change in BCVA score at week 48 using the pre-specified non-inferiority margin of 4 letters. In patients completing week 48, the mean number of injections administered were 5.2 in the HDq16 group (n=312), 6.1 in the HDq12 group (n=316) and 6.9 in the EYLEA q8 group (n=309). Detailed results from the analysis of the PULSAR study are shown in Table 2 and Figure 8 below.

Efficacy results in all subgroups (e.g., age, gender, geographic region, ethnicity, race, baseline BCVA and lesion type) were consistent with those in the overall population.

Table 2: Efficacy Outcomes (Full Analysis Set) in PULSAR Study

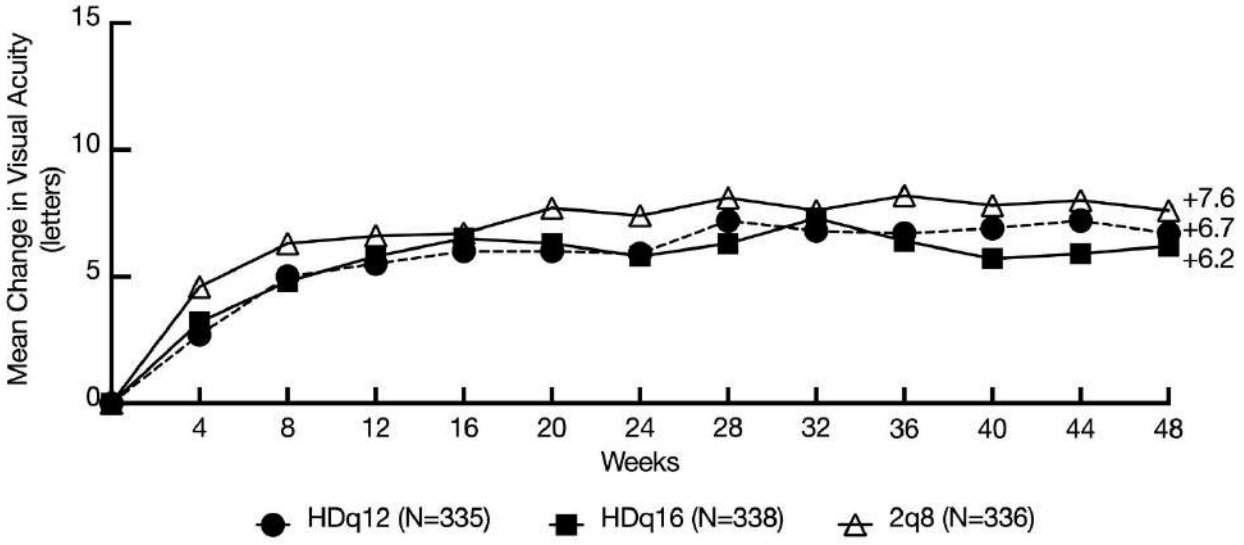
Efficacy Outcomes	EYLEA HDq12	EYLEA HDq16	EYLEA 2q8
Full Analysis Set[a]	N=335	N=338	N=336
Mean change in BCVA as measured by ETDRS letter score from baseline (SD) at week 48[b]	6.7 (12.6)	6.2 (11.7)	7.6 (12.2)
LS mean (SE) change from baseline [c]	6.1 (0.8)	5.9 (0.7)	7.0 (0.7)
Difference in LS mean (95% CI)[c]	-1.0 (-2.9, 0.9)	-1.1 (-3.0, 0.7)	

BCVA = Best Corrected Visual Acuity; ETDRS = Early Treatment Diabetic Retinopathy Study; SD = Standard Deviation; LS = Least Square; SE = Standard Error; CI = Confidence Interval; MMRM = Mixed Model for Repeated Measurements

a. Full Analysis Set (FAS) includes all randomized patients who received at least 1 dose of study medication
b. Observed values at week 48: n=299 for HDq12; n=289 for HDq16; n=285 for 2q8
c. Estimate based on the MMRM model, was computed for the differences of HDq12 minus 2q8 and HDq16 minus 2q8, respectively, with two-sided 95% CIs

PGR2026-00039
Biocon Ex.1065
Page 268 of 595

Figure 8: Mean Change from Baseline in BCVA as measured by ETDRS Letter Score by Visits through Week 48 (Observed Cases)



14.2 Diabetic Macular Edema (DME)

The safety and efficacy of EYLEA HD was assessed in a randomized, multi-center, double-masked, active-controlled study (PHOTON) in patients with DME involving the center of the macula. A total of 658 patients were treated and analyzed for efficacy (491 with EYLEA HD). Patients were randomly assigned in a 2:1:1 ratio to 1 of 3 treatment groups: 1) EYLEA HD administered every 12 weeks following 3 initial monthly doses (HDq12); 2) EYLEA HD administered every 16 weeks following 3 initial monthly doses (HDq16); 3) EYLEA 2 mg administered every 8 weeks (2q8) following 5 initial monthly doses. In the EYLEA HD groups, patients could be treated as frequently as every 8 weeks based on protocol-defined visual and anatomic criteria, starting at week 16. Patient ages ranged from 24 to 90 years with a mean of 62.3 years. A total of 44% of patients were previously treated for DME. At baseline, the overall mean visual acuity was 63 letters (range: 24 to 79 letters).

The primary efficacy endpoint was the change from baseline in BCVA at week 48 as measured by the ETDRS letter score. Both HDq12 and HDq16 treatments were shown to be non-inferior and clinically equivalent to 2q8 treatment with respect to the change in BCVA score at week 48 using the pre-specified non-inferiority margin of 4 letters. In patients completing week 48, the mean number of injections administered were 5.0 in the HDq16 group (n=155), 6.0 in the HDq12 group

PGR2026-00039
Biocon Ex.1065
Page 269 of 595

(n=298) and 7.9 in the EYLEA q8 group (n=156). Detailed results from the analysis of the PHOTON study are shown in Table 3 and Figure 9 below.

Table 3: Efficacy Outcomes (Full Analysis Set) in PHOTON Study

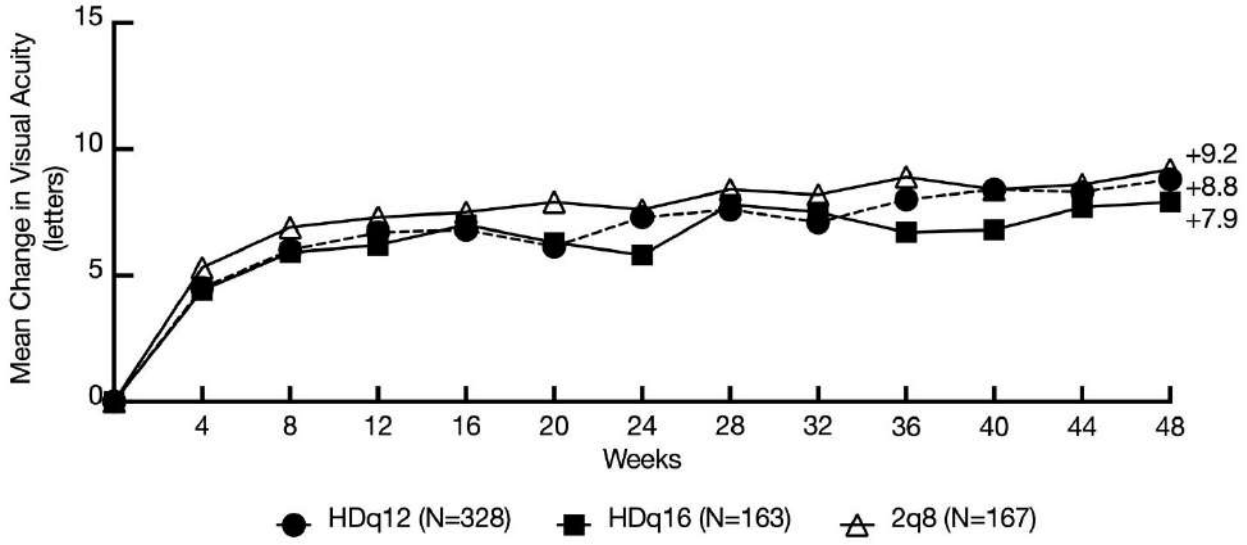
Efficacy Outcomes	EYLEA HDq12	EYLEA HDq16	EYLEA 2q8
Full Analysis Set[a]	N=328	N=163	N=167
Mean change in BCVA as measured by ETDRS letter score from baseline (SD) at week 48[b]	8.8 (9.0)	7.9 (8.4)	9.2 (9.0)
LS mean (SE) change from baseline[c]	8.1 (0.6)	7.2 (0.7)	8.7 (0.7)
Difference in LS mean (95% CI)[c]	-0.6 (-2.3, 1.1)	-1.4 (-3.3, 0.4)	

BCVA = Best Corrected Visual Acuity; ETDRS = Early Treatment Diabetic Retinopathy Study; SD = Standard Deviation; LS = Least Square; SE = Standard Error; CI = Confidence Interval; MMRM = Mixed Model for Repeated Measurements.

a. FAS includes all randomized patients who received at least 1 dose of study medication
b. Observed values at week 48: n=277 for HDq12; n=149 for HDq16; n=150 for 2q8
c. Estimate based on the MMRM model, was computed for the differences of HDq12 minus 2q8 and HDq16 minus 2q8, respectively with two-sided 95% CIs

Efficacy results in all subgroups (e.g., age, gender, geographic region, ethnicity, race, baseline, BCVA, baseline CRT and prior DME treatment) were consistent with those in the overall population.

Figure 9: **Mean Change from Baseline in BCVA as measured by ETDRS Letter Score by Visits through Week 48 (Observed Cases)**



14.3 Diabetic Retinopathy (DR)

Efficacy and safety data of EYLEA HD in diabetic retinopathy (DR) are derived from the PHOTON study.

PGR2026-00039
Biocon Ex.1065
Page 270 of 595

In the PHOTON study, a key efficacy outcome was the change in the Early Treatment Diabetic Retinopathy Study (ETDRS) Diabetic Retinopathy Severity Scale (ETDRS-DRSS). Each EYLEA HD group was compared to the 2q8 group using a NI margin of 10%.

The ETDRS-DRSS score was assessed at baseline and approximately every 3 months thereafter for the duration of the study *[see Clinical Studies (14.2)]*. Baseline ETDRS-DRSS scores were generally balanced across treatment groups.

Results from the analysis of ETDRS-DRSS scores at week 48 in the PHOTON study are shown in Table 4 below:

Table 4: Proportion of Patients Who Achieved a ≥2-Step Improvement from Baseline in the ETDRS-DRSS Score at Week 48 (Full Analysis Set) in PHOTON

Efficacy Outcomes	EYLEA HDq12	EYLEA HDq16	EYLEA 2q8
Full Analysis Set[a]	N=328	N=163	N=167
Proportion of patients with a ≥2-step improvement on ETDRS-DRSS from Baseline (%)[b]	29%	20%	27%
Difference[c](%) (95% CI)	2% (-6.6, 10.6)	-8% (-16.9, 1.8)	

Missing or non-gradable post-baseline ETDRS-DRSS values were imputed using the last gradable ETDRS-DRSS values. Patients were considered as non-responders if all post-baseline measurements were missing or non-gradable. Missing or ungradable baseline was not included in the denominator.

a. FAS includes all randomized patients who received at least 1 dose of study medication
b. Last observation carried forward
c. Difference with confidence interval (CI) was calculated using Mantel-Haenszel weighting scheme

The EYLEA HDq16 did not meet the non-inferiority criteria for the proportion of patients with a ≥2-step improvement on ETDRS-DRSS and is not considered clinically equivalent to EYLEA administered every 8 weeks.

Results of the subgroups (e.g., age, gender, race, ethnicity, baseline BCVA and prior DME treatment) on the proportion of patients who achieved a ≥2-step improvement on the ETDRS-DRSS from baseline to week 48 were, in general, consistent with those in the overall population.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

EYLEA HD (aflibercept) is a clear to slightly opalescent, colorless to pale yellow solution supplied in the following presentations *[see Dosage and Administration (2.5) and (2.6)]*. Each vial is for single eye use only. Discard unused portion.

PGR2026-00039
Biocon Ex.1065
Page 271 of 595

NDC NUMBER	CARTON TYPE	CARTON CONTENTS
61755-050-01	Vial Kit with Injection Components	• one EYLEA HD 8 mg (0.07 mL of a 114.3 mg/mL solution), single-dose glass vial • one 18-gauge x 1½-inch, 5-micron, filter needle for withdrawal of the vial contents • one 30-gauge x ½-inch injection needle for intravitreal injection • one 1-mL syringe for administration • one Prescribing Information
61755-051-01	Vial Only	• one EYLEA HD 8 mg (0.07 mL of a 114.3 mg/mL solution) single-dose glass vial • one Prescribing Information

16.2 Storage and Handling

Refrigerate EYLEA HD at 2°C to 8ºC (36°F to 46ºF). Do not freeze. Do not use beyond the date stamped on the carton and container label. Store in the original carton until time of use to protect from light.

17 PATIENT COUNSELING INFORMATION

In the days following EYLEA HD administration, patients are at risk of developing endophthalmitis, retinal detachment, or retinal vasculitis with or without occlusion. If the eye becomes red, sensitive to light, painful, or develops a change in vision, advise patients and/or caregivers to seek immediate care from an ophthalmologist *[see Warnings and Precautions (5.1)]*.

Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA HD and the associated eye examinations *[see Adverse Reactions (6)]*. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

PGR2026-00039
Biocon Ex.1065
Page 272 of 595

REGENERON

Manufactured by:
Regeneron Pharmaceuticals, Inc.
777 Old Saw Mill River Road
Tarrytown, NY 10591-6707
U.S. License Number 1760
For patent information: https://www.regeneron.com/downloads/us-patent-products.pdf
EYLEA HD is a registered trademark of Regeneron Pharmaceuticals, Inc.
©2024, Regeneron Pharmaceuticals, Inc.
All rights reserved.
Date: October 2024

PGR2026-00039
Biocon Ex.1065
Page 273 of 595

APPENDIX GENE01

https://web.archive.org/web/20170615000000*/https://www.gene.com/download/pdf/lucentis_prescribing.pdf September 17, 2025

INTERNET ARCHIVE WEB TEXTS VIDEO AUDIO SOFTWARE IMAGES SIGN UP | LOG IN UPLOAD Search

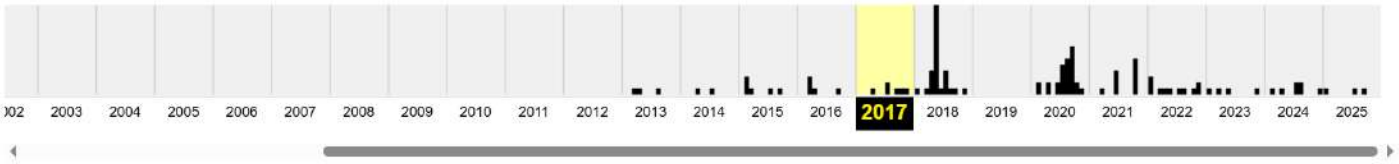
ABOUT BLOG PROJECTS HELP DONATE CONTACT JOBS VOLUNTEER PEOPLE

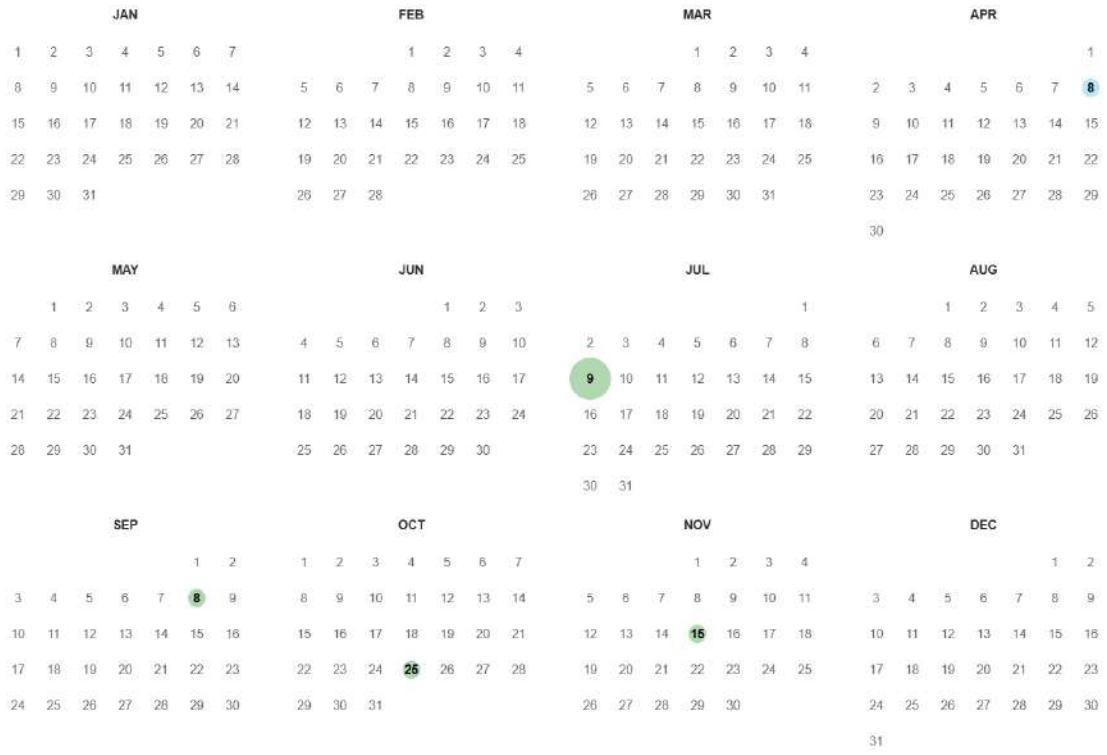
DONATE INTERNET ARCHIVE WayBackMachine Explore more than 946 billion web pages saved over time

https://www.gene.com/download/pdf/lucentis_prescribing.pdf

Calendar · Collections · Changes · Summary · Site Map · URLs

Saved **115 times** between March 3, 2013 and September 8, 2025.





Note

This calendar view maps the number of times **https://www.gene.com/download/pdf/lucentis_prescribing.pdf** was crawled by the Wayback Machine, *not* how many times the site was actually updated. More info in the FAQ. Green indicates redirects (3xx).

FAQ | Contact Us | Terms of Service (Dec 31, 2014)

The Wayback Machine is an initiative of the Internet Archive, a 501(c)(3) non-profit, building a digital library of Internet sites and other cultural artifacts in digital form. Other projects include Open Library & archive-it.org.

Your use of the Wayback Machine is subject to the Internet Archive's Terms of Use.

https://web.archive.org/web/20170408234317/https://www.gene.com/download/pdf/lucentis_prescribing.pdf September 17, 2025

INTERNET ARCHIVE WayBack Machine https://www.gene.com/download/pdf/lucentis_prescribing.pdf Go SEP APR JUL
115 captures 08
3 Mar 2013 - 8 Sep 2025 2016 2017 2018 About this capture







HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use LUCENTIS safely and effectively. See full prescribing information for LUCENTIS.

LUCENTIS® (ranibizumab injection)
For Intravitreal Injection
Initial U.S. Approval: 2006

----------RECENT MAJOR CHANGES----------

Indications and Usage, Myopic Choroidal Neovascularization (mCNV) (1.5)	01/2017
General Dosing Information (2.1)	11/2016
Dosage and Administration, Myopic Choroidal Neovascularization (mCNV) (2.6)	01/2017
Dosage and Administration, Preparation for Administration (2.7)	11/2016
Dosage and Administration, Administration (2.8)	10/2016

----------INDICATIONS AND USAGE----------
LUCENTIS, a vascular endothelial growth factor (VEGF) inhibitor, is indicated for the treatment of patients with:
- Neovascular (Wet) Age-Related Macular Degeneration (AMD) (1.1)
- Macular Edema Following Retinal Vein Occlusion (RVO) (1.2)
- Diabetic Macular Edema (DME) (1.3)
- Diabetic Retinopathy in patients with DME (1.4)
- Myopic Choroidal Neovascularization (mCNV) (1.5)

----------DOSAGE AND ADMINISTRATION----------
For Ophthalmic Intravitreal Injection Only (2.1)

Neovascular (Wet) Age-Related Macular Degeneration (AMD) (2.2)
LUCENTIS 0.5 mg (0.05 mL) is recommended to be administered by intravitreal injection once a month (approximately 28 days).

Diabetic Macular Edema (DME) and Diabetic Retinopathy (DR) in patients with Diabetic Macular Edema (2.4, 2.5)
- LUCENTIS 0.3 mg (0.05 mL) is recommended to be administered by intravitreal injection once a month (approximately 28 days).

Myopic Choroidal Neovascularization (mCNV) (2.6)
- LUCENTIS 0.5 mg (0.05 mL) is recommended to be initially administered by intravitreal injection once a month (approximately 28 days) for up to three months. Patients may be retreated if needed.

----------DOSAGE FORMS AND STRENGTHS----------
Single-use prefilled syringe designed to provide 0.05 mL for intravitreal injections:
- 10 mg/mL solution (LUCENTIS 0.5 mg) (3)

Single-use glass vial designed to provide 0.05 mL for intravitreal injections:
- 10 mg/mL solution (LUCENTIS 0.5 mg) (3)
- 6 mg/mL solution (LUCENTIS 0.3 mg) (3)

----------CONTRAINDICATIONS----------
- Ocular or periocular infections (4.1)
- Hypersensitivity (4.2)

----------WARNINGS AND PRECAUTIONS----------
- Endophthalmitis and retinal detachments may occur following intravitreal injections. Patients should be monitored following the injection (5.1).
- Increases in intraocular pressure (IOP) have been noted both pre- and post-intravitreal injection (5.2).
- There is a potential risk of arterial thromboembolic events following intravitreal use of VEGF inhibitors (5.3).
- Fatal events occurred more frequently in patients with DME and DR at baseline, who were treated monthly with LUCENTIS compared with control (5.4).

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use LUCENTIS safely and effectively. See full prescribing information for LUCENTIS.

LUCENTIS® (ranibizumab injection)
For Intravitreal Injection
Initial U.S. Approval: 2006

----------RECENT MAJOR CHANGES----------

Indications and Usage, Myopic Choroidal Neovascularization (mCNV) (1.5)	01/2017
General Dosing Information (2.1)	11/2016
Dosage and Administration, Myopic Choroidal Neovascularization (mCNV) (2.6)	01/2017
Dosage and Administration, Preparation for Administration (2.7)	11/2016
Dosage and Administration, Administration (2.8)	10/2016

----------INDICATIONS AND USAGE----------
LUCENTIS, a vascular endothelial growth factor (VEGF) inhibitor, is indicated for the treatment of patients with:
- Neovascular (Wet) Age-Related Macular Degeneration (AMD) (1.1)
- Macular Edema Following Retinal Vein Occlusion (RVO) (1.2)
- Diabetic Macular Edema (DME) (1.3)
- Diabetic Retinopathy in patients with DME (1.4)
- Myopic Choroidal Neovascularization (mCNV) (1.5)

----------DOSAGE AND ADMINISTRATION----------
For Ophthalmic Intravitreal Injection Only (2.1)

Neovascular (Wet) Age-Related Macular Degeneration (AMD) (2.2)
LUCENTIS 0.5 mg (0.05 mL) is recommended to be administered by intravitreal injection once a month (approximately 28 days).

Although not as effective, patients may be treated with 3 monthly doses followed by less frequent dosing with regular assessment.

Although not as effective, patients may also be treated with one dose every 3 months after 4 monthly doses. Patients should be assessed regularly.

Macular Edema Following Retinal Vein Occlusion (RVO) (2.3)
- LUCENTIS 0.5 mg (0.05 mL) is recommended to be administered by intravitreal injection once a month (approximately 28 days).

Diabetic Macular Edema (DME) and Diabetic Retinopathy (DR) in patients with Diabetic Macular Edema (2.4, 2.5)
- LUCENTIS 0.3 mg (0.05 mL) is recommended to be administered by intravitreal injection once a month (approximately 28 days).

Myopic Choroidal Neovascularization (mCNV) (2.6)
- LUCENTIS 0.5 mg (0.05 mL) is recommended to be initially administered by intravitreal injection once a month (approximately 28 days) for up to three months. Patients may be retreated if needed.

----------DOSAGE FORMS AND STRENGTHS----------
Single-use prefilled syringe designed to provide 0.05 mL for intravitreal injections:
- 10 mg/mL solution (LUCENTIS 0.5 mg) (3)

Single-use glass vial designed to provide 0.05 mL for intravitreal injections:
- 10 mg/mL solution (LUCENTIS 0.5 mg) (3)
- 6 mg/mL solution (LUCENTIS 0.3 mg) (3)

----------CONTRAINDICATIONS----------
- Ocular or periocular infections (4.1)
- Hypersensitivity (4.2)

----------WARNINGS AND PRECAUTIONS----------
- Endophthalmitis and retinal detachments may occur following intravitreal injections. Patients should be monitored following the injection (5.1).
- Increases in intraocular pressure (IOP) have been noted both pre- and post-intravitreal injection (5.2).
- There is a potential risk of arterial thromboembolic events following intravitreal use of VEGF inhibitors (5.3).
- Fatal events occurred more frequently in patients with DME and DR at baseline, who were treated monthly with LUCENTIS compared with control (5.4).

----------ADVERSE REACTIONS----------
- The most common adverse reactions (reported more frequently in LUCENTIS-treated subjects than control subjects) are conjunctival hemorrhage, eye pain, vitreous floaters, and increased IOP (6.2).

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 01/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
- 1.1 Neovascular (Wet) Age-Related Macular Degeneration (AMD)
- 1.2 Macular Edema Following Retinal Vein Occlusion (RVO)
- 1.3 Diabetic Macular Edema (DME)
- 1.4 Diabetic Retinopathy in patients with DME
- 1.5 Myopic Choroidal Neovascularization (mCNV)

2 DOSAGE AND ADMINISTRATION
- 2.1 General Dosing Information
- 2.2 Neovascular (Wet) Age-Related Macular Degeneration (AMD)
- 2.3 Macular Edema Following Retinal Vein Occlusion (RVO)
- 2.4 Diabetic Macular Edema (DME)
- 2.5 Diabetic Retinopathy in patients with DME
- 2.6 Myopic Choroidal Neovascularization (mCNV)
- 2.7 Preparation for Administration
- 2.8 Administration

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS
- 4.1 Ocular or Periocular Infections
- 4.2 Hypersensitivity

5 WARNINGS AND PRECAUTIONS
- 5.1 Endophthalmitis and Retinal Detachments
- 5.2 Increases in Intraocular Pressure
- 5.3 Thromboembolic Events
- 5.4 Fatal Events in Patients with DME and DR at baseline

6 ADVERSE REACTIONS
- 6.1 Injection Procedure
- 6.2 Clinical Studies Experience
- 6.3 Immunogenicity
- 6.4 Postmarketing Experience

7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS
- 8.1 Pregnancy
- 8.2 Lactation
- 8.3 Females and Males of Reproductive Potential
- 8.4 Pediatric Use
- 8.5 Geriatric Use

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY
- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY
- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES
- 14.1 Neovascular (Wet) Age-Related Macular Degeneration (AMD)
- 14.2 Macular Edema Following Retinal Vein Occlusion (RVO)
- 14.3 Diabetic Macular Edema (DME)
- 14.4 Diabetic Retinopathy in patients with DME
- 14.5 Myopic Choroidal Neovascularization (mCNV)

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the Full Prescribing Information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

LUCENTIS is indicated for the treatment of patients with:

1.1 Neovascular (Wet) Age-Related Macular Degeneration (AMD)

1.2 Macular Edema Following Retinal Vein Occlusion (RVO)

1.3 Diabetic Macular Edema (DME)

1.4 Diabetic Retinopathy (Non Proliferative Diabetic Retinopathy (NPDR), Proliferative Diabetic Retinopathy (PDR)) in patients with Diabetic Macular Edema (DME)

1.5 Myopic Choroidal Neovascularization (mCNV)

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

FOR OPHTHALMIC INTRAVITREAL INJECTION ONLY.
Vials: A 5-micron sterile filter needle (19-gauge x 1-1/2 inch), a 1-mL Luer lock syringe and a 30-gauge x ½ inch sterile injection needle are needed but not included.

2.2 Neovascular (Wet) Age-Related Macular Degeneration (AMD)

LUCENTIS 0.5 mg (0.05 mL of 10 mg/mL LUCENTIS solution) is recommended to be administered by intravitreal injection once a month (approximately 28 days).

Although not as effective, patients may be treated with 3 monthly doses followed by less frequent dosing with regular assessment. In the nine months after 3 initial monthly doses, less frequent dosing with 4-5 doses on average is expected to maintain visual acuity while monthly dosing may be expected to result in an additional average 1-2 letter gain. Patients should be assessed regularly [*see Clinical Studies (14.1)*].

Although not as effective, patients may also be treated with one dose every 3 months after 4 monthly doses. Compared with continued monthly dosing, dosing every 3 months over the next 9 months will lead to an approximate 5-letter (1-line) loss of visual acuity benefit, on average. Patients should be assessed regularly [*see Clinical Studies (14.1)*].

2.3 Macular Edema Following Retinal Vein Occlusion (RVO)

LUCENTIS 0.5 mg (0.05 mL of 10 mg/mL LUCENTIS solution) is recommended to be administered by intravitreal injection once a month (approximately 28 days).

In Studies RVO-1 and RVO-2, patients received monthly injections of LUCENTIS for 6 months. In spite of being guided by optical coherence tomography and visual acuity re-treatment criteria, patients who were then not treated at Month 6 experienced on average, a loss of visual acuity at Month 7, whereas patients who were treated at Month 6 did not. Patients should be treated monthly [*see Clinical Studies (14.2)*].

2.4 Diabetic Macular Edema (DME)

LUCENTIS 0.3 mg (0.05 mL of 6 mg/mL LUCENTIS solution) is recommended to be administered by intravitreal injection once a month (approximately 28 days).

2.5 Diabetic Retinopathy in Patients with Diabetic Macular Edema (DME)

LUCENTIS 0.3 mg (0.05 mL of 6 mg/mL LUCENTIS solution) is recommended to be administered by intravitreal injection once a month (approximately 28 days).

2.6 Myopic Choroidal Neovascularization (mCNV)

LUCENTIS 0.5 mg (0.05 mL of 10 mg/mL LUCENTIS solution) is recommended to be initially administered by intravitreal injection once a month (approximately 28 days) for up to three months. Patients may be retreated if needed [(*see Clinical Studies 14.5*)].

2.7 Preparation for Administration

Prefilled Syringe:

To prepare LUCENTIS for intravitreal administration, please adhere to these instructions for use. Read all the instructions carefully before using the prefilled syringe.

How to store LUCENTIS:

1. LUCENTIS should be refrigerated at 2°-8°C (36°-46°F). **Do not** freeze.
2. **Do not** use beyond the expiration date stamped on the label.
3. Protect LUCENTIS prefilled syringes from light and store in the original carton until time of use.
4. **Do not** open the sealed tray until time of use.

The prefilled syringe is for single use only. The prefilled syringe is sterile. **Do not** use the product if the packaging is damaged or has been tampered with.

The opening of the sealed tray and all subsequent steps should be done under aseptic conditions.

For the intravitreal injection, a 30-gauge x ½ inch sterile injection needle should be used (not provided).

Note: the dose must be set to 0.05 mL.

Device description

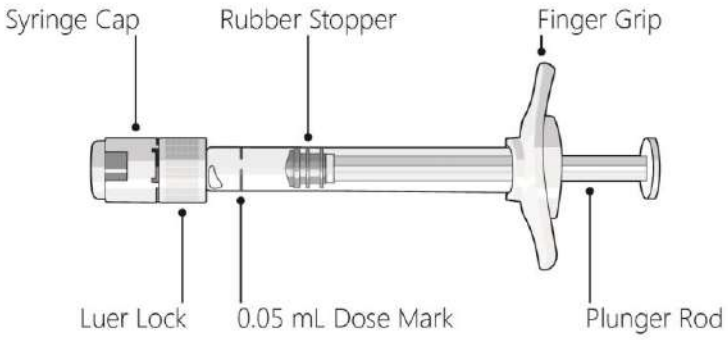


Figure 1

Step 1: Prepare

- Make sure that your pack contains a sterile prefilled syringe in a sealed tray.
- Peel the lid off the syringe tray and, using aseptic technique, remove the syringe.

Step 2: Inspect syringe

- LUCENTIS should be colorless to pale yellow.
- **Do not** use the prefilled syringe if:
  - the syringe cap is detached from the Luer lock.
  - the syringe is damaged.
  - particulates, cloudiness, or discoloration are visible.

Step 3: Remove syringe cap

- Snap off (**do not** turn or twist) the syringe cap (see Figure 2).

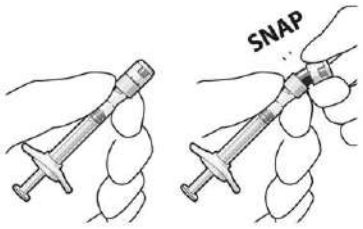


Figure 2

Step 4: Attach needle

- Attach a 30G x ½ inch sterile injection needle firmly onto the syringe by screwing it tightly onto the Luer lock (see Figure 3).
- Carefully remove the needle cap by pulling it straight off.

Note: Do not wipe the needle at any time.

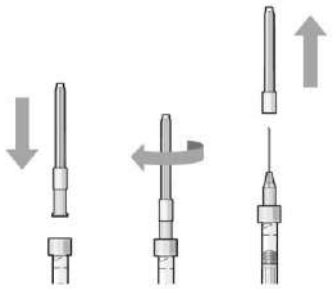


Figure 3

Step 5: Dislodge air bubbles

- Hold the syringe with the needle pointing up.
- If there are any air bubbles, gently tap the syringe with your finger until the bubbles rise to the top (see Figure 4).

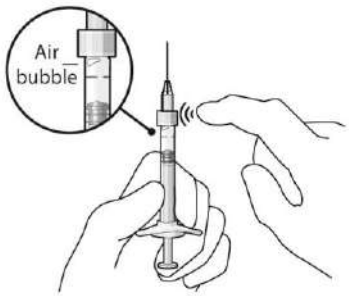


Figure 4

Step 6: Expel air and adjust drug dose

Hold the syringe at eye level, and carefully push the plunger rod until the **edge below the dome** of the rubber stopper is aligned with the 0.05 mL dose mark (see Figure 5).

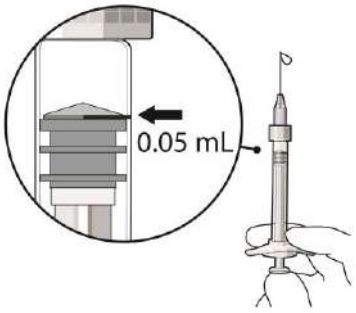


Figure 5

Note: The plunger rod is not attached to the rubber stopper – this is to prevent air being drawn into the syringe.

Step 7: Inject

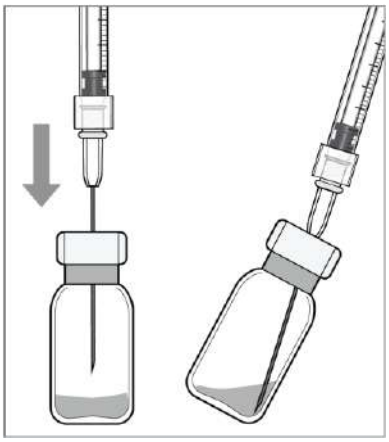
- The injection procedure should be carried out under aseptic conditions.
- Insert the needle into the injection site.
- Inject slowly until rubber stopper reaches the bottom of the syringe to deliver the volume of 0.05 mL.
- After injection, **do not** recap the needle or detach it from the syringe. Dispose of the used syringe together with the needle in a sharps disposal container or in accordance with local requirements.

Vial:

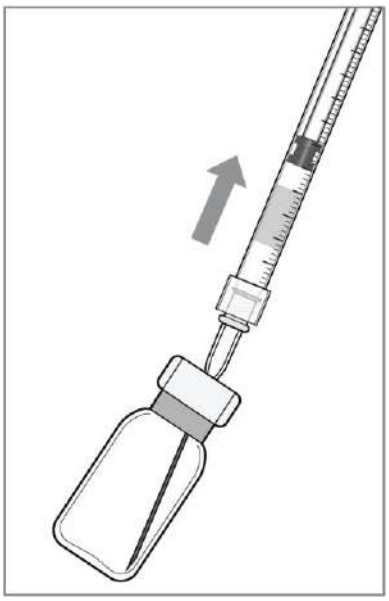
Using aseptic technique, all of the LUCENTIS vial contents are withdrawn through a 5-micron (19-gauge x 1-1/2 inch), sterile filter needle attached to a 1 mL syringe (not included). The filter needle should be discarded after withdrawal of the vial contents and should not be used for intravitreal injection. The filter needle should be replaced with a sterile 30-gauge x ½ inch needle for the intravitreal injection.

Use aseptic technique to carry out the following preparation steps.

1. Prepare for intravitreal injection with the following medical devices for single use (not included):
   - a 5-micron sterile filter needle (19-gauge x 1-1/2 inch)
   - a 1 mL sterile Luer lock syringe (with marking to measure 0.05 mL)
   - a sterile injection needle (30-gauge x 1/2-inch)
2. Before withdrawal, disinfect the outer part of the rubber stopper of the vial.
3. Place a 5-micron filter needle (19-gauge x 1-1/2 inch) onto a 1 mL Luer lock syringe using aseptic technique.
4. Push the filter needle into the center of the vial stopper until the needle touches the bottom edge of the vial.
5. Withdraw all the liquid from the vial, keeping the vial in an upright position, slightly inclined to ease complete withdrawal.

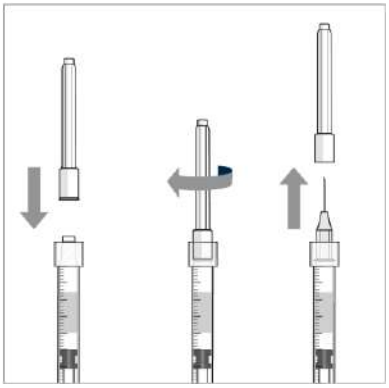


6. Ensure that the plunger rod is drawn sufficiently back when emptying the vial in order to completely empty the filter needle.



7. The filter needle should be discarded after withdrawal of the vial contents and must not be used for the intravitreal injection.

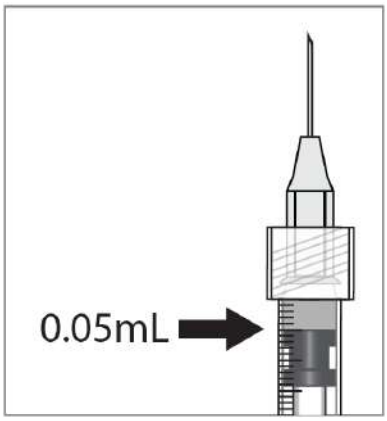
8. Attach a 30-gauge x 1/2-inch sterile injection needle firmly onto the syringe by screwing it tightly onto the Luer lock. Carefully remove the needle cap by pulling it straight off. Do not wipe the needle at any time.



9. Hold the syringe with the needle pointing up. If there are any air bubbles, gently tap the syringe with your finger until the bubbles rise to the top.



10. Hold the syringe at eye level, and carefully push the plunger rod until the plunger tip is aligned with the line that marks 0.05 mL on the syringe.



2.8 Administration

The intravitreal injection procedure should be carried out under controlled aseptic conditions, which include the use of sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent). Adequate anesthesia and a broad-spectrum microbicide should be given prior to the injection.

Prior to and 30 minutes following the intravitreal injection, patients should be monitored for elevation in intraocular pressure using tonometry. Monitoring may also consist of a check for perfusion of the optic nerve

head immediately after the injection [*see Warnings and Precautions (5.2)*]. Patients should also be monitored for and instructed to report any symptoms suggestive of endophthalmitis without delay following the injection [*see Warnings and Precautions (5.1)*].

Each prefilled syringe or vial should only be used for the treatment of a single eye. If the contralateral eye requires treatment, a new prefilled syringe or vial should be used and the sterile field, syringe, gloves, drapes, eyelid speculum, filter needle (vial only), and injection needles should be changed before LUCENTIS is administered to the other eye.

No special dosage modification is required for any of the populations that have been studied (e.g., gender, elderly).

3 DOSAGE FORMS AND STRENGTHS

Single-use prefilled syringe designed to provide 0.05 mL for intravitreal injection.

- 10 mg/mL solution (LUCENTIS 0.5 mg)

Single-use glass vial designed to provide 0.05 mL for intravitreal injection.

- 10 mg/mL solution (LUCENTIS 0.5 mg)
- 6 mg/mL solution (LUCENTIS 0.3 mg)

4 CONTRAINDICATIONS

4.1 Ocular or Periocular Infections

LUCENTIS is contraindicated in patients with ocular or periocular infections.

4.2 Hypersensitivity

LUCENTIS is contraindicated in patients with known hypersensitivity to ranibizumab or any of the excipients in LUCENTIS. Hypersensitivity reactions may manifest as severe intraocular inflammation.

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis and Retinal Detachments

Intravitreal injections, including those with LUCENTIS, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique should always be used when administering LUCENTIS. In addition, patients should be monitored following the injection to permit early treatment should an infection occur [*see Dosage and Administration (2.7, 2.8) and Patient Counseling Information (17)*].

5.2 Increases in Intraocular Pressure

Increases in intraocular pressure have been noted both pre-injection and post-injection (at 60 minutes) while being treated with LUCENTIS. Monitor intraocular pressure prior to and following intravitreal injection with LUCENTIS and manage appropriately [*see Dosage and Administration (2.8)*].

5.3 Thromboembolic Events

Although there was a low rate of arterial thromboembolic events (ATEs) observed in the LUCENTIS clinical trials, there is a potential risk of ATEs following intravitreal use of VEGF inhibitors. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause).

Neovascular (Wet) Age-Related Macular Degeneration

The ATE rate in the three controlled neovascular AMD studies (AMD-1, AMD-2, AMD-3) during the first year was 1.9% (17 of 874) in the combined group of patients treated with 0.3 mg or 0.5 mg LUCENTIS compared with 1.1% (5 of 441) in patients from the control arms [*see Clinical Studies (14.1)*]. In the second year of Studies AMD-1 and AMD-2, the ATE rate was 2.6% (19 of 721) in the combined group of LUCENTIS-treated patients compared with 2.9% (10 of 344) in patients from the control arms. In Study AMD-4, the ATE rates observed in the 0.5 mg arms during the first and second year were similar to rates observed in Studies AMD-1, AMD-2, and AMD-3.

In a pooled analysis of 2-year controlled studies (AMD-1, AMD-2, and a study of LUCENTIS used adjunctively with verteporfin photodynamic therapy), the stroke rate (including both ischemic and hemorrhagic stroke) was 2.7% (13 of 484) in patients treated with 0.5 mg LUCENTIS compared to 1.1% (5 of 435) in patients in the control arms (odds ratio 2.2 (95% confidence interval (0.8-7.1))).

Macular Edema Following Retinal Vein Occlusion
The ATE rate in the two controlled RVO studies during the first 6 months was 0.8% in both the LUCENTIS and control arms of the studies (4 of 525 in the combined group of patients treated with 0.3 mg or 0.5 mg LUCENTIS and 2 of 260 in the control arms) [*see Clinical Studies (14.2)*]. The stroke rate was 0.2% (1 of 525) in the combined group of LUCENTIS-treated patients compared to 0.4% (1 of 260) in the control arms.

Diabetic Macular Edema and Diabetic Retinopathy
Safety data are derived from studies D-1 and D-2. All enrolled patients had DME and DR at baseline [*see Clinical Studies (14.3, 14.4)*].

In a pooled analysis of Studies D-1 and D-2 [*see Clinical Studies (14.3)*], the ATE rate at 2 years was 7.2% (18 of 250) with 0.5 mg LUCENTIS, 5.6% (14 of 250) with 0.3 mg LUCENTIS, and 5.2% (13 of 250) with control. The stroke rate at 2 years was 3.2% (8 of 250) with 0.5 mg LUCENTIS, 1.2% (3 of 250) with 0.3 mg LUCENTIS, and 1.6% (4 of 250) with control. At 3 years, the ATE rate was 10.4% (26 of 249) with 0.5 mg LUCENTIS and 10.8% (27 of 250) with 0.3 mg LUCENTIS; the stroke rate was 4.8% (12 of 249) with 0.5 mg LUCENTIS and 2.0% (5 of 250) with 0.3 mg LUCENTIS.

5.4 Fatal Events in Patients with DME and DR at baseline

Diabetic Macular Edema and Diabetic Retinopathy
Safety data are derived from studies D-1 and D-2. All enrolled patients had DME and DR at baseline [*see Clinical Studies (14.3, 14.4)*].

A pooled analysis of Studies D-1 and D-2 [*see Clinical Studies (14.3)*], showed that fatalities in the first 2 years occurred in 4.4% (11 of 250) of patients treated with 0.5 mg LUCENTIS, in 2.8% (7 of 250) of patients treated with 0.3 mg LUCENTIS, and in 1.2% (3 of 250) of control patients. Over 3 years, fatalities occurred in 6.4% (16 of 249) of patients treated with 0.5 mg LUCENTIS and in 4.4% (11 of 250) of patients treated with 0.3 mg LUCENTIS. Although the rate of fatal events was low and included causes of death typical of patients with advanced diabetic complications, a potential relationship between these events and intravitreal use of VEGF inhibitors cannot be excluded.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label:

- Endophthalmitis and Retinal Detachments [*see Warnings and Precautions (5.1*)]
- Increases in Intraocular Pressure [*see Warnings and Precautions (5.2)*]
- Thromboembolic Events [*see Warnings and Precautions (5.3)*]
- Fatal Events in patients with DME and DR at baseline *[see Warnings and Precautions (5.4)]*

6.1 Injection Procedure

Serious adverse reactions related to the injection procedure have occurred in < 0.1% of intravitreal injections, including endophthalmitis [*see Warnings and Precautions (5.1)*], rhegmatogenous retinal detachment, and iatrogenic traumatic cataract.

6.2 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in one clinical trial of a drug cannot be directly compared with rates in the clinical trials of the same or another drug and may not reflect the rates observed in practice.

The data below reflect exposure to 0.5 mg LUCENTIS in 440 patients with neovascular AMD in Studies AMD-1, AMD-2, and AMD-3; in 259 patients with macular edema following RVO. The data also reflect exposure to 0.3 mg LUCENTIS in 250 patients with DME and DR at baseline [*see Clinical Studies (14)*].

Safety data observed in Study AMD-4 and in 224 patients with mCNV were consistent with these results. On average, the rates and types of adverse reactions in patients were not significantly affected by dosing regimen.

Ocular Reactions

Table 1 shows frequently reported ocular adverse reactions in LUCENTIS-treated patients compared with the control group.

Table 1

Ocular Reactions in the DME and DR, AMD, and RVO Studies

Adverse Reaction	DME and DR 2-year		AMD 2-year		AMD 1-year		RVO 6-month	
	LUCENTIS 0.3 mg	Control	LUCENTIS 0.5 mg	Control	LUCENTIS 0.5 mg	Control	LUCENTIS 0.5 mg	Control
	n=250	n=250	n=379	n=379	n=440	n=441	n=259	n=260
Conjunctival hemorrhage	47%	32%	74%	60%	64%	50%	48%	37%
Eye pain	17%	13%	35%	30%	26%	20%	17%	12%
Vitreous floaters	10%	4%	27%	8%	19%	5%	7%	2%
Intraocular pressure increased	18%	7%	24%	7%	17%	5%	7%	2%
Vitreous detachment	11%	15%	21%	19%	15%	15%	4%	2%
Intraocular inflammation	4%	3%	18%	8%	13%	7%	1%	3%
Cataract	28%	32%	17%	14%	11%	9%	2%	2%
Foreign body sensation in eyes	10%	5%	16%	14%	13%	10%	7%	5%
Eye irritation	8%	5%	15%	15%	13%	12%	7%	6%
Lacrimation increased	5%	4%	14%	12%	8%	8%	2%	3%
Blepharitis	3%	2%	12%	8%	8%	5%	0%	1%
Dry eye	5%	3%	12%	7%	7%	7%	3%	3%
Visual disturbance or vision blurred	8%	4%	18%	15%	13%	10%	5%	3%
Eye pruritis	4%	4%	12%	11%	9%	7%	1%	2%
Ocular hyperemia	9%	9%	11%	8%	7%	4%	5%	3%
Retinal disorder	2%	2%	10%	7%	8%	4%	2%	1%
Maculopathy	5%	7%	9%	9%	6%	6%	11%	7%
Retinal degeneration	1%	0%	8%	6%	5%	3%	1%	0%
Ocular discomfort	2%	1%	7%	4%	5%	2%	2%	2%
Conjunctival hyperemia	1%	2%	7%	6%	5%	4%	0%	0%
Posterior capsule opacification	4%	3%	7%	4%	2%	2%	0%	1%
Injection site hemorrhage	1%	0%	5%	2%	3%	1%	0%	0%

Non-Ocular Reactions

Non-ocular adverse reactions with an incidence of ≥ 5% in patients receiving LUCENTIS for DR, DME, AMD, and/or RVO and which occurred at a ≥ 1% higher frequency in patients treated with LUCENTIS compared to control are shown in Table 2. Though less common, wound healing complications were also observed in some studies.

Table 2
Non-Ocular Reactions in the DME and DR, AMD, and RVO Studies

Adverse Reaction	DME and DR 2-year		AMD 2-year		AMD 1-year		RVO 6-month	
	LUCENTIS 0.3 mg	Control	LUCENTIS 0.5 mg	Control	LUCENTIS 0.5 mg	Control	LUCENTIS 0.5 mg	Control
	n=250	n=250	n=379	n=379	n=440	n=441	n=259	n=260
Nasopharyngitis	12%	6%	16%	13%	8%	9%	5%	4%
Anemia	11%	10%	8%	7%	4%	3%	1%	1%
Nausea	10%	9%	9%	6%	5%	5%	1%	2%
Cough	9%	4%	9%	8%	5%	4%	1%	2%
Constipation	8%	4%	5%	7%	3%	4%	0%	1%
Seasonal allergy	8%	4%	4%	4%	2%	2%	0%	2%
Hypercholesterolemia	7%	5%	5%	5%	3%	2%	1%	1%
Influenza	7%	3%	7%	5%	3%	2%	3%	2%
Renal failure	7%	6%	1%	1%	0%	0%	0%	0%
Upper respiratory tract infection	7%	7%	9%	8%	5%	5%	2%	2%
Gastroesophageal reflux disease	6%	4%	4%	6%	3%	4%	1%	0%
Headache	6%	8%	12%	9%	6%	5%	3%	3%
Edema peripheral	6%	4%	3%	5%	2%	3%	0%	1%
Renal failure chronic	6%	2%	0%	1%	0%	0%	0%	0%
Neuropathy peripheral	5%	3%	1%	1%	1%	0%	0%	0%
Sinusitis	5%	8%	8%	7%	5%	5%	3%	2%
Bronchitis	4%	4%	11%	9%	6%	5%	0%	2%
Atrial fibrillation	3%	3%	5%	4%	2%	2%	1%	0%
Arthralgia	3%	3%	11%	9%	5%	5%	2%	1%
Chronic obstructive pulmonary disease	1%	1%	6%	3%	3%	1%	0%	0%
Wound healing complications	1%	0%	1%	1%	1%	0%	0%	0%

6.3 Immunogenicity

As with all therapeutic proteins, there is the potential for an immune response in patients treated with LUCENTIS. The immunogenicity data reflect the percentage of patients whose test results were considered

positive for antibodies to LUCENTIS in immunoassays and are highly dependent on the sensitivity and specificity of the assays.

The pre-treatment incidence of immunoreactivity to LUCENTIS was 0%-5% across treatment groups. After monthly dosing with LUCENTIS for 6 to 24 months, antibodies to LUCENTIS were detected in approximately 1%-9% of patients.

The clinical significance of immunoreactivity to LUCENTIS is unclear at this time. Among neovascular AMD patients with the highest levels of immunoreactivity, some were noted to have iritis or vitritis. Intraocular inflammation was not observed in patients with DME and DR at baseline, or RVO patients with the highest levels of immunoreactivity.

6.4 Postmarketing Experience

The following adverse reaction has been identified during post-approval use of LUCENTIS. Because this reaction was reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure.

- Ocular: Tear of retinal pigment epithelium among patients with neovascular AMD

7 DRUG INTERACTIONS

Drug interaction studies have not been conducted with LUCENTIS.

LUCENTIS intravitreal injection has been used adjunctively with verteporfin photodynamic therapy (PDT). Twelve (12) of 105 (11%) patients with neovascular AMD developed serious intraocular inflammation; in 10 of the 12 patients, this occurred when LUCENTIS was administered 7 days (± 2 days) after verteporfin PDT.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies of LUCENTIS administration in pregnant women.

Administration of ranibizumab to pregnant monkeys throughout the period of organogenesis resulted in a low incidence of skeletal abnormalities at intravitreal doses 13-times the predicted human exposure (based on maximal serum trough levels [C_{max}]) after a single eye treatment at the recommended clinical dose. No skeletal abnormalities were observed at serum trough levels equivalent to the predicted human exposure after a single eye treatment at the recommended clinical dose [*see Animal Data*].

Animal reproduction studies are not always predictive of human response, and it is not known whether ranibizumab can cause fetal harm when administered to a pregnant woman. Based on the anti-VEGF mechanism of action for ranibizumab [*see Clinical Pharmacology (12.1)*], treatment with LUCENTIS may pose a risk to human embryofetal development.

LUCENTIS should be given to a pregnant woman only if clearly needed.

Data

Animal Data

An embryo-fetal developmental toxicity study was performed on pregnant cynomolgus monkeys. Pregnant animals received intravitreal injections of ranibizumab every 14 days starting on Day 20 of gestation, until Day 62 at doses of 0, 0.125, and 1 mg/eye. Skeletal abnormalities including incomplete and/or irregular ossification of bones in the skull, vertebral column, and hindlimbs and shortened supernumerary ribs were seen at a low incidence in fetuses from animals treated with 1 mg/eye of ranibizumab. The 1 mg/eye dose resulted in

trough serum ranibizumab levels up to 13 times higher than predicted C_{max} levels with single eye treatment in humans. No skeletal abnormalities were seen at the lower dose of 0.125 mg/eye, a dose which resulted in trough exposures equivalent to single eye treatment in humans. No effect on the weight or structure of the placenta, maternal toxicity, or embryotoxicity was observed.

8.2 Lactation

Risk Summary

There are no data available on the presence of ranibizumab in human milk, the effects of ranibizumab on the breastfed infant or the effects of ranibizumab on milk production/excretion.

Because many drugs are excreted in human milk, and because the potential for absorption and harm to infant growth and development exists, caution should be exercised when LUCENTIS is administered to a nursing woman.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for LUCENTIS and any potential adverse effects on the breastfed child from ranibizumab.

8.3 Females and Males of Reproductive Potential

Infertility

No studies on the effects of ranibizumab on fertility have been conducted. and it is not known whether ranibizumab can affect reproduction capacity. Based on the anti-VEGF mechanism of action for ranibizumab, treatment with LUCENTIS may pose a risk to reproductive capacity..

8.4 Pediatric Use

The safety and effectiveness of LUCENTIS in pediatric patients have not been established.

8.5 Geriatric Use

In the clinical studies, approximately 76% (2449 of 3227) of patients randomized to treatment with LUCENTIS were ≥ 65 years of age and approximately 51% (1644 of 3227) were ≥ 75 years of age [*see Clinical Studies (14)*]. No notable differences in efficacy or safety were seen with increasing age in these studies. Age did not have a significant effect on systemic exposure.

10 OVERDOSAGE

More concentrated doses as high as 2 mg ranibizumab in 0.05 mL have been administered to patients. No additional unexpected adverse reactions were seen.

11 DESCRIPTION

LUCENTIS® (ranibizumab injection) is a recombinant humanized IgG1 kappa isotype monoclonal antibody fragment designed for intraocular use. Ranibizumab binds to and inhibits the biologic activity of human vascular endothelial growth factor A (VEGF-A). Ranibizumab, which lacks an Fc region, has a molecular weight of approximately 48 kilodaltons and is produced by an *E. coli* expression system in a nutrient medium containing the antibiotic tetracycline. Tetracycline is not detectable in the final product.

LUCENTIS is a sterile, colorless to pale yellow solution in a single-use prefilled syringe or a single-use glass vial. LUCENTIS is supplied as a preservative-free, sterile solution in a single-use container designed to deliver 0.05 mL of 10 mg/mL LUCENTIS (0.5 mg dose prefilled syringe or vial) or 6 mg/mL LUCENTIS (0.3 mg dose vial) aqueous solution with 10 mM histidine HCl, 10% α,α-trehalose dihydrate, 0.01% polysorbate 20, pH 5.5.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ranibizumab binds to the receptor binding site of active forms of VEGF-A, including the biologically active, cleaved form of this molecule, $VEGF_{110}$. VEGF-A has been shown to cause neovascularization and leakage in models of ocular angiogenesis and vascular occlusion and is thought to contribute to pathophysiology of neovascular AMD, mCNV, DR, DME and macular edema following RVO. The binding of ranibizumab to VEGF-A prevents the interaction of VEGF-A with its receptors (VEGFR1 and VEGFR2) on the surface of endothelial cells, reducing endothelial cell proliferation, vascular leakage, and new blood vessel formation.

12.2 Pharmacodynamics

Increased retinal thickness (i.e., center point thickness (CPT) or central foveal thickness (CFT)), as assessed by optical coherence tomography (OCT) is associated with neovascular AMD, mCNV, macular edema following RVO, and DME. Leakage from choroidal neovascularization (CNV) as assessed by fluorescein angiography (FA) is associated with neovascular AMD and mCNV. Microvascular retinal changes and neovascularization, as assessed by color fundus photography, are associated with diabetic retinopathy.

Neovascular (Wet) Age-Related Macular Degeneration

In Study AMD-3, CPT was assessed by time domain (TD)-OCT in 118 of 184 patients. TD-OCT measurements were collected at baseline, Months 1, 2, 3, 5, 8, and 12. In patients treated with LUCENTIS, CPT decreased, on average, more than in the sham group from baseline through Month 12. CPT decreased by Month 1 and decreased further at Month 3, on average. In this study, CPT data did not provide information useful in influencing treatment decisions [*see Clinical Studies (14.1)*].

In Study AMD-4, CFT was assessed by spectral domain (SD)-OCT in all patients; on average, CFT reductions were observed beginning at Day 7 following the first LUCENTIS injection through Month 24. CFT data did not provide information capable of predicting final visual acuity results [see *Clinical Studies (14.1)*].

In patients treated with LUCENTIS, the area of CNV leakage, on average, decreased by Month 3 as assessed by FA. The area of CNV leakage for an individual patient was not correlated with visual acuity.

Macular Edema Following Retinal Vein Occlusion

On average, CPT reductions were observed in Studies RVO-1 and RVO-2 beginning at Day 7 following the first LUCENTIS injection through Month 6. CPT was not evaluated as a means to guide treatment decisions [*see Clinical Studies (14.2)*].

Diabetic Macular Edema

On average, CPT reductions were observed in Studies D-1 and D-2 beginning at Day 7 following the first LUCENTIS injection through Month 36. CPT data did not provide information useful in influencing treatment decisions [*see Clinical Studies (14.3)*].

Diabetic Retinopathy in patients with Diabetic Macular Edema

Improvements from baseline in DR severity as assessed on fundus photography were observed in Studies D-1 and D-2 at Month 3 (first scheduled DR photographic assessment after randomization) through Month 36 [*see Clinical Studies (14.4)*].

Myopic Choroidal Neovascularization

On average CFT reductions were observed as early as Month 1, and were greater in the LUCENTIS groups compared to vPDT [*see Clinical Studies (14.5)*].

12.3 Pharmacokinetics
In patients with neovascular AMD, following monthly intravitreal administration of 0.5 mg LUCENTIS, mean (±SD) maximum ranibizumab serum concentrations were 1.7 (± 1.1) ng/mL. These concentrations were below the concentration range of ranibizumab (11 to 27 ng/mL) that was necessary to inhibit the biological activity of VEGF-A by 50%, as measured in an in vitro cellular proliferation assay (based on human umbilical vein endothelial cells (HUVEC)). No significant change from baseline was observed in the mean plasma VEGF concentrations following three monthly 0.5 mg intravitreal injections. The maximum observed serum concentration was dose proportional over the dose range of 0.05 to 2 mg/eye. Serum ranibizumab concentrations in RVO and DME and DR patients were similar to those observed in neovascular AMD patients.

Based on a population pharmacokinetic analysis of patients with neovascular AMD, maximum serum concentrations are predicted to be reached at approximately 1 day after monthly intravitreal administration of LUCENTIS 0.5 mg/eye. Based on the disappearance of ranibizumab from serum, the estimated average vitreous elimination half-life was approximately 9 days. Steady-state minimum concentration is predicted to be 0.22 ng/mL with a monthly dosing regimen. In humans, serum ranibizumab concentrations are predicted to be approximately 90,000-fold lower than vitreal concentrations.

In pharmacokinetic covariate analyses, 48% (520/1091) of patients had renal impairment (35% mild, 11% moderate, and 2% severe). Because the increases in plasma ranibizumab exposures in these patients are not considered clinically significant, no dosage adjustment is needed based on renal impairment status.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Animal studies have not been conducted to determine the carcinogenic potential of ranibizumab. Based on the anti-VEGF mechanism of action of ranibizumab, treatment with LUCENTIS may pose a risk to reproductive capacity *[see Females and Males of Reproductive Potential (8.3)]*.

14 CLINICAL STUDIES
Unless otherwise noted, visual acuity was measured at a distance of 4 meters.

14.1 Neovascular (Wet) Age-Related Macular Degeneration (AMD)
The safety and efficacy of LUCENTIS were assessed in three randomized, double-masked, sham- or active-controlled studies in patients with neovascular AMD. A total of 1323 patients (LUCENTIS 879, control 444) were enrolled in the three studies.

Studies AMD-1 and AMD-2
In Study AMD-1, patients with minimally classic or occult (without classic) CNV lesions received monthly LUCENTIS 0.3 mg or 0.5 mg intravitreal injections or monthly sham injections. Data are available through Month 24. Patients treated with LUCENTIS in Study AMD-1 received a mean of 22 total treatments out of a possible 24 from Day 0 to Month 24.

In Study AMD-2, patients with predominantly classic CNV lesions received one of the following: 1) monthly LUCENTIS 0.3 mg intravitreal injections and sham PDT; 2) monthly LUCENTIS 0.5 mg intravitreal injections and sham PDT; or 3) sham intravitreal injections and active verteporfin PDT. Sham PDT (or active verteporfin PDT) was given with the initial LUCENTIS (or sham) intravitreal injection and every 3 months thereafter if fluorescein angiography showed persistence or recurrence of leakage. Data are available through Month 24. Patients treated with LUCENTIS in Study AMD-2 received a mean of 21 total treatments out of a possible 24 from Day 0 through Month 24.

In both studies, the primary efficacy endpoint was the proportion of patients who maintained vision, defined as losing fewer than 15 letters of visual acuity at 12 months compared with baseline. Almost all LUCENTIS-treated patients (approximately 95%) maintained their visual acuity. Among LUCENTIS-treated patients, 31% to 37% experienced a clinically significant improvement in vision, defined as gaining 15 or more letters at 12 months. The size of the lesion did not significantly affect the results. Detailed results are shown in Table 3, Table 4, and Figure 1 below.

Table 3
Visual Acuity Outcomes at Month 12 and Month 24 in Study AMD-1

Outcome Measure	Month	Sham n=229	LUCENTIS 0.5 mg n=230	Estimated Difference (95% CI)[a]
Loss of <15 letters in visual acuity (%)	12	60%	91%	30% (23%, 37%)
	24	56%	89%	33% (26%, 41%)
Gain of ≥15 letters in visual acuity (%)	12	6%	31%	25% (18%, 31%)
	24	4%	30%	25% (18%, 31%)
Mean change in visual acuity (letters) (SD)	12	–11.0 (17.9)	+6.3 (14.1)	17.1 (14.2, 20.0)
	24	–15.0 (19.7)	+5.5 (15.9)	20.1 (16.9, 23.4)

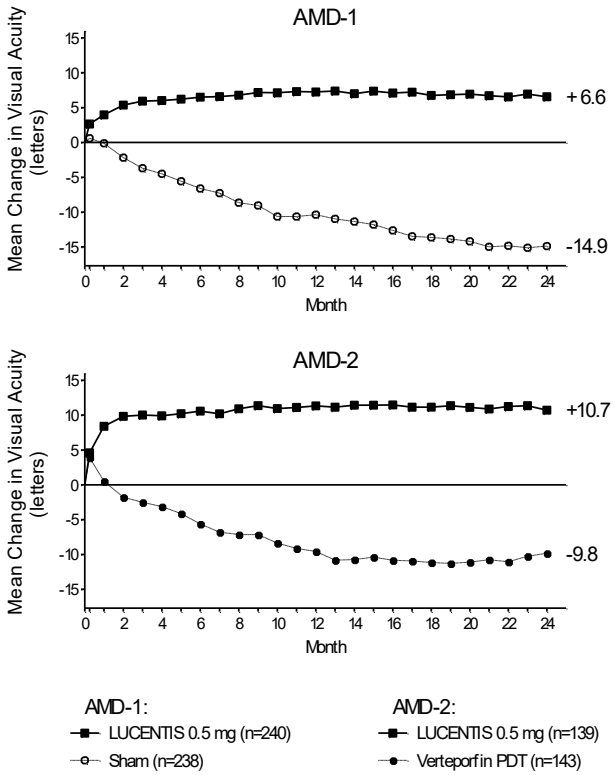
[a]Adjusted estimate based on the stratified model; $p < 0.01$

Table 4
Visual Acuity Outcomes at Month 12 and Month 24 in Study AMD-2

Outcome Measure	Month	Verteporfin PDT n=141	LUCENTIS 0.5 mg n=139	Estimated Difference (95% CI)[a]
Loss of <15 letters in visual acuity (%)	12	66%	98%	32% (24%, 40%)
	24	65%	93%	28% (19%, 37%)
Gain of ≥15 letters in visual acuity (%)	12	11%	37%	26% (17%, 36%)
	24	9%	37%	29% (20%, 39%)
Mean change in visual acuity (letters) (SD)	12	–8.5 (17.8)	+11.0 (15.8)	19.8 (15.9, 23.7)
	24	–9.1 (18.7)	+10.9 (17.3)	20 (16.0, 24.4)

[a] Adjusted estimate based on the stratified model; $p < 0.01$

Figure 1
Mean Change in Visual Acuity from Baseline
to Month 24 in Study AMD-1 and Study AMD-2



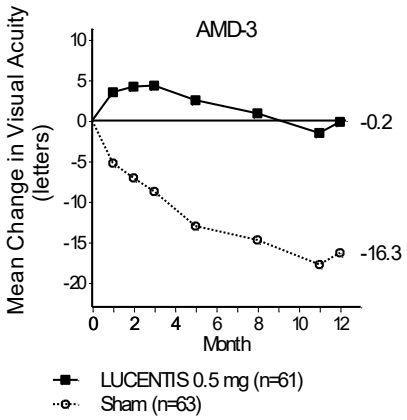
Visual acuity was measured at a distance of 2 meters

Patients in the group treated with LUCENTIS had minimal observable CNV lesion growth, on average. At Month 12, the mean change in the total area of the CNV lesion was 0.1-0.3 disc areas (DA) for LUCENTIS versus 2.3-2.6 DA for the control arms. At Month 24, the mean change in the total area of the CNV lesion was 0.3-0.4 DA for LUCENTIS versus 2.9-3.1 DA for the control arms.

Study AMD-3
Study AMD-3 was a randomized, double-masked, sham-controlled, two-year study designed to assess the safety and efficacy of LUCENTIS in patients with neovascular AMD (with or without a classic CNV component). Data are available through Month 12. Patients received LUCENTIS 0.3 mg or 0.5 mg intravitreal injections or sham injections once a month for 3 consecutive doses, followed by a dose administered once every 3 months for 9 months. A total of 184 patients were enrolled in this study (LUCENTIS 0.3 mg, 60; LUCENTIS 0.5 mg, 61; sham, 63); 171 (93%) completed 12 months of this study. Patients treated with LUCENTIS in Study AMD-3 received a mean of 6 total treatments out of a possible 6 from Day 0 through Month 12.

In Study AMD-3, the primary efficacy endpoint was mean change in visual acuity at 12 months compared with baseline (see Figure 2). After an initial increase in visual acuity (following monthly dosing), on average, patients dosed once every 3 months with LUCENTIS lost visual acuity, returning to baseline at Month 12. In Study AMD-3, almost all LUCENTIS-treated patients (90%) lost fewer than 15 letters of visual acuity at Month 12.

Figure 2
Mean Change in Visual Acuity from Baseline to Month 12 in Study AMD-3



Study AMD-4
Study AMD-4 was a randomized, double-masked, active treatment-controlled, two-year study designed to assess the safety and efficacy of LUCENTIS 0.5 mg administered monthly or less frequently than monthly in patients with neovascular AMD. Patients randomized to the LUCENTIS 0.5 mg less frequent dosing arm received 3 monthly doses followed by monthly assessments where patients were eligible to receive LUCENTIS injections guided by pre-specified re-treatment criteria. A total of 550 patients were enrolled in the two 0.5 mg treatment groups with 467 (85%) completing through Month 24. Data are available through Month 24. Clinical results at Month 24 remain similar to that observed at Month 12.

From Month 3 through Month 24, visual acuity decreased by 0.3 letters in the 0.5 mg less frequent dosing arm and increased by 0.7 letters in the 0.5 mg monthly arm (see Figure 3). Over this 21 month period, patients in the 0.5 mg less frequent dosing and the 0.5 mg monthly arms averaged 10.3 and 18.5 injections, respectively. The distribution of injections received in the less frequent dosing arm is shown in Figure 4.

Figure 3
Mean Change in Visual Acuity from Baseline to Month 24 in Study AMD-4

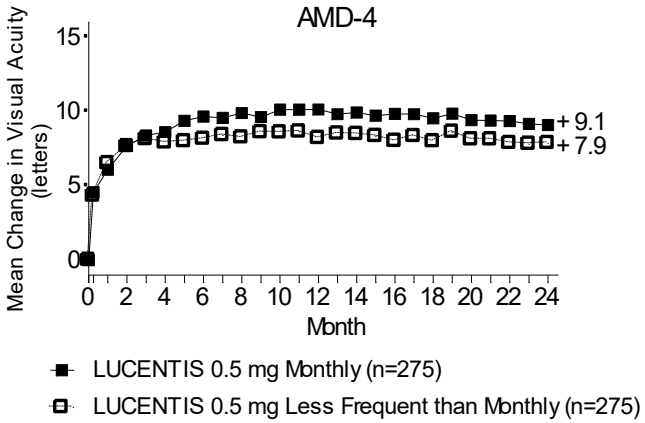
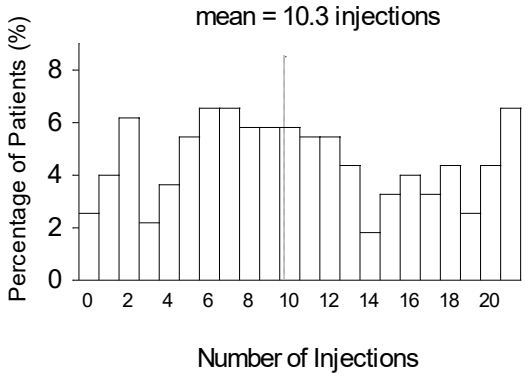


Figure 4
Distribution of Injections from Month 3 to Month 24 in the Less Frequent Dosing Arm in Study AMD-4



14.2 Macular Edema Following Retinal Vein Occlusion (RVO)

The safety and efficacy of LUCENTIS were assessed in two randomized, double-masked, 1-year studies in patients with macular edema following RVO. Sham controlled data are available through Month 6. Patient age ranged from 20 to 91 years, with a mean age of 67 years. A total of 789 patients (LUCENTIS 0.3 mg, 266 patients; LUCENTIS 0.5 mg, 261 patients; sham, 262 patients) were enrolled, with 739 (94%) patients completing through Month 6. All patients completing Month 6 were eligible to receive LUCENTIS injections guided by pre-specified re-treatment criteria until the end of the studies at Month 12.

In Study RVO-1, patients with macular edema following branch or hemi-RVO, received monthly LUCENTIS 0.3 mg or 0.5 mg intravitreal injections or monthly sham injections for 6 months. All patients were eligible for macular focal/grid laser treatment beginning at Month 3 of the 6-month treatment period. Macular focal/grid laser treatment was given to 26 of 131 (20%) patients treated with 0.5 mg LUCENTIS and 71 of 132 (54%) patients treated with sham.

In Study RVO-2, patients with macular edema following central RVO received monthly LUCENTIS 0.3 mg or 0.5 mg intravitreal injections or monthly sham injections for 6 months.

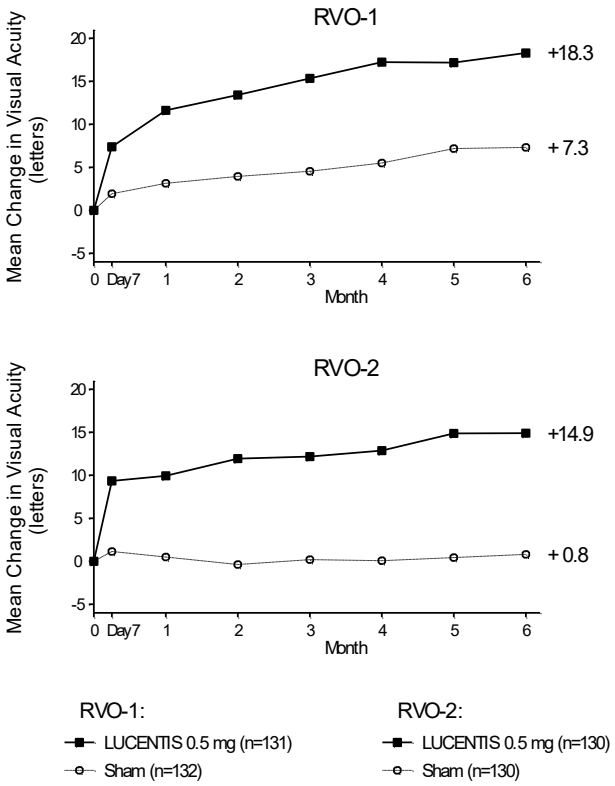
At Month 6, after monthly treatment with 0.5 mg LUCENTIS, the following clinical results were observed:

Table 5
Visual Acuity Outcomes at Month 6 in Study RVO-1 and Study RVO-2

Outcome Measure	Study [a]	Sham	LUCENTIS 0.5 mg	Estimated Difference (95% CI) [b]
Gain of ≥15 letters in visual acuity (%)	RVO-1	29%	61%	31% (20%, 43%)
Gain of ≥15 letters in visual acuity (%)	RVO-2	17%	48%	30% (20%, 41%)

[a] RVO-1: Sham, n=131; LUCENTIS 0.5 mg, n=132
RVO-2: Sham, n=130; LUCENTIS 0.5 mg, n=130
[b] Adjusted estimate based on stratified model; $p < 0.01$

Figure 5
Mean Change in Visual Acuity from Baseline
to Month 6 in Study RVO-1 and Study RVO-2



$p < 0.01$ for all time points

14.3 Diabetic Macular Edema (DME)
Efficacy and safety data of LUCENTIS are derived from studies D-1 and D-2 (See Section 14.4 Diabetic Retinopathy below). All enrolled patients had DR and DME at baseline.

The safety and efficacy of LUCENTIS were assessed in two randomized, double-masked, 3-year studies. The studies were sham-controlled through Month 24. Patient age ranged from 21 to 91 years, with a mean age of 62 years. A total of 759 patients (LUCENTIS 0.3 mg, 250 patients; LUCENTIS 0.5 mg, 252 patients; sham, 257 patients) were enrolled, with 582 (77%) completing through Month 36.

In Studies D-1 and D-2, patients received monthly LUCENTIS 0.3 mg or 0.5 mg intravitreal injections or monthly sham injections during the 24-month controlled treatment period. From Months 25 through 36, patients who previously received sham were eligible to receive monthly LUCENTIS 0.5 mg and patients originally randomized to monthly LUCENTIS 0.3 mg or 0.5 mg continued to receive their assigned dose. All patients were eligible for macular focal/grid laser treatment beginning at Month 3 of the 24-month treatment period or panretinal photocoagulation (PRP) as needed. Through Month 24, macular focal/grid laser treatment was administered in 94 of 250 (38%) patients treated with LUCENTIS 0.3 mg and 185 of 257 (72%) patients treated with sham; PRP was administered in 2 of 250 (1%) patients treated with LUCENTIS 0.3 mg and 30 of 257 (12%) patients treated with sham.

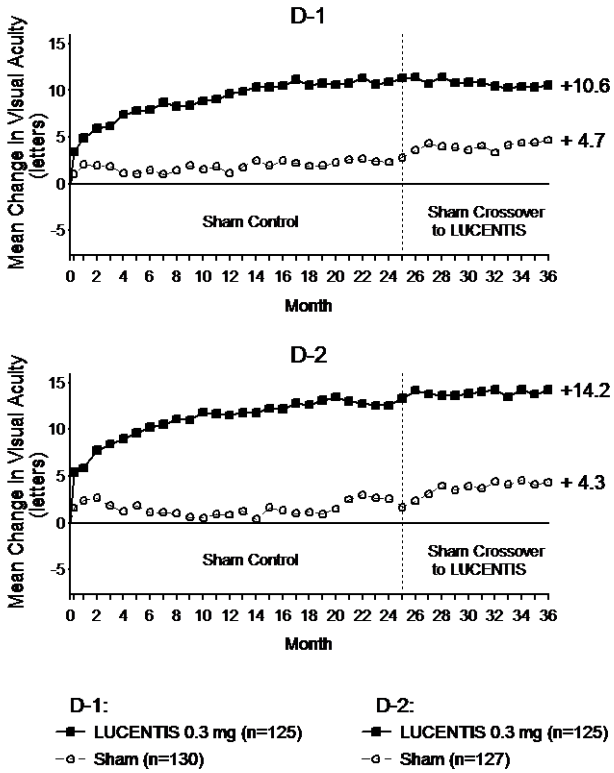
Compared to monthly LUCENTIS 0.3 mg, no additional benefit was observed with monthly treatment with LUCENTIS 0.5 mg. At Month 24, after monthly treatment with LUCENTIS 0.3 mg, the following clinical results were observed:

Table 6
Visual Acuity Outcomes at Month 24 in Study D-1 and D-2

Outcome Measure	Study[a]	Sham	LUCENTIS 0.3 mg	Estimated Difference (95% CI)[b]
Gain of ≥15 letters in visual acuity (%)	D-1	12%	34%	21% (11%, 30%)
	D-2	18%	45%	24% (14%, 35%)
Loss of <15 letters in visual acuity (%)	D-1	92%	98%	7% (2%, 13%)
	D-2	90%	98%	8% (2%, 14%)
Mean change in visual acuity (letters)	D-1	2.3	10.9	8.5 (5.4, 11.5)
	D-2	2.6	12.5	9.6 (6.1, 13.0)

[a] D-1: Sham, n=130; LUCENTIS 0.3 mg, n=125
D-2: Sham, n=127; LUCENTIS 0.3 mg, n=125
[b] Adjusted estimate based on stratified model; $p \leq 0.01$

Figure 6
Mean Change in Visual Acuity from Baseline to Month 36 in Study D-1 and Study D-2



$p < 0.01$ for all time points comparing LUCENTIS 0.3 mg to sham through Month 24

VA outcomes observed at Month 24 in patients treated with LUCENTIS 0.3 mg were maintained with continued treatment through Month 36 in both DME studies. Patients in the sham arms who received LUCENTIS 0.5 mg beginning at Month 25 achieved lesser VA gains compared to patients who began treatment with LUCENTIS at the beginning of the studies.

In Studies D-1 and D-2, patients received monthly injections of LUCENTIS for 12 or 36 months, after which 500 patients opted to continue in the long-term follow-up study. Of 298 patients who had at least 12 months of follow-up from Month 36, 58 (19.5%) patients maintained vision with no further therapy. The remaining 202 patients were followed for less than 12 months.

14.4 Diabetic Retinopathy in patients with Diabetic Macular Edema (DME)

Efficacy and safety data of LUCENTIS are derived from studies D-1 and D-2 [*see Clinical Studies (14.3)*]. All enrolled patients had DR and DME at baseline.

Of the 759 patients enrolled, 746 patients had a baseline assessment of fundus photography. Patients had baseline Early Treatment Diabetic Retinopathy Study (ETDRS) Retinopathy Severity Scores (ETDRS-RSS) ranging from 10 to 75. At baseline, 62% of patients had non-proliferative diabetic retinopathy (NPDR) (ETDRS-RSS less than 60) and 31% had PDR (ETDRS-RSS greater than or equal to 60). The ETDRS-RSS could not be graded in 5% of patients at baseline, and 2% of patients had absent or questionable DR at baseline. Approximately 20% of the overall population had prior PRP.

After monthly treatment with LUCENTIS 0.3 mg, the following clinical results were observed (Table 7; Figure 7):

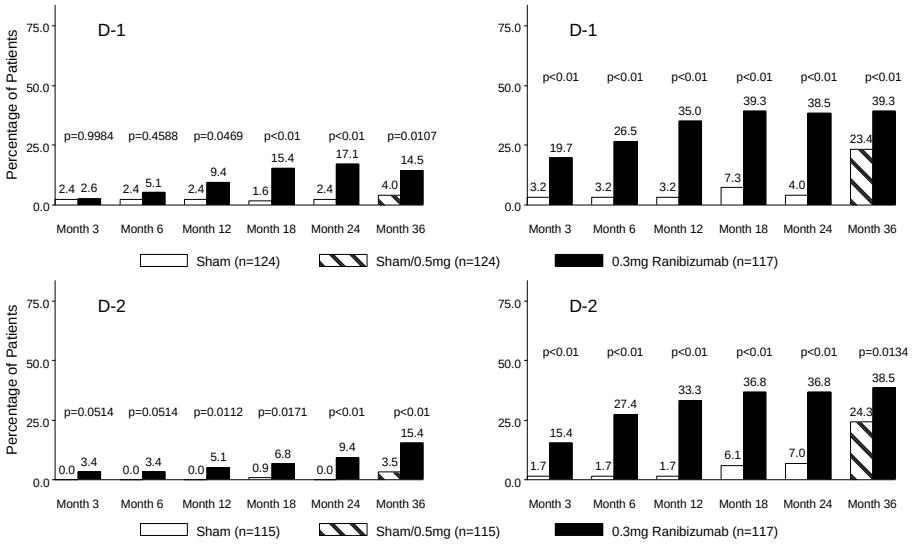
Table 7
≥3-step and ≥2-step improvement at Month 24 in
Study D-1 and Study D-2

Outcome Measure	Study[a]	Sham	LUCENTIS 0.3 mg	Estimated Difference (95% CI)[b]
≥3-step improvement from baseline in ETDRS-DRSS [c]	D-1	2%	17%	15% (7%, 22%)
	D-2	0%	9%	9% (4%, 14%)
≥2-step improvement from baseline in ETDRS-DRSS [d]	D-1	4%	39%	35% (26%, 44%)
	D-2	7%	37%	31% (21%, 40%)

[a] D-1: Sham, n=124; LUCENTIS 0.3 mg, n=117
D-2: Sham, n=115; LUCENTIS 0.3 mg, n=117
[b] Adjusted estimate based on stratified model
[c] $p < 0.05$ for all time points comparing LUCENTIS 0.3 mg to sham from Month 12 through Month 24
[d] $p < 0.05$ for all time points comparing LUCENTIS 0.3 mg to sham from Month 3 through Month 24

At Month 24, DR improvement by ≥3-steps in ETDRS-RSS from baseline in subgroups examined (e.g., age, gender, race, baseline visual acuity, baseline HbA1c, prior DME therapy at baseline, baseline DR severity (NPDR, PDR)) were generally consistent with the results in the overall population.

The difference in the proportion of patients treated with LUCENTIS 0.3 mg compared to sham who achieved DR improvement based on the ETDRS-RSS was observed as early as Month 3 for ≥2-step improvement or at Month 12 for ≥3-step improvement.



14.5 Myopic Choroidal Neovascularization (mCNV)

The efficacy and safety data of LUCENTIS were assessed in a randomized, double-masked, active-controlled 3-month study in patients with mCNV. Patients age ranged from 18 to 87 years, with a mean age of 55 years. A total of 276 patients (222 patients in the LUCENTIS treated Groups I and II; 55 patients in the active control verteporfin photodynamic therapy (vPDT) group) were enrolled. Patients randomized to the LUCENTIS groups received injections guided by pre-specified re-treatment criteria. The retreatment criteria in Group I were vision stability guided, with the BCVA at the current visit being assessed for changes compared with the two preceding monthly BCVA values. The retreatment criteria in Group II were disease activity guided, based on BCVA decrease from the previous visit that was attributable to intra- or sub-retinal fluid or active leakage secondary to mCNV as assessed by OCT and/or FA compared to the previous monthly visit.

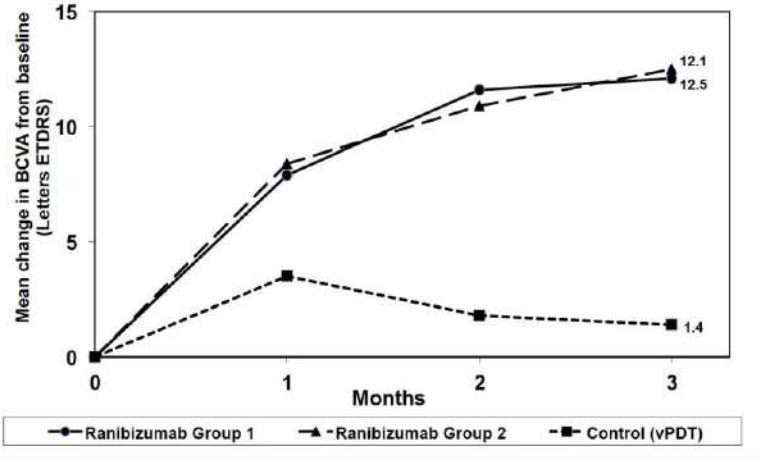
Visual gains for the two LUCENTIS 0.5 mg treatment arms were superior to the active control arm. The mean change in BCVA from baseline at Month 3 was: +12.1 letters for Group I, +12.5 letters for Group II and +1.4 letters for the vPDT group. (Figure 8; Table 8). Efficacy was comparable between Group I and Group II.

Table 8
Mean Change in Visual Acuity and Proportion of patients who gained ≥15 letters from Baseline at Month 3

Study Arms	Mean change in BCVA from baseline (Letters)		Proportion of patients who gained ≥15 letters from baseline	
	Mean (SD)	Estimated Difference (95% CI)[a]	Percent	Estimated Difference (95% CI)[a]
Group I	12.1 (10.2)	10.9 (7.6, 14.3)	37.1	22.6 (9.5, 35.7)
Group II	12.5 (8.8)	11.4 (8.3, 14.5)	40.5	26.0 (13.1, 38.9)
Control (vPDT)	1.4 (12.2)		14.5	

[a] Adjusted estimates based on stratified models; $p < 0.01$

Figure 8
Mean Change in Visual Acuity from Baseline to Month 3 in mCNV Study



The proportion of patients who gained ≥15 letters (ETDRS) by Month 3 was 37.1% and 40.5% for LUCENTIS Groups I and II, respectively and 14.5% for the vPDT group. The mean number of injections between baseline and Month 3 was 2.5 and 1.8 for Groups I and II, respectively. 41% of patients received 1, 2 or 3 injections between baseline and Month 3 with no injections afterwards.

16 HOW SUPPLIED/STORAGE AND HANDLING

- Each LUCENTIS 0.5 mg carton (NDC 50242-080-03) contains a single-use, prefilled syringe designed to deliver 0.05 mL of 10 mg/mL ranibizumab solution. The prefilled syringe has a non-retractable plunger stopper and a syringe cap consisting of a tamper-evident rigid seal with a rubber tip cap including a Luer lock adapter. The prefilled syringe has a plunger rod and a CLEAR finger grip. The prefilled syringe is sterile and is packed in a sealed tray.

- Each LUCENTIS 0.5 mg carton (NDC 50242-080-02) contains a single-use, 2-mL glass vial with a BLUE CAP designed to deliver 0.05 mL of 10 mg/mL ranibizumab solution.

- Each LUCENTIS 0.3 mg carton (NDC 50242-082-02) contains a single-use, 2-mL glass vial with a WHITE CAP designed to deliver 0.05 mL of 6 mg/mL ranibizumab solution.

EACH CARTON IS FOR SINGLE-EYE USE ONLY.

LUCENTIS should be refrigerated at 2°-8°C (36°-46°F). DO NOT FREEZE. Do not use beyond the date stamped on the label. Protect LUCENTIS prefilled syringe and vials from light and store in the original carton until time of use. Do not open LUCENTIS prefilled syringe sealed tray until time of use.

17 PATIENT COUNSELING INFORMATION

Advise patients that in the days following LUCENTIS administration, patients are at risk of developing endophthalmitis. If the eye becomes red, sensitive to light, painful, or develops a change in vision, advise the patient to seek immediate care from an ophthalmologist [*see Warnings and Precautions (5.1)*].

LUCENTIS® [ranibizumab injection]	
Manufactured by: **Genentech, Inc.** A Member of the Roche Group 1 DNA Way South San Francisco, CA 94080-4990	LUCENTIS® is a registered trademark of Genentech, Inc. ©2017Genentech, Inc.

APPENDIX FDA09

https://web.archive.org/web/20220201000000*/https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761235s000lbl.pdf September 13, 2025

INTERNET ARCHIVE WEB TEXTS VIDEO AUDIO SOFTWARE IMAGES SIGN UP | LOG IN UPLOAD Search

ABOUT BLOG PROJECTS HELP DONATE CONTACT JOBS VOLUNTEER PEOPLE

DONATE INTERNET ARCHIVE WayBackMachine Explore more than 946 billion web pages saved over time

https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761

Calendar · Collections · Changes · Summary · Site Map · URLs

Saved **36 times** between February 3, 2022 and August 10, 2025.

002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018 2019 2020 2021 **2022** 2023 2024 2025

JAN

						1
2	3	4	5	6	7	8
9	10	11	12	13	14	15
16	17	18	19	20	21	22
23	24	25	26	27	28	29
30	31					

FEB

		1	2	**3**	4	5
6	7	8	9	10	11	12
13	14	15	**16**	17	18	19
20	21	22	23	24	25	26
27	28					

MAR

		1	2	3	4	5
6	7	8	9	10	11	12
13	14	15	16	17	18	19
20	21	22	23	24	25	26
27	28	29	30	31		

APR

					1	2
3	4	5	6	7	8	9
10	11	12	13	14	15	16
17	18	19	20	21	22	23
24	25	26	27	28	29	30

MAY

1	2	3	4	5	6	7
8	9	10	11	12	13	14
15	16	17	18	19	20	21
22	23	24	25	26	27	**28**
29	30	31				

JUN

			1	2	3	4
5	6	7	8	9	10	11
12	13	14	15	16	17	18
19	20	21	22	23	24	25
26	27	28	29	30		

JUL

					1	2
3	4	5	6	7	8	9
10	11	12	13	14	15	**16**
17	18	19	20	21	22	23
24	25	26	27	28	29	30
31						

AUG

	1	2	3	4	5	6
7	8	9	10	11	12	13
14	15	16	17	18	19	20
21	22	23	24	25	26	27
28	29	30	31			

SEP

			1	2	3	
4	5	6	7	8	9	10
11	12	13	14	15	16	17
18	19	20	21	22	23	24
25	26	27	28	29	30	

OCT

						1
2	3	4	5	6	**7**	8
9	10	11	12	13	14	15
16	17	18	19	20	21	22
23	24	25	26	27	28	29
30	31					

NOV

		1	2	3	4	5
6	7	8	9	10	11	12
13	14	15	16	17	18	19
20	21	22	23	24	25	26
27	28	29	30			

DEC

				1	2	3
4	5	6	7	8	9	10
11	12	13	14	15	16	17
18	19	20	21	22	23	24
25	26	27	28	29	30	31

Note

This calendar view maps the number of times **https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761235s000lbl.pdf** was crawled by the Wayback Machine, *not* how many times the site was actually updated. More info in the FAQ.

FAQ | Contact Us | Terms of Service (Dec 31, 2014)

The Wayback Machine is an initiative of the Internet Archive, a 501(c)(3) non-profit, building a digital library of Internet sites and other cultural artifacts in digital form. Other projects include Open Library & archive-it.org.

Your use of the Wayback Machine is subject to the Internet Archive's Terms of Use.

https://web.archive.org/web/20220216194214/https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761235s000lbl.pdf September 13, 2025

INTERNET ARCHIVE Wayback Machine https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761235s000lbl.pdf Go JAN FEB MAY
36 captures 16
3 Feb 2022 - 10 Aug 2025 2021 2022 2023 About this capture

label 1 / 17 − 100% +



1



2



3



HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use VABYSMO safely and effectively. See full prescribing information for VABYSMO.

VABYSMO™ (faricimab-svoa) injection, for intravitreal use
Initial U.S. Approval: 2022

INDICATIONS AND USAGE

VABYSMO is a vascular endothelial growth factor (VEGF) and angiopoietin-2 (Ang-2) inhibitor indicated for the treatment of patients with:

- Neovascular (Wet) Age-Related Macular Degeneration (nAMD) (1.1)
- Diabetic Macular Edema (DME) (1.2)

DOSAGE AND ADMINISTRATION

For intravitreal injection. (2.1)

- Neovascular (Wet) Age-Related Macular Degeneration (nAMD)
  - The recommended dose for VABYSMO is 6 mg (0.05 mL of 120 mg/mL solution) administered by intravitreal injection every 4 weeks (approximately every 28 ± 7 days, monthly) for the first 4 doses, followed by optical coherence tomography and visual acuity evaluations 8 and 12 weeks later to inform whether to give a 6 mg dose via intravitreal injection on one of the following three regimens: 1) Weeks 28 and 44; 2) Weeks 24, 36 and 48; or 3) Weeks 20, 28, 36 and 44. Although additional efficacy was not demonstrated in most patients when VABYSMO was dosed every 4 weeks compared to every 8 weeks, some patients may need every 4 week (monthly) dosing after the first 4 doses. Patients should be assessed regularly. (2.2)

increments based on CST and visual acuity evaluations through week 52; or 2) 6 mg dose of VABYSMO can be administered every 4 weeks for the first 6 doses, followed by 6 mg dose via intravitreal injection at intervals of every 8 weeks (2 months) over the next 28 weeks. Although additional efficacy was not demonstrated in most patients when VABYSMO was dosed every 4 weeks compared to every 8 weeks, some patients may need every 4 week (monthly) dosing after the first 4 doses. Patients should be assessed regularly. (2.3)

DOSAGE FORMS AND STRENGTHS

Injection: 120 mg/mL solution in a single-dose vial (3)

CONTRAINDICATIONS

- Ocular or periocular infection (4.1)
- Active intraocular inflammation (4.2)
- Hypersensitivity (4.3)

WARNINGS AND PRECAUTIONS

- Endophthalmitis and retinal detachments may occur following intravitreal injections. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay, to permit prompt and appropriate management. (5.1)
- Increases in intraocular pressure have been seen within 60 minutes of an intravitreal injection. (5.2)
- There is a potential risk of arterial thromboembolic events (ATEs) associated with VEGF inhibition. (5.3)

ADVERSE REACTIONS

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use VABYSMO safely and effectively. See full prescribing information for VABYSMO.

VABYSMO™ (faricimab-svoa) injection, for intravitreal use
Initial U.S. Approval: 2022

——————————INDICATIONS AND USAGE——————————
VABYSMO is a vascular endothelial growth factor (VEGF) and angiopoietin-2 (Ang-2) inhibitor indicated for the treatment of patients with:
- Neovascular (Wet) Age-Related Macular Degeneration (nAMD) (1.1)
- Diabetic Macular Edema (DME) (1.2)

——————————DOSAGE AND ADMINISTRATION——————————
For intravitreal injection. (2.1)
- Neovascular (Wet) Age-Related Macular Degeneration (nAMD)
  - The recommended dose for VABYSMO is 6 mg (0.05 mL of 120 mg/mL solution) administered by intravitreal injection every 4 weeks (approximately every 28 ± 7 days, monthly) for the first 4 doses, followed by optical coherence tomography and visual acuity evaluations 8 and 12 weeks later to inform whether to give a 6 mg dose via intravitreal injection on one of the following three regimens: 1) Weeks 28 and 44; 2) Weeks 24, 36 and 48; or 3) Weeks 20, 28, 36 and 44. Although additional efficacy was not demonstrated in most patients when VABYSMO was dosed every 4 weeks compared to every 8 weeks, some patients may need every 4 week (monthly) dosing after the first 4 doses. Patients should be assessed regularly. (2.2)

- Diabetic Macular Edema (DME)
  - VABYSMO is recommended to be dosed by following one of these two dose regimens: 1) 6 mg (0.05 mL of 120 mg/mL solution) administered by intravitreal injection every 4 weeks (approximately every 28 days ± 7 days, monthly) for at least 4 doses. If after at least 4 doses, resolution of edema based on the central subfield thickness (CST) of the macula as measured by optical coherence tomography is achieved, then the interval of dosing may be modified by extensions of up to 4 week interval increments or reductions of up to 8 week interval increments based on CST and visual acuity evaluations through week 52; or 2) 6 mg dose of VABYSMO can be administered every 4 weeks for the first 6 doses, followed by 6 mg dose via intravitreal injection at intervals of every 8 weeks (2 months) over the next 28 weeks. Although additional efficacy was not demonstrated in most patients when VABYSMO was dosed every 4 weeks compared to every 8 weeks, some patients may need every 4 week (monthly) dosing after the first 4 doses. Patients should be assessed regularly. (2.3)

——————————DOSAGE FORMS AND STRENGTHS——————————
Injection: 120 mg/mL solution in a single-dose vial (3)

——————————CONTRAINDICATIONS——————————
- Ocular or periocular infection (4.1)
- Active intraocular inflammation (4.2)
- Hypersensitivity (4.3)

——————————WARNINGS AND PRECAUTIONS——————————
- Endophthalmitis and retinal detachments may occur following intravitreal injections. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay, to permit prompt and appropriate management. (5.1)
- Increases in intraocular pressure have been seen within 60 minutes of an intravitreal injection. (5.2)
- There is a potential risk of arterial thromboembolic events (ATEs) associated with VEGF inhibition. (5.3)

——————————ADVERSE REACTIONS——————————
The most common adverse reaction (≥ 5%) reported in patients receiving VABYSMO was conjunctival hemorrhage (7%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 1/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
1.1 Neovascular (Wet) Age-Related Macular Degeneration (nAMD)
1.2 Diabetic Macular Edema (DME)
2 DOSAGE AND ADMINISTRATION
2.1 General Dosing Information
2.2 Neovascular (Wet) Age-Related Macular Degeneration (nAMD)
2.3 Diabetic Macular Edema (DME)
2.5 Preparation for Administration
2.6 Injection Procedure
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
4.1 Ocular or Periocular Infections
4.2 Active Intraocular Inflammation
4.3 Hypersensitivity
5 WARNINGS AND PRECAUTIONS
5.1 Endophthalmitis and Retinal Detachments
5.2 Increase in Intraocular Pressure
5.3 Thromboembolic Events
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Immunogenicity
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation
8.3 Females and Males of Reproductive Potential
8.4 Pediatric Use
8.5 Geriatric Use
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
14.1 Neovascular (Wet) Age-Related Macular Degeneration (nAMD)
14.2 Diabetic Macular Edema (DME)
16 HOW SUPPLIED/STORAGE AND HANDLING
16.1 How Supplied
16.2 Storage and Handling
17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

VABYSMO is a vascular endothelial growth factor (VEGF) and angiopoietin 2 (Ang-2) inhibitor indicated for the treatment of patients with:

1.1 Neovascular (wet) Age-Related Macular Degeneration (nAMD)

1.2 Diabetic Macular Edema (DME)

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

For intravitreal injection. VABYSMO must be administered by a qualified physician. Each vial should only be used for the treatment of a single eye.

2.2 Neovascular (wet) Age-Related Macular Degeneration (nAMD)

The recommended dose for VABYSMO is 6 mg (0.05 mL of 120 mg/mL solution) administered by intravitreal injection every 4 weeks (approximately every 28 ± 7 days, monthly) for the first 4 doses, followed by optical coherence tomography and visual acuity evaluations 8 and 12 weeks later to inform whether to give a 6 mg dose via intravitreal injection on one of the following three regimens: 1) Weeks 28 and 44; 2) Weeks 24, 36 and 48; or 3) Weeks 20, 28, 36 and 44. Although additional efficacy was not demonstrated in most patients when VABYSMO was dosed every 4 weeks compared to every 8 weeks, some patients may need every 4 week (monthly) dosing after the first 4 doses. Patients should be assessed regularly.

2.3 Diabetic Macular Edema (DME)

VABYSMO is recommended to be dosed by following one of these two dose regimens: 1) 6 mg (0.05 mL of 120 mg/mL solution) administered by intravitreal injection every 4 weeks (approximately every 28 days ± 7 days, monthly) for at least 4 doses. If after at least 4 doses, resolution of edema based on the central subfield thickness (CST) of the macula as measured by optical coherence tomography is achieved, then the interval of dosing may be modified by extensions of up to 4 week interval increments or reductions of up to 8 week interval increments based on CST and visual acuity evaluations through week 52; or 2) 6 mg dose of VABYSMO can be administered every 4 weeks for the first 6 doses, followed by 6 mg dose via intravitreal injection at intervals of every 8 weeks (2 months) over the next 28 weeks. Although additional efficacy was not demonstrated in most patients when VABYSMO was dosed every 4 weeks compared to every 8 weeks, some patients may need every 4 week (monthly) dosing after the first 4 doses. Patients should be assessed regularly.

2.5 Preparation for Administration

1. Before you start:

- Read all the instructions carefully before using VABYSMO.
- The VABYSMO kit includes a glass vial and transfer filter needle. The glass vial is for a single dose only. The filter needle is for single use only.
- VABYSMO should be stored refrigerated at temperatures between 2ºC to 8ºC (36ºF to 46ºF). **Do not** freeze. **Do not** shake.

- Allow VABYSMO to reach room temperature, 20°C to 25°C (68°F to 77°F) before proceeding with the administration. The VABYSMO vial may be kept at room temperature for up to 24 hours. Keep the vial in the original carton to protect from light.

- VABYSMO should be inspected visually for particulate matter and discoloration prior to administration. VABYSMO is a clear to opalescent and colorless to brownish-yellow liquid solution.
  Do not use if particulates, cloudiness, or discoloration are visible.
  Do not use if the packaging, vial and/or transfer filter needle are expired, damaged, or have been tampered with (see **Figure A**).

- Use aseptic technique to carry out the preparation of the intravitreal injection.

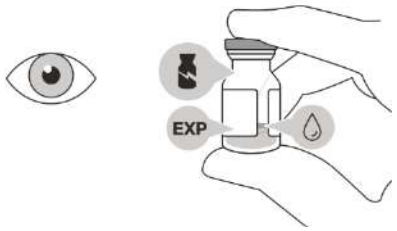


Figure A

2. Gather the following supplies:
   - One VABYSMO vial (included)
   - One sterile 5-micron blunt transfer filter needle 18-gauge x 1½ inch (included)
   - One sterile 1 mL Luer lock syringe with a 0.05 mL dose mark (**not included**)
   - One sterile injection needle 30-gauge x ½ inch (**not included**)
     Note that a 30-gauge injection needle is recommended to avoid increased injection forces that could be experienced with smaller diameter needles.
   - Alcohol swab (**not included**).

3. To ensure all liquid settles at the bottom of the vial, place the vial upright on a flat surface (for about 1 minute) after removal from packaging (see Figure B). Gently tap the vial with your finger (see Figure C), as liquid may stick to the top of the vial.

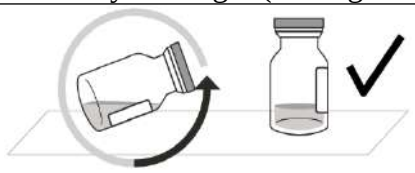


Figure B

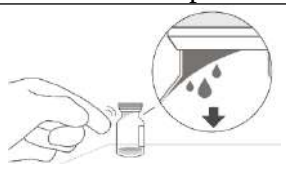


Figure C

4. Remove the flip-off cap from the vial (see **Figure D**) and wipe the vial septum with an alcohol swab (see **Figure E**).



Figure D

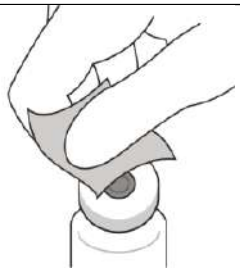


Figure E

5. Aseptically and firmly attach the included 18-gauge x 1½ inch transfer filter needle onto a 1 mL Luer lock syringe (see **Figure F**).

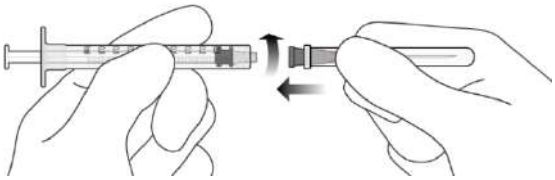


Figure F

6. Using aseptic technique, push the transfer filter needle into the center of the vial septum (see **Figure G**), push it all the way in, then tilt the vial slightly so that the needle touches the bottom edge of the vial (see **Figure H**).

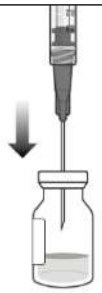


Figure G

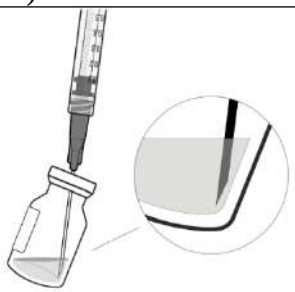


Figure H

7. Hold the vial slightly inclined and **slowly** withdraw all the liquid from the vial (see **Figure I**). Keep the bevel of the transfer filter needle submerged in the liquid, to avoid introduction of air.

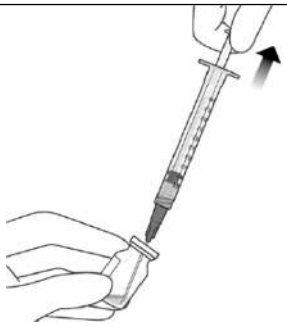


Figure I

8.	Ensure that the plunger rod is drawn sufficiently back when emptying the vial, in order to completely empty the transfer filter needle (see **Figure I**).
9.	Disconnect the transfer filter needle from the syringe and dispose of it in accordance with local regulations.

Do not use the transfer filter needle for the intravitreal injection.

10.	Aseptically and firmly attach a 30-gauge x ½ inch injection needle onto the Luer lock syringe (see **Figure J**).

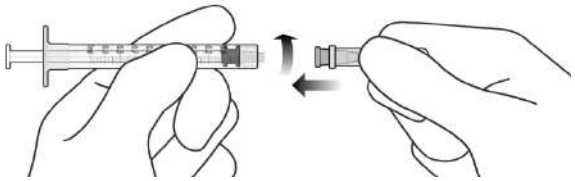


Figure J

11.	Carefully remove the plastic needle shield from the needle by pulling it straight off.
12.	To check for air bubbles, hold the syringe with the needle pointing up. If there are any air bubbles, gently tap the syringe with your finger until the bubbles rise to the top (see **Figure K**).

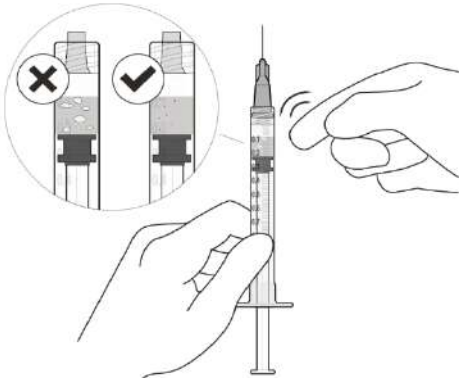


Figure K

13.	Carefully expel the air from the syringe and needle, and **slowly** depress the plunger to align the rubber stopper tip to the 0.05 mL dose mark. The syringe is ready for the injection (see **Figure L**). Ensure that the injection is given **immediately** after preparation of the dose.

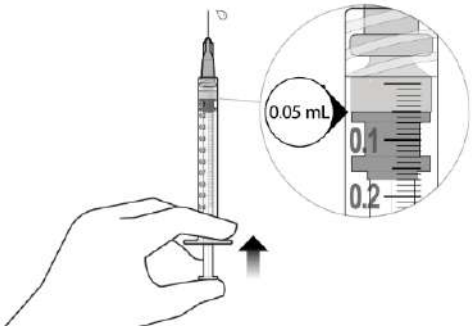


Figure L

2.6 Injection Procedure

The intravitreal injection procedure must be carried out under aseptic conditions, which includes the use of surgical hand disinfection, sterile gloves, a sterile drape and a sterile eyelid speculum (or equivalent), and the availability of sterile paracentesis equipment (if required). Adequate anesthesia and a broad-spectrum microbicide should be administered prior to the injection. Inject slowly until the rubber stopper reaches the end of the syringe to deliver the volume of 0.05 mL. Confirm delivery of the full dose by checking that the rubber stopper has reached the end of the syringe barrel.

Any unused medicinal product or waste material should be disposed of in accordance with local regulations.

Immediately following the intravitreal injection, patients should be monitored for elevation in intraocular pressure. Appropriate monitoring may consist of a check for perfusion of the optic nerve head or tonometry. If required, a sterile paracentesis needle should be available. Following intravitreal injection, patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment (e.g., vision loss, eye pain, redness of the eye, photophobia, blurring of vision) without delay *[see Patient Counseling Information (17)]*. Each syringe should only be used for the treatment of a single eye. If the contralateral eye requires treatment, a new syringe should be used and the sterile field, syringe, gloves, drapes, eyelid speculum, filter, and injection needles should be changed before VABYSMO is administered to the other eye.

3 DOSAGE FORMS AND STRENGTHS

Injection: 120 mg/mL clear to opalescent, colorless to brownish-yellow solution in a single-dose vial.

4 CONTRAINDICATIONS

4.1 Ocular or Periocular Infections

VABYSMO is contraindicated in patients with ocular or periocular infections.

4.2 Active Intraocular Inflammation

VABYSMO is contraindicated in patients with active intraocular inflammation.

4.3 Hypersensitivity

VABYSMO is contraindicated in patients with known hypersensitivity to faricimab or any of the excipients in VABYSMO. Hypersensitivity reactions may manifest as rash, pruritus, urticaria, erythema, or severe intraocular inflammation.

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis and Retinal Detachments

Intravitreal injections have been associated with endophthalmitis and retinal detachments *[see Adverse Reactions (6.1)]*. Proper aseptic injection techniques must always be used when administering VABYSMO. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay, to permit prompt and appropriate management *[see Dosage and Administration (2.6) and Patient Counseling Information (17)]*.

5.2 Increase in Intraocular Pressure

Transient increases in intraocular pressure (IOP) have been seen within 60 minutes of intravitreal injection, including with VABYSMO *[see Adverse Reactions (6.1)]*. IOP and the perfusion of the optic nerve head should be monitored and managed appropriately *[see Dosage and Administration (2.6)]*.

5.3 Thromboembolic Events

Although there was a low rate of arterial thromboembolic events (ATEs) observed in the VABYSMO clinical trials, there is a potential risk of ATEs following intravitreal use of VEGF inhibitors. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause).

The incidence of reported ATEs in the nAMD studies during the first year was 1% (7 out of 664) in patients treated with VABYSMO compared with 1% (6 out of 662) in patients treated with aflibercept *[see Clinical Studies (14.1)]*.

The incidence of reported ATEs in the DME studies during the first year was 2% (25 out of 1,262) in patients treated with VABYSMO compared with 2% (14 out of 625) in patients treated with aflibercept *[see Clinical Studies (14.2)]*.

6 ADVERSE REACTIONS

The following potentially serious adverse reactions are described elsewhere in the labeling:

- Hypersensitivity *[see Contraindications (4)]*
- Endophthalmitis and retinal detachments *[see Warnings and Precautions (5.1)]*
- Increase in intraocular pressure *[see Warnings and Precautions (5.2)]*
- Thromboembolic events *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in other clinical trials of the same or another drug and may not reflect the rates observed in practice.

The data described below reflect exposure to VABYSMO in 1,926 patients, which constituted the safety population in four Phase 3 studies *[see Clinical Studies (14.1, 14.2)]*.

Table 1: Common Adverse Reactions (≥ 1%)

Adverse Reactions	VABYSMO		Active Control (aflibercept)	
	AMD N=664	DME N=1262	AMD N=622	DME N=625
Conjunctival hemorrhage	7%	7%	8%	6%
Vitreous floaters	3%	3%	2%	2%
Retinal pigment epithelial tear[a]	3%		1%	
Intraocular pressure increased	3%	3%	2%	2%
Eye pain	3%	2%	3%	3%
Intraocular inflammation[b]	2%	1%	1%	1%
Eye irritation	1%	1%	< 1%	1%
Ocular discomfort	1%	1%	< 1%	< 1%
Vitreous hemorrhage	< 1%	1%	1%	< 1%

[a] AMD only
[b] Including iridocyclitis, iritis, uveitis, vitritis

Less common adverse reactions reported in < 1% of the patients treated with VABYSMO were corneal abrasion, eye pruritus, lacrimation increased, ocular hyperemia, blurred vision, eye irritation, sensation of foreign body, endophthalmitis, visual acuity reduced transiently, retinal tear and rhegmatogenous retinal detachment.

6.2 Immunogenicity

The immunogenicity of VABYSMO was evaluated in plasma samples. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to VABYSMO in immunoassays. The detection of an immune response is highly dependent on the sensitivity and specificity of the assays used, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to VABYSMO with the incidence of antibodies to other products may be misleading.

There is a potential for an immune response in patients treated with VABYSMO. In the nAMD and DME studies, the pre-treatment incidence of anti-faricimab antibodies was approximately 1.8% and 0.8%, respectively. After initiation of dosing, anti-faricimab antibodies were detected in approximately 10.4% and 8.4% of patients with nAMD and DME respectively, treated with VABYSMO across studies and across treatment groups. As with all therapeutic proteins, there is a potential for immunogenicity with VABYSMO.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies of VABYSMO administration in pregnant women.

Administration of VABYSMO to pregnant monkeys throughout the period of organogenesis resulted in an increased incidence of abortions at intravenous (IV) doses 158 times the human exposure (based on C_{max}) of the maximum recommended human dose *[see Animal Data]*. Based on the mechanism of action of VEGF and Ang-2 inhibitors, there is a potential risk to female

reproductive capacity, and to embryo-fetal development. VABYSMO should not be used during pregnancy unless the potential benefit to the patient outweighs the potential risk to the fetus.

All pregnancies have a background risk of birth defect, loss, and other adverse outcomes. The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects is 2%-4% and of miscarriage is 15%-20% of clinically recognized pregnancies.

Data

Animal Data

An embryo fetal developmental toxicity study was performed on pregnant cynomolgus monkeys. Pregnant animals received 5 weekly IV injections of VABYSMO starting on day 20 of gestation at 1 or 3 mg/kg. A non-dose dependent increase in pregnancy loss (abortions) was observed at both doses evaluated. Serum exposure (C_{max}) in pregnant monkeys at the low dose of 1 mg/kg was 158 times the human exposure at the maximum recommended intravitreal dose of 6 mg once every 4 weeks. A no observed adverse effect level (NOAEL) was not identified in this study.

8.2 Lactation

Risk Summary

There is no information regarding the presence of faricimab in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. Many drugs are transferred in human milk with the potential for absorption and adverse reactions in the breastfed child.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for VABYSMO and any potential adverse effects on the breastfed child from VABYSMO.

8.3 Females and Males of Reproductive Potential

Contraception

Females of reproductive potential are advised to use effective contraception prior to the initial dose, during treatment and for at least 3 months following the last dose of VABYSMO.

Infertility

No studies on the effects of faricimab on human fertility have been conducted and it is not known whether faricimab can affect reproduction capacity. Based on the mechanism of action, treatment with VABYSMO may pose a risk to reproductive capacity.

8.4 Pediatric Use

The safety and efficacy of VABYSMO in pediatric patients have not been established.

8.5 Geriatric Use

In the four clinical studies, approximately 60% (1,149/1,929) of patients randomized to treatment with VABYSMO were ≥ 65 years of age. No significant differences in efficacy or safety of faricimab were seen with increasing age in these studies. No dose adjustment is required in patients 65 years and above.

11 DESCRIPTION

Faricimab-svoa is a humanized bispecific immunoglobulin G1 (IgG1) antibody that binds both vascular endothelial growth factor A (VEGF-A) and angiopoietin-2 (Ang-2). The fragment crystallizable (Fc) region of faricimab was engineered by selected point mutations to abolish binding interactions with Fcγ and FcRn receptors. Faricimab-svoa has a total molecular weight of approximately 149 kDa and is produced by recombinant DNA technology using mammalian Chinese Hamster Ovary (CHO) cell culture.

VABYSMO (faricimab-svoa) injection is a sterile, clear to opalescent, colorless to brownish-yellow solution in a single-dose glass vial for intravitreal administration. Each single-dose vial is designed to deliver 0.05 mL (50 microliters) of solution containing 6 mg faricimab-svoa, L-histidine (155 mcg), L-methionine (52.2 mcg), polysorbate 20 (20 mcg), sodium chloride (73.1 mcg), D-sucrose (2.74 mg) and Water for Injection, adjusted to pH 5.5 with acetic acid. The product does not contain an anti-microbial preservative.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Faricimab is a humanized bispecific antibody that acts through inhibition of two pathways by binding to VEGF-A and Ang-2. By inhibiting VEGF-A, faricimab suppresses endothelial cell proliferation, neovascularization and vascular permeability. By inhibiting Ang-2, faricimab is thought to promote vascular stability and desensitize blood vessels to the effects of VEGF-A. Ang-2 levels are increased in some patients with nAMD and DME. The contribution of Ang-2 inhibition to the treatment effect and clinical response for nAMD and DME has yet to be established.

12.2 Pharmacodynamics

Increased retinal thickness, assessed by optical coherence tomography (OCT), is associated with nAMD and DME. Leakage of blood and fluid from choroidal neovascularization, assessed by fluorescein angiography, is associated with nAMD. Reductions in central subfield thickness (CST) were observed from baseline through the first year of treatment across all treatment arms in the four Phase 3 studies in nAMD and DME.

12.3 Pharmacokinetics

Absorption/Distribution

Maximum faricimab plasma concentrations (Cmax) are estimated to occur approximately 2 days post-dose. Mean (±SD) free faricimab (unbound to VEGF-A and Ang-2) plasma Cmax are estimated to be 0.23 (0.07) mcg/mL and 0.22 (0.07) mcg/mL in nAMD and in DME patients, respectively. After repeated intravitreal administrations, mean plasma free faricimab trough concentrations are predicted to be 0.002-0.003 mcg/mL for Q8W dosing. Although not directly measured in the vitreous, no accumulation of faricimab is expected in the vitreous and no accumulation has been observed in plasma when faricimab has been administered as repeat doses in the vitreous.

Metabolism/Elimination

Metabolism and elimination of faricimab has not been fully characterized. Faricimab is expected to be catabolized in lysosomes to small peptides and amino acids, which may be excreted

renally, in a similar manner to the elimination of endogenous IgG. The estimated mean apparent systemic half-life of faricimab is 7.5 days.

Specific Populations
The systemic pharmacokinetics of faricimab were not influenced by gender, race, or mild to severe renal impairment (i.e., estimated normalized creatinine clearance by Cockroft-Gault equation: 15 to 89 mL/min/1.73 m^2). The effect of severe renal impairment or any degree of hepatic impairment on the pharmacokinetics of VABYSMO is unknown. No special dosage modification is required for any of the populations that have been studied (e.g., elderly, gender, race).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity or mutagenicity data are available for VABYSMO injection in animals or humans.

Based on the anti-VEGF and Ang-2 mechanisms of action, treatment with VABYSMO may pose a risk to reproductive capacity *[see Females and Males of Reproductive Potential (8.3)]*.

14 CLINICAL STUDIES

14.1 Neovascular (wet) Age-Related Macular Degeneration (nAMD)

The safety and efficacy of VABYSMO were assessed in two randomized, multi-center, double-masked, active comparator-controlled, 2-year studies (TENAYA – NCT03823287 and LUCERNE – NCT03823300) in patients with nAMD.

A total of 1,329 newly diagnosed, treatment-naive patients were enrolled in these studies, and 664 patients received at least one dose of VABYSMO. Patient ages ranged from 50 to 99 with a mean of 75.9 years. The studies were identically designed two year studies. Patients were randomized in a 1:1 ratio to one of two treatment arms: 1) aflibercept 2 mg administered fixed every 8 weeks (Q8W) after three initial monthly doses; and VABYSMO 6 mg (0.05 mL of 120 mg/mL solution) administered by intravitreal injection every 4 weeks (approximately every 28 ± 7 days, monthly) for the first 4 doses, followed by optical coherence tomography and visual acuity evaluations 8 and 12 weeks later to determine whether to give a 6 mg (0.05 mL of 120 mg/mL solution) dose via intravitreal injection on one of the following three regimens: 1) Weeks 28 and 44; (also referred to as Q16W dosing); 2) Weeks 24, 36 and 48 (also referred to as Q12W dosing); or 3) Weeks 20, 28, 36 and 44 (also referred to as Q8W dosing). However, the utility of these criteria to guide dosing intervals has not been established.

At week 48, after 4 initial monthly doses in the VABYSMO arm, 45% of patients received the Weeks 28 and 44 dosing, 33% of patients received the Weeks 24, 36 and 48 dosing, and the remaining 22% of patients received dosing every 8 weeks. These percentages are reflective of what happened within the conduct of these trials and indicate that some patients did well on two (2) doses spaced 16 weeks apart, or three (3) doses spaced 12 weeks apart, but the percentages may not be generalizable to a broader nAMD population for a variety of reasons. The inclusion/exclusion criteria limited enrollment to a select subset of treatment naive, newly diagnosed nAMD patients and there is no empirical data that a similar magnitude would be observed if eligibility criteria allowed for broader enrollment. The disease activity criteria, which

was instrumental in determining dose frequency, is unvalidated. Stricter criteria would have changed how patients were treated resulting in different percentages of subjects in each dose interval cohort. There was not a similarly dosed aflibercept arm for comparison, which makes the percentages difficult to interpret.

Both studies demonstrated non-inferiority to the comparator control (aflibercept) at the primary endpoint, defined as the mean change from baseline in Best Corrected Visual Acuity (BCVA) when averaged over the week 40, 44, and 48 visits and measured by the Early Treatment Diabetic Retinopathy Study (ETDRS) letter chart. The primary endpoint analysis was a non-inferiority comparison for the mean change in BCVA between the aflibercept and the VABYSMO arm. The lower bound of the 95% confidence interval for the mean change in BCVA could not be lower than minus 4 letters to declare non-inferiority. In both studies, VABYSMO treated patients had a non-inferior mean change from baseline in BCVA compared to patients treated with aflibercept. Detailed results of both studies are shown in Table 2, Figure 1, and Figure 2 below. The clinical efficacy for the second year of the study has not been reviewed.

Table 2: Primary Endpoint Results[a] in the TENAYA and LUCERNE Studies

	TENAYA		**LUCERNE**	
	VABYSMO N = 334	Aflibercept N = 337	VABYSMO N = 331	Aflibercept N = 327
Mean change in BCVA as measured by ETDRS letter score from baseline (95% CI)	5.8 (4.6, 7.1)	5.1 (3.9, 6.4)	6.6 (5.3, 7.8)	6.6 (5.3, 7.8)
Difference in LS mean (95% CI)	0.7 (-1.1, 2.5)		0.0 (-1.7, 1.8)	

[a] Average of weeks 40, 44 and 48
BCVA: Best Corrected Visual Acuity
ETDRS: Early Treatment Diabetic Retinopathy Study
CI: Confidence Interval
LS: Least Square

Figure 1: Mean Change in Visual Acuity from Baseline to Week 48 in TENAYA

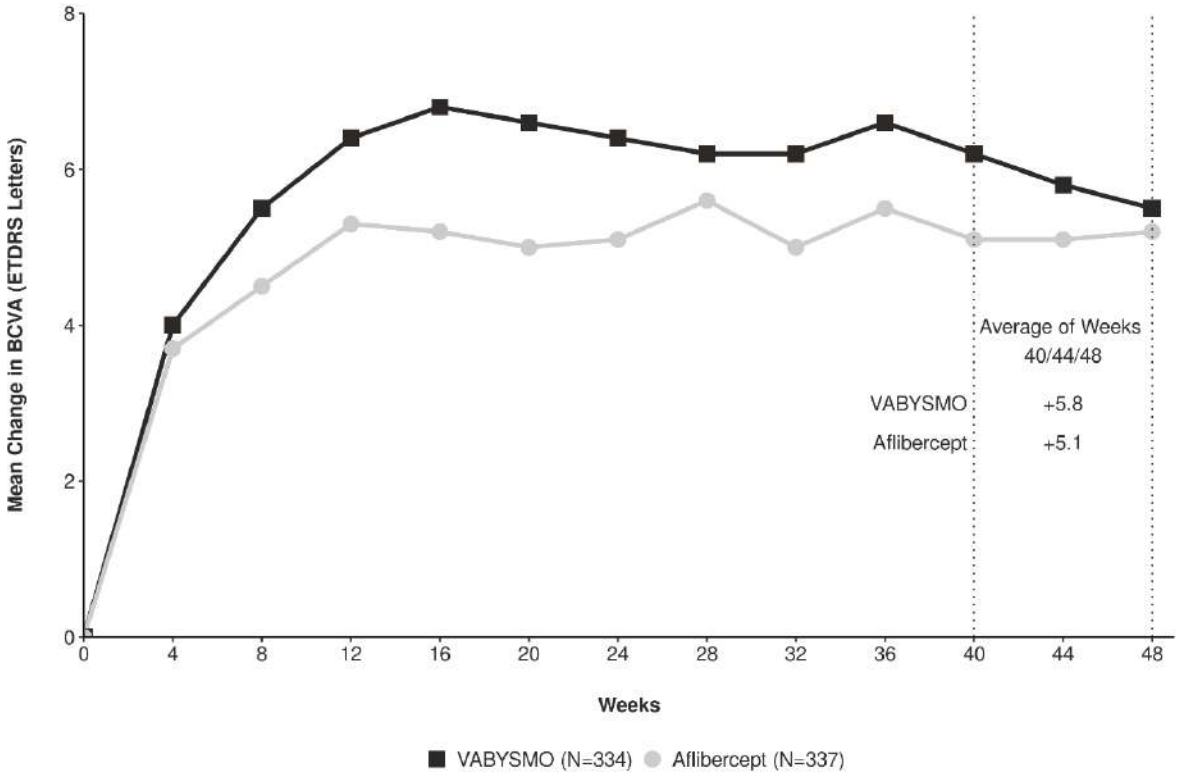
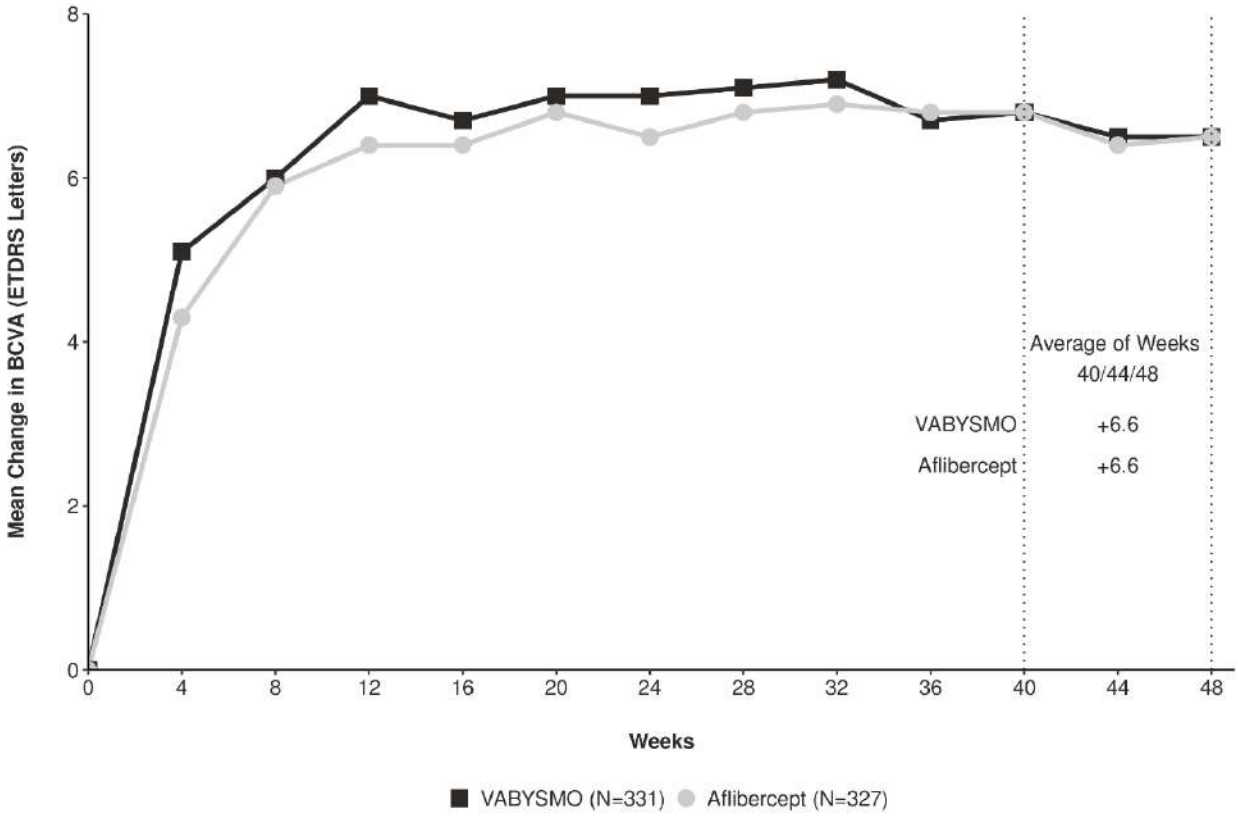


Figure 2: Mean Change in Visual Acuity from Baseline to Week 48 in LUCERNE



PGR2026-00039
Biocon Ex.1065
Page 318 of 595

Treatment effects in evaluable subgroups (e.g., age, gender, race, baseline visual acuity) in each study were consistent with the results in the overall population.

14.2 Diabetic Macular Edema (DME)

The safety and efficacy of VABYSMO were assessed in two randomized, multi-center, double-masked, active comparator-controlled 2-year studies (YOSEMITE – NCT03622580 and RHINE – NCT03622593) in patients with DME.

A total of 1,891 diabetic patients were enrolled in the two studies with a total of 1,262 patients treated with at least one dose of VABYSMO. Patient ages ranged from 24 to 91 with a mean of 62.2 years. The overall population included both anti-VEGF naive patients (78%) and patients who had been previously treated with a VEGF inhibitor prior to study participation (22%).

The studies were identically designed 2 year studies. Patients were randomized in a 1:1:1 ratio to one of three treatment regimens: 1) aflibercept Q8W, patients received fixed aflibercept 2 mg administered every 8 weeks (Q8W) after the first five monthly doses; 2) VABYSMO Q8W, patients received fixed VABYSMO 6 mg administered Q8W after the first six monthly doses; and 3) VABYSMO Variable, patients received VABYSMO 6 mg administered every 4 weeks for at least 4 doses and until the central subfield thickness (CST) of the macula measured by optical coherence tomography was less than approximately 325 microns, then the interval of dosing was modified by up to 4 week interval extensions or reductions in up to 8 week interval increments based on CST and visual acuity disease activity criteria at study drug dosing visits. However, the utility of these disease activity criteria to guide dosing intervals has not been established.

After 4 initial monthly doses, the patients in the VABYSMO Variable arm could have received between the minimum of three and the maximum of eleven total injections through Week 56 inclusive. At Week 56, 32% of patients had completed at least one Q12W interval followed by one full Q16W interval. Seventeen percent (17%) of patients were treated on Q8W and/or Q4W dosing intervals through Week 56 (7% only on Q4W). Sustainability of the Q16W dosing interval cannot be determined based on year one data alone. These percentages are reflective of what happened within the conduct of these trials, but the percentages are not generalizable to a broader DME population for a variety of reasons. The inclusion/exclusion criteria limited enrollment to a select subset of DME patients and there is no empirical data that a similar magnitude would be observed if eligibility criteria allowed for broader enrollment. The disease activity criteria, which was instrumental in determining dose frequency, is unvalidated. Stricter criteria would have changed how patients were treated resulting in different percentages of subjects in each dose interval cohort. There was not a similarly dosed aflibercept arm for comparison which makes the percentages difficult to interpret.

Both studies demonstrated non-inferiority to the comparator control (aflibercept) at the primary endpoint, defined as the primary endpoint, defined as the mean change from baseline in BCVA at year 1 (average of the week 48, 52, and 56 visits), measured by the ETDRS Letter Score. The primary endpoint analysis was a non-inferiority comparison for the mean change in BCVA between the aflibercept and VABYSMO groups. The lower bound of the 97.5% confidence interval for the mean change in BCVA could not be lower than minus 4 letters to declare non-inferiority. In both studies, VABYSMO Q8W and VABYSMO Variable treated patients had a

mean change from baseline in BCVA that was non-inferior to the patients treated with aflibercept Q8W. Detailed results of both studies are shown in Table 3, Figure 3, and Figure 4 below. The clinical efficacy for the second year of the study has not been reviewed.

Table 3: Primary Endpoint Results[a] in the YOSEMITE and RHINE Studies

	YOSEMITE			RHINE		
	VABYSMO Q8W N = 315	VABYSMO Variable N = 313	Aflibercept Q8W N = 312	VABYSMO Q8W N = 317	VABYSMO Variable N = 319	Aflibercept Q8W N = 315
Mean change in BCVA as measured by ETDRS letter score from baseline (97.5% CI)	10.7 (9.4, 12.0)	11.6 (10.3, 12.9)	10.9 (9.6, 12.2)	11.8 (10.6, 13.0)	10.8 (9.6, 11.9)	10.3 (9.1, 11.4)
Difference in LS mean (97.5% CI)	-0.2 (-2.0, 1.6)	0.7 (-1.1, 2.5)		1.5 (-0.1, 3.2)	0.5 (-1.1, 2.1)	

[a]Average of weeks 48, 52, 56
BCVA: Best Corrected Visual Acuity
ETDRS: Early Treatment Diabetic Retinopathy Study
CI: Confidence Interval
LS: Least Square

Figure 3: Mean Change in Visual Acuity from Baseline to Year 1 (Week 56) in YOSEMITE

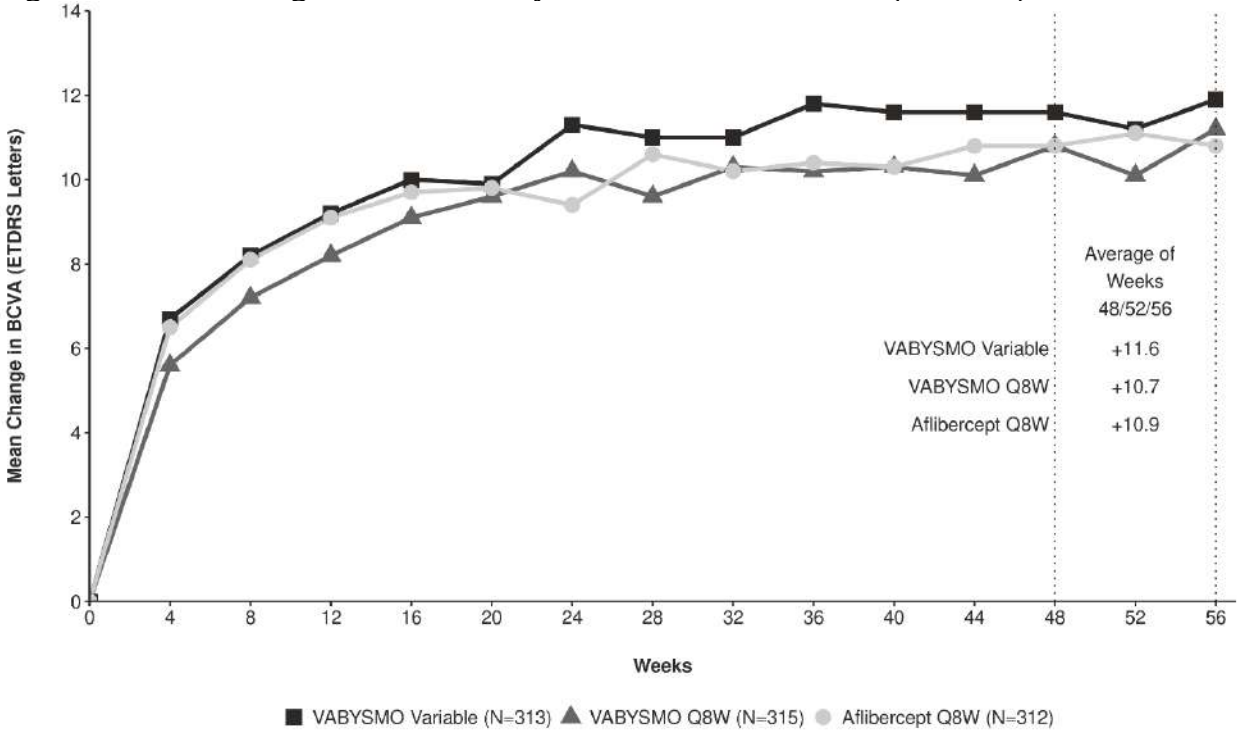
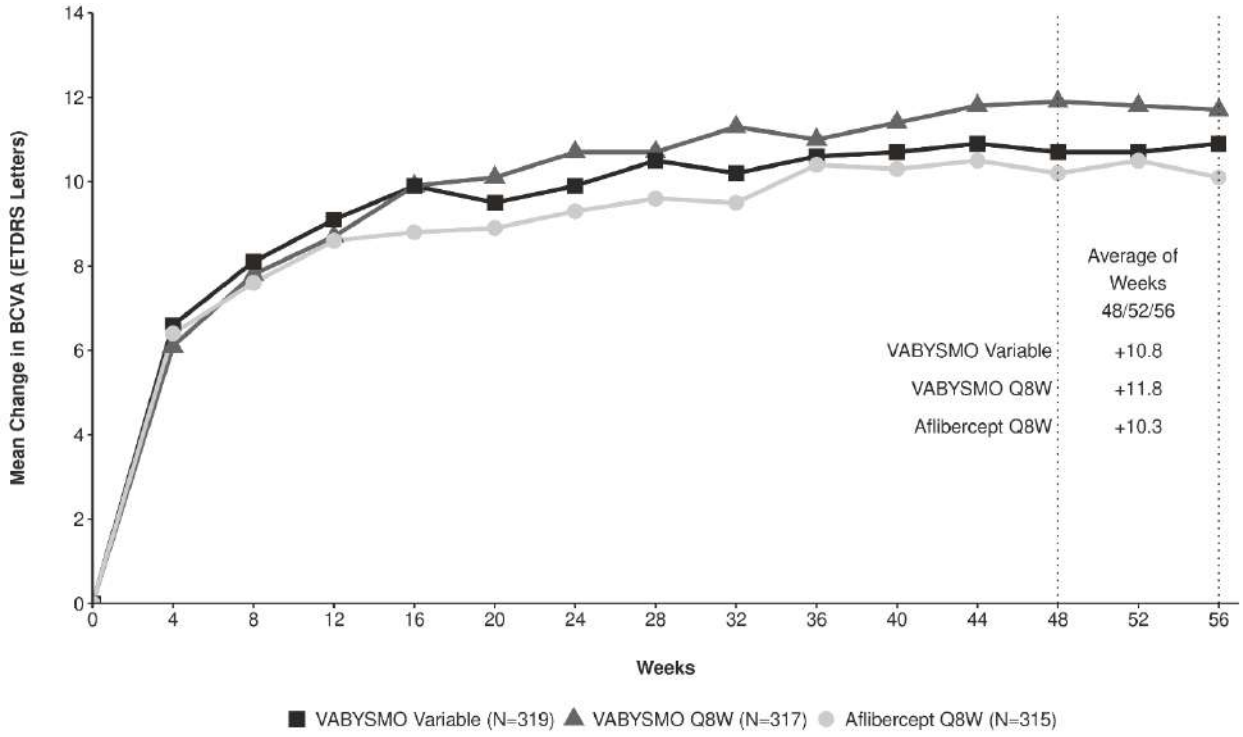


Figure 4: Mean Change in Visual Acuity from Baseline to Year 1 (Week 56) in RHINE



Treatment effects in the subgroup of patients who were anti-VEGF naive prior to study participation were similar to those observed in the overall population. Treatment effects in evaluable subgroups (e.g., by age, gender, race, baseline HbA1c, baseline visual acuity) in each study were generally consistent with the results in the overall population.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

VABYSMO (faricimab-svoa) injection is supplied as a clear to opalescent, colorless to brownish-yellow 120 mg/mL solution in a single-dose glass vial. Each glass vial contains an overfill amount to allow for administration of a single 0.05 mL dose of solution containing 6 mg of VABYSMO. Each VABYSMO carton (NDC 50242-096-01) contains one glass vial and one sterile 5-micron blunt transfer filter needle (18-gauge x 1½ inch, 1.2 mm x 40 mm).

16.2 Storage and Handling

Store VABYSMO in the refrigerator between 2°C to 8°C (36°F to 46°F). Do not freeze. Do not shake. Keep the vial in the original carton to protect from light.

Prior to use, the unopened glass vial of VABYSMO may be kept at room temperature, 20°C to 25°C (68°F to 77°F), for up to 24 hours. Ensure that the injection is given immediately after preparation of the dose.

17 PATIENT COUNSELING INFORMATION

Advise patients that in the days following VABYSMO administration, patients are at risk of developing endophthalmitis. If the eye becomes red, sensitive to light, painful, or develops a change in vision, advise the patient to seek immediate care from an ophthalmologist *[see Warnings and Precautions (5)]*.

Patients may experience temporary visual disturbances after an intravitreal injection with VABYSMO and the associated eye examinations *[see Adverse Reactions (6)]*. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

VABYSMO™ [faricimab-svoa]
Manufactured by:
Genentech, Inc.
A Member of the Roche Group
1 DNA Way
South San Francisco, CA 94080-4990
U.S. License No.: 1048

VABYSMO is a trademark of Genentech, Inc.
©2022 Genentech, Inc.

PGR2026-00039
Biocon Ex.1065

APPENDIX EMA01

INTERNET ARCHIVE WEB TEXTS VIDEO AUDIO SOFTWARE IMAGES SIGN UP | LOG IN UPLOAD Search
ABOUT BLOG PROJECTS HELP DONATE CONTACT JOBS VOLUNTEER PEOPLE

DONATE INTERNET ARCHIVE WayBackMachine Explore more than 946 billion web pages saved over time
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_

Calendar · Collections · Changes · Summary · Site Map · URLs

Saved **21 times** between April 7, 2013 and July 11, 2025.

002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 **2015** 2016 2017 2018 2019 2020 2021 2022 2023 2024 2025

JAN
1 2 3
4 5 6 7 8 9 10
11 12 13 14 15 16 17
18 19 20 21 22 23 24
25 26 27 28 29 30 31

FEB
1 2 3 4 5 6 7
8 9 10 11 12 13 14
15 16 17 18 19 20 21
22 23 24 25 26 27 28

MAR
1 2 3 4 5 6 7
8 9 10 11 12 13 14
15 16 17 18 19 20 21
22 23 24 25 26 27 28
29 30 31

APR
1 2 3 4
5 6 7 8 9 10 11
12 13 14 15 16 17 18
19 20 21 22 23 24 25
26 27 28 29 30

MAY
1 2
3 4 5 6 7 8 9
10 11 12 13 14 15 16
17 18 19 20 21 22 23
24 25 26 27 28 29 30
31

JUN
1 2 3 4 5 6
7 8 9 10 11 12 13
14 15 16 17 18 19 20
21 22 23 24 25 26 27
28 29 30

JUL
1 2 3 4
5 6 7 8 9 10 11
12 13 14 15 16 17 18
19 20 21 22 23 24 25
26 27 28 29 30 31

AUG
1
2 3 4 5 6 7 8
9 10 11 12 13 14 15
16 17 18 19 20 21 22
23 24 25 26 27 28 29
30 31

SEP
1 2 3 4 5
6 7 8 9 10 11 12
13 14 15 16 17 18 19
20 21 22 23 24 25 26
27 28 29 30

OCT
1 2 3
4 5 6 7 8 9 10
11 12 13 14 15 16 17
18 19 20 21 22 23 24
25 26 27 28 29 30 31

NOV
1 2 3 4 5 6 7
8 9 10 11 12 13 14
15 16 17 18 19 20 21
22 23 24 25 26 27 28
29 30

DEC
1 2 3 4 5
6 7 8 9 10 11 12
13 14 15 16 17 18 19
20 21 22 23 24 25 26
27 28 29 30 31

Note
This calendar view maps the number of times **http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002392/WC500135744.pdf** was crawled by the Wayback Machine, *not* how many times the site was actually updated. More info in the FAQ.

FAQ | Contact Us | Terms of Service (Dec 31, 2014)

The Wayback Machine is an initiative of the Internet Archive, a 501(c)(3) non-profit, building a digital library of Internet sites and other cultural artifacts in digital form. Other projects include Open Library & archive-it.org.

Your use of the Wayback Machine is subject to the Internet Archive's Terms of Use.

https://web.archive.org/web/20151026043159/http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002392/WC500135744.pdf September 17, 2025

INTERNET ARCHIVE Wayback Machine http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002392/WC500135744.pdf Go JUL OCT DEC
21 captures 26
7 Apr 2013 - 11 Jul 2025 2013 2015 2017 About this capture



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 September 2012
EMA/646256/2012 corr
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Eylea

aflibercept

Procedure No.: EMEA/H/C/002392/

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 September 2012
EMA/646256/2012 corr
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Eylea

aflibercept

Procedure No.: EMEA/H/C/002392/

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7455
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

Table of contents

1. Background information on the procedure 6
1.1. Submission of the dossier 6
1.2. Steps taken for the assessment of the product 7
2. Scientific discussion 8
2.1. Introduction 8
2.2. Quality aspects 9
2.2.1. Introduction 9
2.2.2. Active Substance 10
2.2.3. Finished Medicinal Product 12
2.2.4. Discussion on chemical, pharmaceutical and biological aspects 14
2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects 14
2.3. Non-clinical aspects 14
2.3.1. Introduction 14
2.3.2. Pharmacology 15
2.3.3. Pharmacokinetics 17
2.3.4. Toxicology 19
2.3.5. Ecotoxicity/environmental risk assessment 23
2.3.6. Discussion on non-clinical aspects 23
2.3.7. Conclusion on the non-clinical aspects 24
2.4. Clinical aspects 25
2.4.1. Introduction 25
2.4.2. Pharmacokinetics 26
2.4.3. Pharmacodynamics 28
2.4.4. Discussion on clinical pharmacology 29
2.4.5. Conclusions on clinical pharmacology 29
2.5. Clinical efficacy 30
2.5.1. Dose response study(ies) 30
2.5.2. Main study(ies) 30
2.5.3. Discussion on clinical efficacy 53
2.5.4. Conclusions on the clinical efficacy 55
2.6. Clinical safety 56
2.6.1. Discussion on clinical safety 68
2.6.2. Conclusions on the clinical safety 69
2.7. Pharmacovigilance 70
2.8. User consultation 78
3. Benefit-Risk Balance 78
4. Recommendations 81

PGR2026-00039
Biocon Ex.1065
Page 327 of 595

List of abbreviations

Ab	Antibody
ADA	Anti-drug antibody
ADR	Adverse drug reaction
AE	Adverse event
AEI	AE of interest
ALT	Alanine aminotransferase
AMD	Age-related macular degeneration
ANCOVA	Analysis of covariance
APTC	Anti-Platelet Trialists' Collaboration
ATE	Arterial thromboembolic events
AUC	Area under the drug concentration-time curve
BCVA	Best corrected visual acuity
BLA	Biologic License Application
BMI	Body mass index
Capped PRN	Term used for flexible-dosing phase in the VIEW 1 and VIEW 2 studies
CI	Confidence interval
Cmax	Maximum observed plasma drug concentration
CNV	Choroidal neovascularization
CRF	Case report form
CR/LT	Central Retinal Lesion Thickness
CRT	Central retinal thickness
CRVO	Central retinal vein occlusion
CSR	Clinical study report
CVA	Cerebrovascular accident
DA	Disc area (4 DA =10.16 mm2)
DLT	Dose limiting toxicity
DME	Diabetic macular edema
ECG	Electrocardiogram
ELISA	Enzyme-linked immunosorbent assay
ETDRS	Early Treatment Diabetic Retinopathy Study
EU	European Union
FA	Fluorescein angiography
FAS	Full analysis set
Fc	Fragment, crystallizable region or constant
FDA	Food and Drug Administration
Fixed-dosing phase	Fixed protocol- specified schedule
Flexible-dosing phase	Based on specific retreatment criteria "PRN" (as needed) phase
FSH	Follicle-stimulating hormone
GLP	Good Laboratory Practice
Ig	Immunoglobulin
INR	International normalized ratio
IOP	Intraocular pressure
IV	Intravenous
IVT	Intravitreal
LOAEL	Lowest-observable-adverse-effect level
LOCF	Last observation carried forward
LSMean	Least-square mean
MAA	Marketing Authorisation Application
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum tolerated dose
NEI-VFQ-25	National Eye Institute 25-Item Visual Function Questionnaire
NOAEL	No-observed-adverse-effect level
NSCLA	Non-small-cell lung adenocarcinoma
NYHA	New York Heart Association
OCT	Optical coherence tomography

PGR2026-00039
Biocon Ex.1065
Page 328 of 595

PD	Pharmacodynamic
PDT	Photodynamic therapy
PFS	Pre-filled syringe
PK	Pharmacokinetics
PIGE	Placental growth factor
PMDA	Pharmaceutical and Medical Devices Agency
PPS	Per protocol set
PPT	Partial thromboplastin time
PT	Preferred term
PRN	As need (*pro re nata*)
QOL	Quality of life
RAAS	Renin angiotensin aldosterone system
RBC	Red blood cell
RECIST	Response evaluation criteria in solid tumors
Regeneron	Regeneron Pharmaceuticals, Inc.
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard deviation
SOC	System organ class
SPA	Special Protocol Assessment
TEAE	Treatment-emergent adverse event
TJA	Transient ischemic attack
ULN	Upper limit of normal
UPCR	Urine/protein creatinine ratio
US	United States
VEGF-A	Vascular endothelial growth factor – A
VEGFR	VEGF receptor
VA	Visual acuity
VTE	VEGF Trap (formulation for IVT injection
WBC	White blood cell
WET AMD	Neovascular age-related macular degeneration
WHO	World Health Organization
WOCF	Worst observation carried forward

DOSE GROUPS ABBREVIATIONS

Phase-2 Study VGFT-OD-0508	
0.5Q4	0.5 mg VEGF Trap dosed on a monthly basis (ie, every 4 weeks)
2Q4	2 mg VEGF Trap dosed on a monthly basis (ie, every 4 weeks)
0.5Q12	0,5 mg VEGF Trap dosed on a quaterly basis (ie, every 12 weeks)
2Q12	2 mg VEGF Trap dosed on a quaterly basis (ie, every 12 weeks)
4Q12	4 mg VEGF Trap dosed on a quaterly basis (ie, every 4 weeks)
Phase-3 Studies VIEW 1 (VGTF OD 605), VIEW 2 (A36355) – Integrated analysis POOL 1	
RQ4	0.5 mg ranibizumab dosed on a monthly basis (ie, every 4 weeks)
2Q4	2 mg VEGF Trap dosed on a monthly basis (ie, every 4 weeks)
0.5Q4	0.5 mg VEGF Trap dosed on a monthly basis (ie, every 4 weeks)
2Q8	2 mg VEGF Trap dosed every two months (ie, every 0 weeks) after three initial monthly doses

PGR2026-00039
Biocon Ex.1065
Page 330 of 595

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Bayer Pharma AG submitted on 31 May 2011 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Eylea, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication treatment of neovascular (wet) age-related macular degeneration (AMD).

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision (EMEA/56/2008) on the granting of a class waiver.

New active Substance status

The applicant requested the active substance aflibercept contained in the above medicinal product to be considered as a new active substance in itself.

Scientific Advice

Several Scientific Advices were given by the EMA and other regulatory authorities.

EU Scientific Advices
March and June 2007: MPA advice on clinical questions for the planned Phase 3 trial design and non-clinical development programme;

July and August 2007: CHMP advice on the same aspects as discussed with MPA;

May – July 2010: National agency meetings with Denmark, Germany, Spain, Sweden on clinical aspects of the submission package for the MAA;

November 2010: EMA pre-submission meeting on regulatory aspects of the MAA;

January 2011: Rapporteur / Co-Rapporteur meeting on specific issues around the clinical data package for the MAA.

US (FDA)
March 2007: Special Protocol Assistance (SPA) for Phase-3 study design VIEW1 support filing.

July 2007: Second SPA for Phase-3 study VIEW1 agreements on amended Phase-3 study design, including a change in the VEGF Trap dose regimens

September 2010: Pre-Biologic License Application (BLA) meeting on specific clinical questions.

Japan (PMDA)
August 2007: Scientific advice meeting with Pharmaceutical and Medical Devices Agency (PMDA) on Phase-3 study design.

PGR2026-00039
Biocon Ex.1065
Page 331 of 595

Overall, the clinical development programme appears fairly in compliance with the CHMP and national agencies scientific advices. The design/analysis of pivotal studies was widely discussed across these consultations. Some topics were thoroughly discussed with the CHMP (e.g. choice of primary variable and non-inferiority margin in pivotal studies) as they were slightly controversial. Region-specific feedback on each aspect has been implemented as protocols' local, or if relevant, as general amendments to both pivotal studies. Finally, although some preliminary advices were not always fully taken into account by the MAA, there were acceptable justifications for such deviations.

Licensing status

Eylea has been given a Marketing Authorisation in The USA in 2011 and in Colombia and Australia in 2012.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: **Philippe Lechat**

Co-Rapporteur: **Robert James Hemmings**

CHMP Peer reviewer: Conception Prieto Yerro

The EMA Product Team Leader: Francesca Cerreta

The application was received by the EMA on 31 May 2011.

The procedure started on 22 June 2011.

The Rapporteur's first Assessment Report was circulated to all CHMP members on 12 September 2011 (Annex 1). The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 13 September 2011 (Annex 2).

During the meeting on 20 October 2011, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 21 October 2011 (Annex 3).

The applicant submitted the responses to the CHMP consolidated List of Questions on 18 April 2012.

The Rapporteurs circulated the Joint Assessment Reports on the applicant's responses to the List of Questions to all CHMP members on 6 June 2012 (Annex 4).

During the CHMP meeting on 18-21 June 2012, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant (Annex 5).

The applicant submitted the responses to the CHMP List of Outstanding Issues on 20 August 2012.

The Rapporteurs circulated the Joint Assessment Reports on the applicant's responses to the List of Outstanding Issues to all CHMP members on 4 September 2012 (Annex 6).

The Rapporteurs circulated the updated Joint Assessment Reports to all CHMP members on 14 September 2012 (Annex 7).

During the meeting on 17-20 September 2012, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Eylea on 20 September 2011.

2. Scientific discussion

2.1. Introduction

Neovascular age-related macular degeneration (AMD) is a common cause of irreversible blindness among the elderly worldwide. Vision loss results from the abnormal growth and leakage of blood vessels in the macula. Increasing incidence is reported with increasing age (it is suggested that 10% of individuals aged 65 to 74 years, and 30% of those aged 75 to 85 years, show signs of AMD). The main factor of progression remains age, besides genetics and smoking.

AMD is a disease of the photoreceptors and the retinal pigment epithelium (RPE). In the aging eye, Bruch's membrane composition changes, and RPE function diminishes. As a consequence of reduced RPE function, drusen deposits at the level of the RPE and photoreceptors accumulate. Drusen contain lipofuscin and other toxic waste products of metabolism.

There are two forms of AMD, the dry (atrophic) and the wet (i.e. neovascular or exudative) form.

Dry AMD

The dry form is more benign and accounts for 90% of all AMD cases, but only for 10% of cases of blindness due to AMD. In the dry form, no abnormal vascularisation occurs in the subretinal space and drusen deposits are clustered in and around the macula, and these become larger and more numerous over time. Nevertheless, dry AMD with drusen only is generally asymptomatic. If, in addition to drusen, RPE cells degenerate and undergo apoptosis, geographic atrophy develops which can, if involving the fovea, significantly reduce near and distance vision. Eventually, the RPE atrophies. This results in a loss of vision due to the loss of photoreceptor function.

Patients suffering from an atrophic form of AMD do not benefit from the same therapeutic options than wet AMD. Although less progressive, dry AMD is of bad prognosis. Nowadays, treatments remain based on optic systems and re-education. There is no drug therapy for dry AMD.

Wet AMD

Only about 10% of AMD patients have the wet form; however, 80% to 90% of patients with severe vision loss due to AMD have wet AMD. In wet AMD, Bruch's membrane ruptures, and this is associated with a localized inflammatory response and release of VEGF (Vascular endothelial growth factor), which induces choroidal neovascularization (CNV). The CNV is a membrane of abnormal and leaky blood vessels, growing from the choroid through the defects in Bruch's membrane underneath the RPE and the retina. These new, immature blood vessels leak lipids, fluid and blood. This causes edema and elevation of the retina, resulting in blurring and distortion of vision. Onset of visual dysfunction in wet AMD is acute and progresses within a few weeks or even faster, particularly if bleeding occurs. With bleeding under the retina or persistent edema, the loss of central vision becomes permanent.

CNV is characterized clinically, using fluorescein angiography (FA), as occult, mixed or classic/visible CNV. Occult CNV is usually limited to the space beneath the RPE, and the degree of vision loss is usually mild compared with classic CNV. Classic CNV often penetrates the pigment epithelium and grows into the subretinal space with possible retinal serous.

In addition to the gold standard fluorescein angiography test, optical coherence tomography (OCT) is a complementary useful tool to make a diagnosis of wet AMD and identify the presence of subretinal fluid and the central retinal thickness.

Wet AMD Treatments:

Vascular endothelial growth factor-A (VEGF-A) is involved in many forms of angiogenesis, both physiological and pathological. The role of VEGF-A in promoting pathological neovascularization and/or abnormal and excessive vascular permeability in several diseases affecting the eye is now well established.

The VEGF / platelet-derived growth factor gene family includes other members (VEGFB, VEGFC, VEGFD, VEGFE and PlGF). The activity of VEGF-A is mediated primarily by binding to and activation of two transmembrane receptor tyrosine kinases, VEGFR1 and VEGFR2. A third related receptor, VEGFR3, binds VEGFC and VEGFD, and to a lesser extent VEGF-A, and is mainly involved in the regulation of lymphatic vessel development. VEGFA is thought to induce its effects on the vascular endothelium primarily by signalling through VEGFR2.

Intravitreal (IVT) anti-VEGF treatments for wet AMD have been introduced in recent years, first with Pegaptanib (Macugen; Pfizer), and shortly after with Ranibizumab (Lucentis; Genentech-Roche/Novartis). Intravitreal anti-VEGF therapy is nowadays the standard of care in the treatment of neovascular (wet) AMD.

About the product

Aflibercept (also referred to in this document as "VEGF Trap") is intended to be marketed as an intravitreal injection under the name EYLEA.

VEGF Trap belongs to the pharmacological class of VEGF inhibitors: it is a recombinant protein created by fusing the second Ig domain of human VEGFR1 with the third Ig domain of human VEGFR2, which is in turn fused to the constant region of human IgG1.

Aflibercept is a potent, specific inhibitor of VEGF that is active in animal models of ocular neovascularisation after systemic and IVT administration. Aflibercept interferes with the biological actions of VEGF-A by binding to VEGF-A, preventing it from interacting with its receptors.
It also binds to other VEGFR1 ligands, notably PlGF.

Other drugs of this class include, as previously noted, two currently approved treatments for AMD, ranibizumab (Lucentis) and pegaptanib sodium (Macugen).

VEGF Trap showed some differences over other VEGF blockers, which might have been expected to prolong the interval between two IVT injections up to two or three months, to decrease the number of injections needed by year compared to the current regimens:

-a higher affinity (~ 0.5 pM dissociation constant for VEGF165 and VEGF121) than a humanized monoclonal antibody,

-a longer circulating half-life compared to soluble receptor constructs which have been studied in animals.

-a binding to the related factors Placental Growth Factor 1 and 2 (PLGF1 and PLGF2), thought to be advantageous in certain disease situations, including retinal neovascularizations.

2.2. Quality aspects

2.2.1. Introduction

The drug substance aflibercept is a novel biotechnological product, engineered to act as a decoy VEGF receptor. It is a fully human, recombinant fusion protein consisting of sequences derived

PGR2026-00039
Biocon Ex.1065
Page 334 of 595

from vascular endothelial growth factor (VEGF) receptor extracellular domains fused to the Fc portion of immunoglobulin G1(IgG1). Aflibercept is a member of the pharmacological class of VEGF inhibitors formulated for intravitreal (IVT) use.

Its proposed indication is for the treatment of neovascular (wet) age-related macular degeneration in adults.

The drug product is an iso-osmotic sterile solution of 40 mg/mL Aflibercept for IVT injection in an aqueous buffered solution. The drug product is presented either in single dose vials or single use prefilled syringes.

During clinical development, the drug product was supplied primarily in vials.

A pre-filled syringe was developed in order to improve the ease of drug delivery for retinal physicians, and by design of the syringe, to ensure delivery of the correct drug volume to the patient.

Following consultation with regulatory authorities and in accordance with the medical practice as well as guidance for administration of ophthalmologic products, a pre-filled syringe that is terminally sterilised was developed.

2.2.2. Active Substance

Aflibercept is a recombinant fusion protein consisting of two identical polypeptide chains, each comprising the second Ig domain of the human vascular endothelial growth factor (VEGF) receptor 1 and the third Ig domain of the human VEGF receptor 2, with both polypeptide chains fused to the Fc domain of human IgG1. This fusion protein is synthesized by Chinese Hamster Ovary (CHO) cells as a dimeric, secreted, soluble protein.

Aflibercept functions as a decoy receptor that binds to VEGF ligand, thus inhibiting VEGF from binding to its receptor and subsequent stimulation.

Fusion with the Fc region of IgG1 allows prolonging the *in-vivo* half-life of the molecule.

Manufacture

Manufacturer

The drug substance (DS) is manufactured and released by Regeneron Pharmaceuticals Inc., New-York, USA.

Description of manufacturing process and process controls

The upstream process consists on expansion of a single vial of Working Cell Bank (WCB) and production phase into a bioreactor. It is a fed batch fermentation process using step-wise feeding strategy and harvesting.

The downstream process consists of several chromatography steps (protein A affinity chromatography, Cation exchange, Anion exchange, Hydrophobic Interaction and Size Exclusion chromatographies), viral steps (low pH virus inactivation, one nanofiltration) and ultrafiltration-diafiltration steps.

No reprocessing is claimed for the standard manufacturing of the product.

The DS contains sodium phosphate- pH6.2 and is supplied in 1 L polycarbonate (PC) bottle.

During purification, a DS intermediate can be stored frozen at ≤-20°C up to 9 months in two different containers (EVA bags or PC bottles).

The manufacturing process does not directly use any materials of biological origin other than the foetal bovine serum used in the freezing medium for the Master Cell Bank (MCB). The development of the producer cell line and the construction and control of the MCB and WCB are adequate.

In general, the in process controls are appropriate and adequate, including those designed to prevent or reduce bioburden, mycoplasma and adventitious viruses.

Process Validation

The process validation followed a traditional approach and was performed in two stages on four consecutive DS intermediates lots and on four consecutive lots of DS manufactured from the P3 process at commercial scale. The process, including the clearance of potential process-related impurities, was considered acceptably validated.

Manufacturing process development

The manufacturing process evolved over the course of development through three process changes (designated P1, P2 and P3). The P1 material was used in early toxicology and Phase 1 clinical studies. This process was subsequently scaled up and designated P2, while the later replacement of the viral filter with one with a tighter porosity and further minor refinements led to the validated commercial P3 process.

Extensive bioanalytical testing studies have shown that aflibercept produced from all three processes are comparable and the changed processes are not expected to impact the assessment of pre-clinical or clinical studies performed with different process lots. In early 2011, several minor changes were made to the upstream cell culture process to implement process improvements identified subsequent to the validation of the conformance lots. These minor changes to the validated process did not result in changes to the validated performance in terms of cell growth or protein production and no difference in the quality of the product pre- and –post changes was detected.

Specification

Characterization

Aflibercept was well characterised in terms of mass, extinction coefficient, primary sequence, disulphide bond formation, glycosylation, size variants (truncated forms and aggregates), charge variants, process-related impurities, degradation products (fragmented forms, oxidised species and deamidation products) and secondary and tertiary structure.

The DS is a homodimeric glycosylated protein. The primary structure consists of 432 aminoacids for each polypeptide chain. There is 6 methionines, two of which proned to oxidation, and 6 asparagines proned to deamidation.

The secondary structure is stabilised by 4 intra-chain disulfide bridges in each polypeptide.

The protein chain is glycosylated. The monosaccharide contributing to carbohydrate structures are N-acetyl-glucosamine, fucose, galactose, mannose and sialic acids. The N-linked oligosaccharides consist of mainly bi-antennary structures with zero, one or two terminal sialic acids.

Impurities

Impurities are separated into potential product-related impurities identified in forced degradation studies (molecular variants of aflibercept resulting from various types of degradation) and process-related impurities.

Control of Drug Substance

The analytical procedures used to characterise and control aflibercept quality were appropriately validated.

The proposed specifications are in line with international guidance on the setting of specifications (ICH Q6B - Note for Guidance on "Specifications: test procedures and acceptance criteria for biotechnological products").

Routine testing is performed at release for HCP, DNA, Protein A, bioburden, endotoxins. The purity is tested by SDS-PAGE and Size Exclusion HPLC, while charge heterogeneity is monitored by Isoelectric Focusing. Deamidation is also monitored on a routine basis by enzyme-linked detection of isoaspartate with reversed-phase HPLC.

A cell based assay was designed to evaluate potency.

Reference standards or materials

The reference standards used throughout the process development and manufacturing are traceable and well documented.

Stability

Long-term stability data were provided up to 36 months for batches from the P3 process.

The shelf-life has been re-evaluated following a requested re-evaluation of the release specifications and trending analysis for potency.

All data support a storage of 36 months under the proposed conditions at -80°C and protected from light.

2.2.3. Finished Medicinal Product

The drug product (DP) is presented as a solution for intravitreal injection containing 40 mg/ml Aflibercept, sodium phosphate, sodium chloride, sucrose and PS20 at pH 6.2.

The DP appears in two presentations differing in terms of primary container type: 2 ml type I glass vials and 1ml pre-filled syringes.

All presentations are single dose/partial use presentations. There is an overfill in the vial and syringe presentations compared to the volume required to deliver the appropriate dose i.e. 50 µl. These overfills have been justified in both cases as the minimum volumes required in order to consistently achieve accurate dosing (user testing by trained individuals) and the fill volume does not allow preparing 2 doses. The wording of the SmPC highlights overfills, and that excess solution should be discarded.

Pharmaceutical Development

The commercial formulation was designated IVT-2, while an earlier formulation (ITV-1), was used in Phase 1 and Phase 2 clinical studies. IVT-2 was developed to provide greater thermal stability and resistance to agitation-induced aggregate formation, while maintaining isotonicity.

During clinical development, drug product was supplied primarily in vials. In 2007, a pre-filled syringe has been developed. In 2009, an external sterilization step was added to the proposed pre-filled syringe manufacturing process after secondary packaging to render the external surface of the syringe and the internal surface of the blister as sterile.

Comparability studies have been performed comparing:

- Commercial vials to vials from the clinical development site. Un-sterilised syringes to vials from the clinical development site,
- Un-sterilised syringes to syringes sterilised at the commercial site and syringes sterilised at a development site,
- Syringes sterilised at the development site and at the commercial site

The data provided support the comparability of the products tested.

Manufacture of the product

The manufacturing process of the drug product includes manufacture of formulated bulk intermediate (thawing of DS, pooling, formulation, bioburden reduction filtration, and storage at -30°C up to 36 months), filling of vials or syringes (thawing of formulated bulk, pooling, bioburden reduction filtration, sterile filtration, filling) and sterilisation of blister packs of syringes. Only vials and PFS externally sterilised are intended to be used for commercial supply.

The manufacturing process was well described and appropriately validated.

Product specification

Control of drug product

The analytical procedures used to characterise and control the DP quality were appropriately validated.

The proposed specifications are in line with international guidance on the setting of specifications.

Testing for sterility and endotoxin content is routinely performed at release.

As for the DS, the purity is tested by SDS-PAGE and Size Exclusion HPLC, while charge heterogeneity and deamidation are monitored by Isoelectric Focusing and enzyme-linked detection of isoaspartate with reversed-phase HPLC, respectively.

Potency is determined using a cell-based assay.

Stability of the product

36-month supportive real-time stability data are available for the clinical vials and for PFS that were not subjected to a terminal sterilisation step. Long-term stability data have been updated with 24-month data for prefilled syringes externally sterilised and vials.

In general, the results support the shelf-life of 24 months and storage conditions (2-8°C protected from light) as defined in the SPC, for both the PFS and vial presentations.

Adventitious agents

The overall viral safety of Eylea is considered satisfactory based on the fact that:

- No product of biological origin is used during the production process,

- Cell banks were extensively controlled and no viral particles other than retroviral-like particles normally seen in these cell types were observed,

- The starting materials from animal origin are mainly used indirectly or before the establishment of the cell banks,

- The manufacturing process includes several steps shown to be efficient to clear adventitious viruses (two chromatography steps, low pH treatment and nanofiltration). Global reduction factors reported were satisfactory regarding the virus removal/inactivation for enveloped viruses as well as for non-enveloped viruses.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

No major objections were raised during the assessment of the quality part of the dossier.

The Applicant has responded satisfactorily to all of the other quality concerns and questions identified in the Day 120 List of Questions and in the Day 180 List of Outstanding Issues.

Concerning the specifications for both the DS and DP, the approach to determine acceptance criteria was discussed during the procedure. A re-evaluation together with a review of historical drug substance intermediates and DS batches was performed and most specifications were subsequently tightened by the Applicant. Likewise, the DP specifications were re-evaluated during the course of the procedure and most acceptance limits were tightened.

Osmolality of the solution is monitored as part of the formulated bulk in-process controls. Although below the osmolality in vitreous humor, the lower limit was clinically qualified and the proposed acceptance limits were supported by batch data.

The choice of the ligand in the cell based bioassay was justified by the Applicant during the course of the evaluation.

Regarding the sterilisation of the DP in pre-filled syringes, two external sterilisation methods were initially developed. A single method has been retained for marketing and only vials and PFS externally sterilised by the selected method will be used for commercial supply.

In conclusion, information on development, manufacture and control of the drug substance and drug product has been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

Based on the review of the data on quality, the manufacture and control of the aflibercept drug substance and the Eylea drug product are considered acceptable.

The Quality of the product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in satisfactory way.

Data has been presented to give reassurance on viral/TSE safety.

2.3. Non-clinical aspects

2.3.1. Introduction

VEGF Trap interferes with the biological actions of VEGF-A by tightly binding to it, and preventing VEGF-A from interacting with its receptors. Binding of VEGF-A to its receptors leads to endothelial cell proliferation and neovascularisation, as well as vascular leakage, all of which are thought to contribute to the progression of the neovascular (wet) form of age-related macular degeneration. VEGF Trap can also bind to other VEGFR-1 ligands, notably PlGF.

In order to provide proof of concept and clarify the mode of action, the binding of VEGF Trap and effect of phosphorylation of VEGFR-2 have been characterised in a number of in vitro and in vivo studies. The effects of VEGF Trap have also been evaluated in vascular leak and/or neovascularisation in animal models of ocular vascular disease.

2.3.2. Pharmacology

Primary pharmacodynamic studies

A number of in vitro studies have been performed to examine the binding of VEGF Trap to human VEGF-A165 and to human PIGF-2. As the protein sequence for Cynomolgus monkey VEGF-A is identical to that from humans, the binding affinities can be assumed to also be nearly identical, and this has been supported by additional data provided in the Applicant's responses:

- potential glycosylation sites (Asn and Ser/Thr) in VEGFA are well-conserved among species, are not located in VEGFR-1 and VEGFR-2 binding interfaces, and have no effect on VEGF function but are required for efficient secretion;

- sequence alignment of VEGF-A/PlGF indicates that key residues of VEGF-A/PlGF located in the receptor binding interfaces are strictly conserved among species;

- VEGF-A is conserved across species with a sequence homology of approximately 85% between human and rodent VEGF-A. Thus, given the sequence identity between monkey and human VEGF-A, very similar binding affinity of VEGF Trap to monkey VEGF-A is expected.

- VEGF Trap binds to both human and monkey VEGF, at concentrations relevant to support pharmacological and toxicological assessment of VEGF Trap.

- an efficacy study of VEGF Trap in a laser induced-choroidal neovascularisation (CNV) model in Cynomolgus monkeys further supports the presumption of high affinity of VEGF Trap to monkey VEGF.

VEGF Trap displayed binding affinities with human VEGF-A165 and to human PlGF-2 in the pico-molar range, for human VEGF-A165 the KD was calculated as 0.497 pM. For human PIGF-2 the KD was 38.8 pM. VEGF Trap was also shown to bind to VEGF and PlGF isoforms from non-human species such as the mouse, rat and rabbit with similar affinities, and this supported the use of these species in non-clinical studies during the development of VEGF Trap. There is high binding affinity of VEGF Trap to VEGF-A for human, rat, mouse and rabbit, KD values were very low, in the pM range. Binding to PlGF-2 was also high for human and murine PlGF.

VEGF Trap does not bind other VEGF family ligands, VEGF-C and VEGF-D, which bind primarily to the closely related receptor VEGFR3. Thus it can be concluded that the binding of VEGF Trap is selective, even within the VEGF family of ligands. Binding of VEGF Trap to 'non-target' protein ligands is unlikely. PDGF family is closely related to the VEGF family, although PDGFs and VEGFs have been shown to be selective for their own receptors. The difference is consistent with the low sequence homology and the conformational variability of the ligand: receptor binding interfaces between PDGFs and VEGFs. EGF, HGF and NGF are even more distantly related to VEGF, such that there is no basis in the literature, or theory that would lead one to expect that they might interact with VEGFRs.

In vitro, VEGF Trap was shown to completely block VEGF-mediated phosphorylation of VEGFR-2 on HUVEC, at molar concentrations ≥1:1. VEGF Trap exhibited high affinity binding to VEGFA from human, mouse, rat and rabbit with subpicomolar K_D values.

VEGF Trap has been found to effectively inhibit neovascularisation and/or pathological vascular leak in all animal models of ocular neovascular disease and vascular leak tested to date. VEGF Trap inhibits the development of pathological neovascularisation and/or edema in rodent models of diabetic and ischemic retinopathy, and corneal injury, as well as in rodent and primate models of CNV that resemble the neovascular or 'wet' form of age-macular degeneration (AMD). Of particular relevance, intravitreal (IVT) administration of VEGF Trap has been shown to rapidly resolve existing vascular leak in the retinas of diabetic rodents, and in primates with active, laser-induced CNV. Moreover, VEGF Trap ameliorated the associated ocular inflammation. The anti-inflammatory effect of VEGF Trap is likely attributable to its ability to bind VEGF-A and/or PlGF, which are known to mediate leukocyte chemotaxis via VEGFR-1 expressed on the surface of subpopulations of leukocytes, particularly macrophages and neutrophils. VEGF Trap was found to be effective whether administered directly into the vitreous of the eye, or systemically (e.g. by subcutaneous (SC), intraperitoneal (IP) or intravenous (IV) routes).

VEGF Trap prevented the development of active CNV when given IVT at doses of 50, 250 or 500 µg/eye every other week, as effectively as 3 mg/kg or 10 mg/kg given IV weekly. In mice, VEGF Trap was shown to suppress the growth of most tumour xenografts only at doses ≥2.5 mg/kg (SC, twice weekly), with maximal suppression of tumour growth generally seen at doses ≥10 mg/kg (SC, twice weekly). Similarly, SC doses of VEGF Trap ≥10 mg/kg were required to achieve maximal elevations in blood pressure in telemetered rats. VEGF Trap did not produce detectable elevations in blood pressure at doses < 0.5 mg/kg.

The diabetic retina can cause retinal oedema and ischemia-induced retinal neovascularisation. These effects were demonstrated by using i) a single IVT dose of VEGF Trap (3 µg/eye) which resulted in normalisation of retinal vascular permeability in streptozotocin-treated, diabetic male Sprague Dawley rats; ii) a single IVT dose of VEGF Trap (0.5 or 0.24 µg) prevented the development of pathological retinal neovascularisation in a mouse model of oxygen-induced ischemic retinopathy. VEGF Trap (single dose of 12.5 mg/kg IP) also suppressed CNV and reduced the inflammatory response in mice with induced corneal injury.

Secondary pharmacodynamic studies

VEGF Trap at doses greater than 2.5 mg/kg (given s.c, twice weekly) administered to SCID mice bearing subcutaneously implanted mouse B16F1 melanoma, human A673 rhabdomyosarcoma, or mouse MMT mammary carcinoma, were sufficient to achieve maximally attainable VEGF Trap complex concentrations (1-2 µg/ml). Free VEGF Trap concentrations were ≥10 µg/ml at these doses and this appeared to have a significant impact in inhibiting tumour growth in these animal models.

VEGF Trap elevates blood pressure in both rats and mice in a manner that is dose dependent in both amplitude and duration of effect. This effect is also closely tied to circulating levels of free VEGF Trap. In both species, maximal increases in blood pressure were evident at doses which produced peak circulating levels of free VEGF Trap in the excess of 6 µg/ml, and in both species blood pressure remained elevated above baseline until the concentration of VEGF Trap in the serum fell below approximately 1 µg/ml. The expected level of free VEGF Trap following IVT administration in humans is expected to be 0.0193 µg/ml; this is a 50-fold lower level than that determined from the rodent studies.

Blood pressure data taken after systemic single administration of VEGF-Trap from telemetered rodents were sensitive enough (rats>mice) to show a blood pressure increasing effect of VEGF Trap thereby revealing a good correlation with the well known blood pressure increasing mode of action of a VEGF inhibitor. This was in contrast to the data obtained in toxicity studies with physically or chemically restrained Cynomolgus monkeys in which blood pressure was measured with an indirect method, the conventional oscillometric cuff system. VEGF Trap plasma levels in Cynomolgus

monkeys exceeded those in rodents. The lack of an effect of VEGF Trap on blood pressure is most probably due to the effects of chemical/physical restraint on the cardiovascular system of the Cynomolgus monkeys and the limited sensitivity of indirect blood pressure measurement systems as compared to direct, e.g. radiotelemetry techniques which has been used in rodents.

Safety pharmacology programme

In vitro safety pharmacology studies with VEGF Trap have not been carried out, as they are considered to be irrelevant for high molecular weight proteins such as VEGF Trap. CNS safety pharmacology has been reviewed from the repeat dose systemic toxicity studies in Cynomolgus monkeys dosed subcutaneously and intravenously with VEGF Trap. The studies did not reveal any adverse effect on the CNS in monkeys following administration with VEGF Trap.

In vitro cardiovascular safety studies with VEGF Trap were not conducted. The in vivo examination in monkeys treated with the VEGF Trap in the systemic toxicity studies in Cynomolgus monkeys for up to 26 consecutive weeks showed an absence of ECG abnormalities. Based on the overall in vivo results in monkeys, VEGF Trap is not expected to exert a cardiotoxic effect.

The potential effects of VEGF Trap on venous and arterial thrombus formation were evaluated in New Zealand White rabbits after electrolytic injury. The animals were treated with VEGF Trap at doses of 0.3, 3.0, and 30 mg/kg by 30 minute infusion. There was no significant effect on venous and arterial thrombus formation following VEGF Trap treatment.

In line with ICH S6(R1), respiratory effects have been examined as part of the toxicity studies. Following intravenous infusion of VEGF Trap over 30 minutes at 10, 50 or 250 mg/kg in male Sprague-Dawley rats had no effects on the respiratory function up to 7 days after administration.

The effects of VEGF Trap on wound repair and healing were evaluated in the New Zealand White rabbit incisional and excisional wound healing models. Wound repair and healing in the rabbit incisional model was inhibited after repeat administration with VEGF-Trap at dose levels of 0.3, 3, and 30 mg/kg as demonstrated by a reduction in blood vessel density and tensile strength evaluation. There was reduced fibrous response, neovascularisation and epidermal hyperplasia, resulting in larger wound areas following repeat administration with VEGF-Trap in the excisional wound healing model. In both models, the effects of VEGF Trap resulted in delayed wound repair and healing.

Pharmacodynamic drug interactions

Data from formal pharmacodynamic drug-drug interaction studies of VEGF Trap with ophthalmic anaesthetic agents, antimicrobial agents and mydriatics is not available. Because topical ocular medications do not reach the posterior segment, drug-drug interactions with VEGF Trap within this ocular compartment are highly unlikely. In addition, the clinical experience during the clinical development program for VEGF Trap Eye included prior administration of topical mydriatic agents and concomitant topical administration of anaesthetics and disinfectant antimicrobials with intravitreal injection of VEGF Trap Eye. The administration of these topical medications concomitantly with VEGF Trap was well-tolerated.

2.3.3. Pharmacokinetics

The nonclinical pharmacokinetic (PK) profiles of free VEGF Trap were determined following single dose IV and SC administration to mice, rats, and Cynomolgus monkeys and following single dose IVT administration to rabbits. As part of repeated-dose toxicology studies in monkeys, plasma and vitreous free VEGF Trap and plasma VEGF Trap complex concentrations were determined after IVT

administration to assess drug exposure as well as to develop additional understanding of the in vivo disposition of the free and bound forms of VEGF Trap.

Enzyme-linked immunosorbent assays (ELISA) were developed for determining the concentration of free VEGF Trap in mouse, rat and monkey serum and in rabbit and monkey plasma from pharmacology, pharmacokinetic and toxicology studies conducted in these species. The methods for determining the concentration of free and bound VEGF-trap in rabbit and monkey vitreous humour, choroïd and retinal were not evaluated.

The percentage of recovery and the coefficient of variation were calculated using vitreous humour and various eye tissues as matrix for analyzed quality control samples. From these data, it may be concluded that these assays have been performed with good precision, accuracy, and reproducibility.

Following IV administration to mice, rats and monkeys, VEGF Trap displayed a multicompartmental PK plasma or serum profile, as inferred from the serum or plasma concentration vs. time profiles. Clearance was slow, $t_{1/2}$ and MRT long and the V_{ss} was slightly greater than the volume of the central compartment. VEGF Trap SC bioavailability was good in mice (94%) and monkeys (85%) and moderate in rats (33%). Following IVT administration to monkeys, VEGF Trap systemic absorption appears to be relatively high

Tissue distribution following IV administration of [^{125}I]-VEGF Trap to rats supported the assertion that distribution was limited primarily to the circulation. As expected for a protein-based therapeutic, the highest concentration of tissue radioactivity was localized in the liver, followed by other highly perfused tissues. Following IVT dosing of VEGF Trap, distribution to the systemic circulation is slow and prolonged, resulting in the transfer of a substantial fraction of each IVT dose into the blood.

The applicant has performed a number of studies to examine the distribution of radio-labelled VEGF Trap administered systemically to rats. Other studies investigated the distribution of VEGF Trap after IVT administration to rabbits and monkeys. The bio-distribution of ^{125}I-labeled VEGF Trap after IV administration was investigated in female Sprague-Dawley rats.

However, the PK profile of ^{125}I-labeled VEGF Trap differed from VEGF Trap, and so these findings may not be representative of the actual product. Approximately 75% of the total dose of radioactivity was found in the serum at 5 minutes post-dosing and steadily declined to approaching zero by 168 hours. Radioactivity was highest in the organs of clearance and other highly perfused tissues, predominately in the liver (11.4%), but also the kidney, spleen, lung and heart. The decline seen in serum was also replicated in these organs: at 168 hours post-dosing, only 0.16% of the total radioactive dose was detected in the liver. This indicates rapid clearance and limiting the distribution of the labelled VEGF Trap to the circulation.

The distribution of free VEGF Trap in the choroid, retina, vitreous, and plasma after IVT administration was investigated in male, pigmented New Zealand rabbits. The free VEGF Trap mean $t_{1/2}$ was 115 hours in the vitreous and 157 hours in plasma following IVT administration; free VEGF Trap plasma concentrations were also detected for up to 28 days post dose. Vitreous humour contained the majority of VEGF Trap (compared to retina, choroid and plasma), suggesting accumulation in this compartment. Free VEGF Trap in plasma was only detected 72 hours after dosing, displaying a slow distribution from the vitreous to the plasma in systemic circulation.

The vitreous and plasma concentrations of free VEGF Trap and the plasma concentrations of VEGF Trap complex were determined in 4 separate toxicology studies following single or repeated (either monthly or every 6 weeks) IVT dosing to male and female Cynomolgus monkeys. Peak concentration of free VEGF Trap was approximately 24 hours post-dose, levels of free VEGF Trap peaked at 1 week in the vitreous, and results were dose proportional. Approximately 5.5-16% of

PGR2026-00039
Biocon Ex.1065
Page 343 of 595

applied dose was detectable after 1 week in the vitreous humour. The estimated $t_{1/2}$ of free VEGF Trap in the vitreous ranged from approximately 40 to 68 hours and was independent of the dose applied.

Plasma free VEGF Trap concentrations increased in a greater than dose proportional manner at IVT doses of up to 2000 µg/eye, with concentrations becoming slightly less than dose proportional at a doses higher than this. This shows that at lower doses, the lower levels of plasma free VEGF Trap concentrations are due to VEGF Trap binding to endogenous VEGF.

In plasma, concentrations of the VEGF Trap complex increased with increasing dose. Seven days following dosing the total concentration of bound VEGF Trap ranged from 100% (50 µg/eye) to 26-34% (4000 µg/eye). Clearance of the bound VEGF Trap was slow as it was detected well into the recovery phase unlike the free VEGF Trap.

There were no specific non-clinical studies conducted to examine metabolism of VEGF Trap. The expected metabolism of VEGF Trap is expected to be to small peptides and amino acids and so further classical biotransformation studies are not required.

Regarding the excretion, single 1 mg/kg IV doses were administered to functionally-nephrectomized and sham-operated female rats and serial VEGF. Comparison of the key indices of VEGF Trap exposure (C_{max}, time of maximum serum concentration (T_{max}), AUC, and $t_{1/2}$) revealed no apparent differences between the nephrectomized and sham-operated control animals, suggesting that renal excretion of VEGF Trap is insignificant.

Single 1 mg/kg IV doses were administered to functionally-nephrectomized and sham-operated female rats and serial VEGF. Comparison of the key indices of VEGF Trap exposure (C_{max}, time of maximum serum concentration (T_{max}), AUC, and $t_{1/2}$) revealed no apparent differences between the nephrectomized and sham-operated control animals, suggesting that renal excretion of VEGF Trap is insignificant.

There were no specific non-clinical studies conducted to examine potential pharmacokinetic drug interactions with VEGF Trap following IVT administration. No systemic pharmacokinetic drug interactions are expected following intravitreal administration with VEGF Trap since only very low concentrations of free and bound VEGF Trap will reach the systemic circulation.

2.3.4. Toxicology

Single dose toxicity

Single-dose toxicity of VEGF Trap following IVT administration was evaluated in Cynomolgus monkeys. The evaluation did not reveal any signs of an adverse response. Single dose toxicity studies were performed by IV administration (at doses of 50, 150 and 500 mg/kg) to rats. Transient skin lesions and discoloration of the tail (administration site) were observed at a dose of 150 mg/kg. A moderate decrease in body weight gain was noted in both male and female rats at both dose levels, and was associated with a moderate decrease in food consumption in male rats at a dose of 500 mg/kg. The Minimum Lethal Dose and the Maximum Tolerated Dose were >500 mg/kg.

Repeat dose toxicity

The sub-chronic and chronic toxicity of VEGF Trap was evaluated in the most relevant species, the Cynomolgus monkey, using the clinically relevant IVT route of administration. Further systemic toxicity studies with VEGF Trap were undertaken in mice (SCID and CD-1), rats (Sprague Dawley and nude) and Cynomolgus monkeys by IV and SC routes.

IVT: A number of studies were carried out to examine the subchronic toxicity of VEGF Trap following IVT administration was evaluated in monkeys (dosing up to 13 weeks) and the chronic toxicity of the test article was evaluated in monkeys treated up to 8 months by the IVT route. Following IVT administration with VEGF Trap there was a level of inflammatory response characterised as inflammatory cells in the anterior chamber that occurred. This effect was seen predominately in VEGF Trap treated eyes and was not dose-related or treatment duration-related. The inflammatory response peaked at 2 days, and in all instances reversed within 3 weeks post-dosing. There were no angiographic or electroretinographic changes following IVT treatment, however increased ocular pressure was seen in either VEGF Trap or VEGF Trap Placebo treated animals. This effect is due to the increase in vitreal volume following intravitreal injection (volume of 50 µl/eye). Administration of a lower volume (25 µl) of the VEGF Trap test article usually resulted in a much smaller immediate post-dose increase in IOP. This effect was also reversible. In the pivotal 8-month repeat dose toxicity study in monkeys, at a dose of 2000 µg/eye there was increased incidence of epithelial erosion/ulceration of the respiratory epithelium of the nasal turbinates, often accompanied by chronic-active inflammation of the nasal turbinates. This effect is likely a result of local exposure of the nasal epithelium to the nasal cavity by way of anastomoses between the ophthalmic and nasal venous plexuses, or leakage from the IVT injection site into the nasal lacrimal duct. A NOAEL of 500 µg/eye was established based on the findings of epithelial erosion/ulceration of the nasal turbinates noted at the 2 and 4 mg/eye levels. Although the findings of anterior segment cells were present at all dose levels, this effect may be considered as mild and reversible so a tentative NOAEL is proposed. A LOAEL of 2 mg/eye is acceptable, and using this exposure ratios based upon the established LOAEL, Cmax and AUC determined from this toxicity study, was compared to the clinical exposure of VEGF Trap following IVT administration of 2 mg/eye. Exposure multiples were 231-fold higher (based on AUC and LOAEL values) and 708-fold higher (based on Cmax and LOAEL values).

The issue of only reaching 6-times the clinical exposure levels in the monkey intravitreal studies had been discussed in a CHMP advice to the Applicant. Limitations due to the formulation of the product, increasing volume or frequency of administration to the monkey eye were discussed in order to justify this lower safety margin.

No significant pharmacodynamic differences are expected between monkeys and humans because the VEGF molecules are identical in humans and monkeys. The high degree of conservation between species could also be demonstrated by the similar affinity (KD) of VEGF and PlGF from mice and humans. PlGF1 and PlGF2 molecules in monkeys and humans only differ by 2 amino acids that are located outside of the known sites relevant for receptor binding and therefore this difference should not affect binding to VEGF Trap to an appreciable degree.

Systemic: A comprehensive range of systemic toxicity studies were performed in mice, rats and monkeys. Due to the high immunogenicity in the rodent species, the Cynomolgus monkey was the preferred species. Exposure to free VEGF Trap was much higher in these studies compared to IVT administration, and allowed to determine systemic toxicities. Common effects in target organs included bone (interference with growth plate maturation of long bones and osteocartilaginous exostoses of vertebrae), kidney (frequently increased glomerular mesangial matrix, occasionally hyperplasia of parietal epithelium and periglomerular fibrosis), adrenals (decreased vacuolation with eosinophilia in the zona fasciculata), ovary (decreased number of maturing follicles, granulosa cells and/or theca cells), and nasal cavity (respiratory and olfactory epithelium of nasal turbinates). Further microscopic findings were seen in the 6 month monkey study, included vascular alterations in the choroid plexus (≥3 mg/kg) and digestive tract (≥10 mg/kg), vascular degeneration and fibrosis in several tissues (≥10 mg/kg) including the heart, and hepatic portal inflammation and periportal necrosis (30 mg/kg). No NOAEL could be determined in the systemic toxicity studies due to effects seen in each tested dose of VEGF Trap. Exposure ratios based upon the established LOAEL, Cmax and AUC determined from each toxicity study was compared to the clinical exposure

of VEGF Trap following IVT administration of 2 mg/eye. Exposure multiples ranged from 134- to 1546-fold (based on AUC and LOAEL values) and 503- to 4902-fold (based on Cmax and LOAEL values). It is also considered that following IVT VEGF Trap administration, levels of free VEGF Trap are unlikely to be seen at levels to cause systemic toxicity.

Genotoxicity

Due to the fact that this is a biotechnology-derived product, the range and type of genotoxicity studies routinely conducted for pharmaceuticals are generally not applicable, as it is unlikely that the administration of large levels of proteins would yield any meaningful results. It is agreed that VEGF Trap is unlikely to interact with DNA or chromosomal material.

Carcinogenicity

Standard carcinogenicity bioassays are generally inappropriate for biotechnology-derived pharmaceuticals, and this is the case for VEGF Trap. This is in line with previous CHMP scientific advice obtained by the applicant (EMEA/CHMP/SAWP/310870/2007) and the requirements of ICH S6 (R1) guideline for preclinical safety evaluation of biotechnology-derived pharmaceuticals. Product specific assessment of carcinogenic potential may be required for products that act as growth factors or as an immunosuppressive. Studies conducted with VEGF Trap do not indicate that it acts in this way, and due to the high immunogenic potential of VEGF Trap to rodents, classical rodent carcinogenicity studies would be of little relevance. It is acceptable to not perform genotoxicity or carcinogenicity studies.

Reproduction Toxicity The effects of VEGF Trap on fertility were investigated in the context of the 6-month toxicity study in sexually mature Cynomolgus monkeys by IV administration. Results showed decreased sperm motility and increased spermatozoa morphological abnormalities in males and abrogation of ovarian function and follicular development in females during treatment with VEGF Trap, along with abrogation of normal menstruation. These findings were reversible after cessation of treatment. Decreases in ovary weights were noted. Moreover, some females given 30 mg/kg/dose had an evident reduction of maturing follicles compared to controls. Uterine endometrial and myometrial atrophy and vaginal epithelial atrophy also were common findings in VEGF Trap-treated animals. Following recovery, all VEGF Trap-treated females presented normal ovarian folliculogenesis and presence of medium to large size corpora lutea.

There were no test-article related effects on male reproductive hormone levels (FSH, LH, and testosterone) at any dose or time. Weights for the testis, epididymis, prostate and seminal vesicles were not different between treated and control groups, and no histopathological changes were evident in the male sex organs. There were profound effects on sperm motility and quality. In all doses of VEGF Trap there were decreased levels of sperm motility and increased number of abnormalities to sperm. Although these changes are reversible following up to 13 weeks recovery, a clear effect on reduced male fertility is apparent.

As no NOAEL for effects on ovary/ovarian hormones and to sperm could be determined from this study, the applicant has calculated potential exposure ratios based upon the toxicokinetic findings from this study and in comparison to Cmax and AUC determined from humans treated with 2 mg/eye (Study No. VGFT-OD-0702-PK). Exposure was 4902-fold (Cmax) and 1546-fold (AUC0-168h) higher in the monkey study after 3 mg/kg dosing, compared to the anticipated human dose.

The main embryo-foetal development study (Study No. VGFT-TX-06002, GLP) was conducted by administering doses of 0, 3, 15, or 60 mg/kg/administration of VEGF Trap to mated female New Zealand white rabbits once daily 30-minute i.v. infusions on gestational days (GD) 6, 9, 12, 15, and 18. Justification of the dose levels used has been provided by the results of the two range-finding studies in rabbits (VGFT-TX-05007 & VGFT-TX-06001). The doses were selected to

determine levels of maternal toxicity, to establish a dose-response relationship and to establish a NOAEL.

At doses of ≥3 mg/kg there were dose-related increases in fetal resorptions, pregnancy disruptions and numerous foetal (external, visceral and skeletal) malformations observed. Animals treated at the high dose level (60 mg/kg) resulted in abortions and increased levels of skeletal malformations in F1 generation.

A maternal NOAEL is considered to be 3 mg/kg, whereas the developmental NOAEL could not be identified. A calculation of potential exposure ratios based upon the toxicokinetic findings from this study and in comparison to Cmax and AUC determined from humans treated with 2 mg/eye (Study No. VGFT-OD-0702-PK). Exposure was 2907-fold (Cmax) and 678-fold (AUC0.5-72h) higher in the monkey study after 3 mg/kg dosing, compared to the anticipated human dose.

Recommendation that VEGF Trap should not be used during pregnancy is appropriate from the findings of increased disruption to pregnancy and foetal malformations; this has been included in the SmPC in section 4.6. Additional warning to women of child bearing potential to use effective contraception during treatment is appropriate.

For the indication of aged-related macular degeneration (AMD) and target population, pre- and post-natal development studies are not required.

Juvenile Toxicity
VEGF Trap was administered IV at doses of 0, 0.5, 3, or 30 mg/kg/administration once weekly for 3 months in young, skeletally immature Cynomolgus monkeys, with reversibility of systemic findings evaluated after an additional 5 month recovery phase. Effects were seen in bone, kidney, ovaries, adrenal glands and systemic vascular proliferation. A NOAEL was not determined. Based on C_{max} and $AUC_{0\text{-}168h}$ for free VEGF Trap observed at the 0.5 mg/kg IV dose, the lowest dose at which finding were observed, the exposure was 503-fold and 134-fold higher, respectively, than the systemic exposure observed in humans after an IVT dose of 2 mg/eye.

Toxicokinetic data

Local Tolerance

The local tolerance of the intended clinical formulation IVT was studied in the context of the pivotal 8-month study in monkeys after IVT administration. This formulation was well tolerated in the animals, and inflammation was mild and transient. The local tolerance of other formulations was studied in New Zealand White rabbits by other routes of administration at 24.4, 25 and 100 mg/mL (intravenous, intramuscular and subcutaneous routes). The findings resulted in decrease or absence of food intake associated with a minimal body weight loss or reduced body weight gain in animals receiving the 100 mg/mL solution by all of the routes of administration studied.

Other toxicity studies

The VEGF Trap formulation did not induce haemolysis and did not cause the formation of flocculants or precipitates in either serum or plasma. VEGF Trap was evaluated for possible binding to a panel of 33 human tissues. No specific staining was observed with any of the representative human tissues at concentrations of 5 or 25 µg/ml.

Immunogenicity
In preclinical IVT studies, very few animals were positive in the anti-drug antibody (ADA) assay and only 1 animal generated a response that appeared to impact PK. Animals with ADA responses that did not affect plasma drug levels did not exhibit these ocular findings. It is noted that immunogenicity in monkeys is not predictive of immunogenicity in humans, although the very low immunogenicity observed in monkeys was also observed in humans. Following extended intravitreal administration of VEGF Trap in clinical trials, positivity rates in the ADA assay were similar in patients regardless of treatment (VEGF Trap or ranibizumab). It is therefore agreed that, based on the available data, there is no indication that IVT administration of VEGF Trap in patients would elicit a serious immune response.

In some pregnant female rabbits, a total of five IV administrations resulted in the presence of anti-VEGF Trap antibodies associated with decreased levels of free VEGF Trap concentrations. In no case was toxicity in rabbits or monkeys associated with the presence of an anti-VEGF Trap antibody response.

No studies were conducted for dependence or with metabolites.

2.3.5. Ecotoxicity/environmental risk assessment

Aflibercept is exempted from an environmental risk assessment, because it is a protein and therefore unlikely to result in a significant environmental risk.

2.3.6. Discussion on non-clinical aspects

The nonclinical studies were designed to evaluate the pharmacology, pharmacokinetics, and toxicology of VEGF Trap in support of clinical intravitreal (IVT) treatment of VEGF Trap. Studies were conducted in vitro (PD) and in mice, rats, rabbit and monkeys, and their scope is considered to be extensive and adequate.

In order to provide proof of concept and mode of action, the binding of VEGF Trap and effect of phosphorylation of VEGFR-2 have been characterised in *in vitro* and *in vivo* studies.

The assumption that identical or near identical protein sequences are predictive of very similar, if not identical, binding affinities of monkey and human VEGF-A/PlGF has been supported by additional data provided by the Applicant in their responses to the CHMP questions.

The pharmacology studies were acceptable, and the Applicant has shown that the binding of VEGF Trap is selective, even within the VEGF family of ligands. It is agreed that binding of VEGF Trap to 'non-target' protein ligands is unlikely.

Regarding the safety pharmacology, VEGF Trap had no effect on respiratory function or thrombus formation, and no effects on the central nervous system were detected in toxicological studies, even when VEGF Trap was administered at high doses systemically for several months. Concerning the cardiovascular system, the effect of VEGF Trap on blood pressure was assessed after single subcutaneous injections of 2, 5 and 25 mg/kg in telemetered C57BL/6 mice (VGFT-MX-08018) and from 0.05 to 25 mg/kg in telemetered Wistar-Kyoto rats (VGFD-MX-08015). Administration of VEGF Trap resulted in a statistically significant increase in both systolic and diastolic blood pressure dose dependent and lasting several days. In the opposite, single or repeated subcutaneous or intravenous injection of VEGF Trap in Cynomolgus monkey do not change blood pressure levels. It was concluded that the lack of an effect of VEGF Trap on blood pressure is most probably due to the effects of chemical/physical restraint on the cardiovascular system of the Cynomolgus monkeys and the limited sensitivity of indirect blood pressure measurement systems as compared to direct, e.g. radiotelemetry techniques which have been used in rodents.

Data from formal pharmacodynamic drug-drug interaction studies of VEGF Trap with ophthalmic anaesthetic agents, antimicrobial agents and mydriatics is not available. This was considered acceptable, as topical ocular medications do not reach the posterior segment and drug-drug interactions with VEGF Trap within this ocular compartment are therefore unlikely. In addition, the clinical experience included prior administration of topical mydriatic agents and concomitant topical administration of anaesthetics and disinfectant antimicrobials with intravitreal injection of VEGF Trap Eye, which were well-tolerated.

Concerning the pharmacokinetic aspects, SC bioavailability was good in mice (94%) and monkeys (85%) and moderate in rats (33%). Following IVT administration to monkeys, VEGF Trap systemic absorption appears to be relatively high. Tissue distribution following IV administration of [^{125}I]-VEGF Trap to rats supported the assertion that distribution was limited primarily to the circulation. The highest concentration of tissue radioactivity was localized in the liver, followed by other highly perfused tissues. No studies were conducted on metabolism. Renal excretion of VEGF Trap is insignificant.

Regarding the toxicological aspects, the only treatment related post mortem findings observed in the chronic study by intravitreal administration to monkeys were epithelial erosions and/or ulcerations with chronic active inflammation of the nasal turbinates. The SmPC section 4.6 incorporates a warning about women of childbearing potential, following the findings in the rabbit reproductive studies.

The fact that it was possible to reach only 6-times the clinical exposure levels in the monkey intravitreal studies was discussed in CHMP scientific advice and considered acceptable due to the limitations in the formulation of the product, increasing volume or frequency of administration.

No significant pharmacodynamic differences are expected between monkeys and humans because the VEGF molecules are identical in humans and monkeys.

Regarding the antibody formation to VEGF Trap, in preclinical IVT studies, very few animals were positive in the ADA assay and only 1 animal generated a response that appeared to impact PK. Animals with ADA responses that did not affect plasma drug levels did not exhibit these ocular findings. It is noted that immunogenicity in monkeys is not predictive of immunogenicity in humans, although the very low immunogenicity observed in monkeys was also observed in humans. Following extended intravitreal administration of VEGF Trap in clinical trials, positivity rates in the ADA assay were similar in patients regardless of treatment (VEGF Trap or ranibizumab). The CHMP concluded that, based on the available data, there is no indication that IVT administration of VEGF Trap in patients would elicit a serious immune response.

2.3.7. Conclusion on the non-clinical aspects

In conclusion, VEGF Trap had no effect on respiratory function or thrombus formation, and no effects on the central nervous system or cardiac function were detected in toxicological studies, even when VEGF Trap was administered at high doses systemically for several months. However, repeated systemic administration of VEGF Trap did impair the rate and/or extent of healing of both incisional and excisional wounds in rabbits, in a dose related manner, at all doses tested (0.3, 3 and 30 mg/kg/administration). Impairment of wound healing is also a class effect of VEGF inhibitors.

A pregnancy warning is included in Section 4.6 of the SmPC.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

A GCP inspection was carried out at two investigator sites, one in Germany (14-17 November 2011) and in Hungary (28 November-2 December 2011), in relation to the conduct of trial protocol n. 311523. The final integrated inspection report was issued on 6 February 2012. According to the GCP final integrated inspection report, the outcome of this inspection is satisfactory. The inspected investigator sites appeared to be GCP compliant and it was nothing identified to suggest that the data collected at the sites are unreliable.

The Inspection report do not suggest that the deficiencies/findings observed during the course of inspections may impact on the results of the study and according to the recommendation for use of the inspected data, the inspected data of clinical trial 311 523 (VIEW 2) are of an acceptable quality to be used for the evaluation by the assessors in connection with the marketing authorisation application for Eylea.

- Tabular overview of clinical studies

Summary of clinical studies in age-related macular degeneration (AMD)

PGR2026-00039
Biocon Ex.1065
Page 350 of 595

Phase	Study	Description	Route/Dose	Frequency	Subjects/Status
I	PDY6656	Phase I, single centre study to assess cardiovascular PD and PK	**IV**; 1, 2, 4 mg/kg, placebo	Single dose	48 healthy volunteers **Completed**
	PDY6655	Phase I, single-centre study to compare cardiovascular PD and PK	**IV & SC**; 2 mg/kg	Single dose	40 healthy volunteers **Completed**
	VGFT-OD-0305	Phase I, exploratory study of the safety, tolerability and biological activity	**IV**; 0.3, 1, 3, 5, 7, 10 mg/kg, placebo	Repeat dose (4 doses q2w)	26 AMD patients **Completed**
	VGFT-OD-0306	Phase I, safety and tolerability study (open label extension of VGFT-OD-0305)	**IV**; 0.3, 1, 3 mg/kg, placebo	Repeat dose (q2w)	7 AMD patients **Completed**
	VGFT-OD-0502 Part A, B, C (CLEAR-IT 1)	Phase I, exploratory study of the safety tolerability and biological effect	**IVT**; 0.05, 0.15, 0.50, 1, 2, 4 mg	Single and repeat dose (in Part C two doses q8w, with optional monthly dosing for 1 year extension period)	49 AMD patients **Completed**
	VGFT-OD-0603 (CLEAR-IT 1b)	Phase I study to assess the safety and tolerability of VEGF Trap in the ITV-1 and ITV-2 formulations	**IVT**; 4 mg	Repeat dose (3 doses q4w)	20 AMD patients **Completed**
II	VGFT-OD-0508 (CLEAR-IT 2)	Phase II study of the safety, tolerability and biological effect	**IVT**; 0.5, 2, 4 mg	Repeat dose (0.5/2 mg q4w, 0.5/2/4 mg q12w, prn dosing from Week 12 to Week 52)	157 AMD patients **Completed**
	VGFT-OD-0702	Phase I/II long-term safety extension study, with PK sub-study. Open to patients previously enrolled in VGFT-OD-0502, -508, and -0603.	**IVT**; 2 mg	Repeat dose (q8w for 39 months)	120 AMD patients **Completed**
III	VGFT-OD-0605 (VIEW 1)	Phase III, active controlled study of efficacy, safety, and tolerability	**IVT**; 0.5, 2 mg	Repeat dose (Year 1: 0.5/2 mg q4w or 2 mg q8w; Year 2 q4w-q12w)	1038 AMD patients **Completed**
	311523 (VIEW 2)	Phase III, active controlled study of efficacy, safety, and tolerability	**IVT**; 0.5, 2 mg	Repeat dose (Year 1: 0.5/2 mg q4w or 2 mg q8w; Year 2 q4w-q12w)	1025 AMD patients **Completed**
	VGFT-OD-0910	Phase III open label, long-term, safety extension of VIEW 1	**IVT**; 2 mg	Repeat dose 2 mg capped PRN (at least q12w)	323 AMD patients (target 960) **Ongoing**

In addition, one PK study and three efficacy and safety phase III studies using IVT route were not related to the claimed indication (DME : VGFT-OD-0307 and VGFT-OD-0706-DAVINCI / CRVO : VGFT-OD-0319-COPERNICUS and 14130-GALILEO)

2.4.2. Pharmacokinetics

Absorption, Distribution, Elimination

PKs of VEGF Trap could be considered well characterized based on the investigations performed by systemic (mainly IV but also SC) route as well as by IVT (intra-vitreal) routes. These investigations consisted in six Phase I, two Phase II and one Phase III studies. Studies by systemic route were performed in healthy volunteers and patients. Studies by IVT route were conducted in patients.

Analytical techniques. The analytical techniques used through the PK development programme were described and validated. The earlier colorimetric versions of the ELISA techniques used for the determination of free and bound VEGF Trap levels from clinical studies involving systemic

administration of VEGF Trap were modified to luminescence based ELISAs which were used to analyze systemic levels of free and bound VEGF Trap in AMD clinical studies involving IVT administration of VEGF Trap. The analytical techniques used in the IV and IVT were not formally cross-validated. Therefore, the inter-study comparisons should be regarded cautiously. Adequate methods were used for pharmacokinetic and statistical data analysis.

Analysis of different formulations and processes. During the development of VEGF Trap, to improve stability, the drug substance was manufactured using three different processes (IVT P1, P2 and P3) and two formulations of the drug product for IVT administration of VEGF Trap were developed. Subsequently, the different formulations were evaluated with respect to pharmacokinetics (PK), pharmacodynamics (PD) and immunogenicity, in order to demonstrate comparability between the various process and IVT formulations. Considering that VEGF Trap is intended for local administration, the contribution of the systemic exposure in the assessment of the comparability of the different process (active substance) and formulations (drug product) is limited. Reassuringly, the final formulation and process were used for the preparation of the lots tested in the pivotal phase III studies (VIEW1 and VIEW2). As a consequence, the comparability of early process (active substance) and formulations (drug product) was not of concern. The pharmacodynamic and clinical investigations (see relevant parts) revealed no difference between products issued from different process and formulations.

Systemic route. The investigation by systemic route confirmed that VEGF Trap PK behaviour is consistent with that generally observed with large proteins. The VEGF Trap Vd following IV administration is close to plasma volume. At plasma level, VEGF-trap binds to endogenous free VEGF with high affinity to form an inert complex. Due to the saturation of this binding to endogenous VEGF, Free VEGF-trap exhibits a non-linear PK. Data suggests that free VEGF Trap is cleared by relatively rapid, specific and saturable high-affinity binding to VEGF as well as via slower, non-saturable clearance mechanisms. These latter mechanisms are expected to be proteolytic catabolism processes, which affect both free and bound VEGF Trap. The terminal elimination half-life ($t_{1/2}$) of free VEGF Trap was approximately 1.9 days following an IV dose of 0.3 mg/kg, and increased with increasing doses, reaching $t_{1/2}$ estimates of 5 to 6 days after IV administration of doses of 2 to 4 mg/kg VEGF Trap. The systemic exposure to the free VEGF-Trap observed at the clinical MTD i.e. 1mg administered by the IV route is approximately 10 to 20 (µg/mL) for Cmax and 50-80 (day*µg/mL). The systemic exposure observed with the first toxic dose i.e. 2 mg by IV route is 45 ± 36 (µg/mL) for Cmax and 180 ±33 (day*µg/mL) approximately.

Intravitreal route. Since VEGF Trap is administered directly into the target site of pharmacological activity, the eye, the bioavailability within the target organ is assumed to be 100%. Following IVT administration of VEGF Trap, a fraction of the administered dose is expected to bind to free endogenous VEGF in the eye to form a stable, high affinity VEGF:VEGF-Trap complex. Excess free VEGF Trap is available to bind newly synthesized VEGF in the eye or endogenously available VEGF in the central compartment. VEGF Trap is slowly absorbed from the eye into the systemic circulation after IVT administration and is predominantly observed in the systemic circulation as an inactive, stable complex with VEGF. In most patients plasma levels of free VEGF-Trap were below the LLOQ. Some measurable plasma levels (up to 0.473 µg/mL) were actually observed in patients. Based on Cmax comparison the highest level observed in the clinical Phase III study VIEW2 is 200-250 times lower than that observed with the MTD (1 mg, IV route) and approximately 100 times lower than that observed with the first toxic dose (2 mg by IV route). Therefore, the level of this exposure is deemed to be too low to lead to significant systemic (non-ocular) side effects. However this needs to be confirmed by safety clinical data.

Dose proportionality and time dependencies

Data obtained with the IV route showed that Free VEGF Trap exhibits non-linear PK consistent with saturable, target-mediated drug disposition. However, this is not relevant for the IVT route.

Data from phase III study (VIEW 2) revealed no unexpected accumulation at plasma level of VEGF Trap after repeated IVT administration (up to 1 year).

Special populations

Age, sex, body mass index (BMI), renal function, hepatic function and ethnicity are not expected to influence the plasma concentrations of free and bound VEGF Trap.

Pharmacokinetic interaction studies

Considering the administration pathway (IVT) and the very low systemic level of VEGF trap, neither *in vitro* nor *in vivo* interactions studies have been performed.

Since the systemic exposure to both free and bound VEGF Trap following intravitreal injection is low, the potential for drug interactions is low. In addition, systemic or topically applied drugs usually reach the vitreous cavity in very low concentrations, so interactions within the eye are also unlikely. However, some clinicians may manage AMD with concomitant therapies, such as verteporfin with PDT or use off label intraocular steroids. The potential for such treatments to influence the intraocular effect of VEGF Trap has not been appropriately addressed in the documentation provided, therefore clarifying statements have been inserted in the section 4.5 of the SmPC.

Pharmacokinetics using human biomaterials

None.

2.4.3. Pharmacodynamics

No specific studies dedicated to human pharmacodynamics have been performed for aflibercept. The pharmacodynamics data derive from in vitro, animal and human efficacy studies.

VEGF Trap (aflibercept) exerts inhibitory effects on angiogenesis and stabilizing actions on vessel permeability through the blocking of VEGF-A.

IVT injection permits direct targeting of the areas of abnormal neovascularization in the retina, and this route of administration is considered as the more relevant for retinal pathologies. In addition, the IVT route of administration also permits to decrease systemic toxicity linked to anti-VEGF activity.

Mechanism of action

Aflibercept belongs to the pharmacological class of VEGF inhibitors. The role of VEGF in promoting pathological neovascularization and/or abnormal and excessive vascular permeability in several diseases affecting the eye is now well established.

Primary and Secondary pharmacology

Primary pharmacology:
The clinical pharmacology programme consists of phase I and II studies that were designed to explore, in patients suffering from wet AMD, the bioeffects of VEGF Trap on the retina. Central

retinal/lesion thickness and CNV lesion size were assessed using Optical coherence tomography (OCT), and fluorescein angiography (FA) as pharmacodynamic endpoints, concomitantly with evolution of visual acuity (according to the ETDRS Chart). Retinal thickness is an accepted PD marker for neovascular AMD, but it is known to have a variable correlation with visual acuity.

IV injections were firstly explored in studies VGTF OD 305-306-307; a favourable trend of improvements in central retinal thickness and visual acuity at the VEGF Trap dose levels of 1.0 and 3.0 mg/kg was identified in Study VGTF OD 305.

Single and repeated IVT injections of escalating doses of VEGF Trap (0.05 to 4 mg) were further explored in VGTF OD 502, VGTF OD 508 and VGFT-OD-0603 studies, and were shown to reduce both retinal thickness and the size of the CNV lesion, in a dose-proportional fashion.

In these studies central retinal thickness was not always well correlated with visual acuity. An important lack of correlation was specifically observed in study VGTF OD 508 at the end of the fixed dosing phase and at Week 16 for the 4 mg dose administered every 12 weeks. This is thought to be probably related to the high variability observed in the results for prolonged interval duration beyond 8-week.

Bioeffects were also explored as secondary or additional outcome measures using FA and OCT measurements, in pivotal studies VIEW 1 and VIEW 2. After treatment initiation, retinal thickness decreased > 100 microns and reduced mean CNV lesion size were observed, consistent with the results seen in phase I and II studies.

Secondary pharmacology:

Systemic VEGF inhibition is known to cause dose-related increases in systolic and diastolic blood pressure. Although this was observed in subjects following IV and SC dosing with VEGF Trap at all dose levels between 0.3 and 3 mg/kg, no such changes were detected when VEGF Trap was administered intravitreally. This is likely to be due to the low amounts of free VEGF Trap reaching the systemic circulation (approximately 50 ng/mL). The Michaelis-Menten constant (K_m – the concentration of free VEGF Trap corresponding to the half-maximal binding capacity) value was calculated to be 2.91 µg/mL for free VEGF Trap binding to human VEGF.

The Applicant considered that the increase risk of blood pressure in the target population is unlikely. However, 15-20% of aflibercept passes to the systemic circulation and during the pivotal studies, hypertension have been reported in 14.6% patients. The CHMP considered that systemic side effect on blood pressure should not be ruled out and need to be further monitored even if the product is locally administered. This is identified as an important potential risk in the RMP.

2.4.4. Discussion on clinical pharmacology

Intravitreal VEGF Trap has been shown to reduce both retinal thickness and CNV lesion size in patients with neovascular AMD in a dose-proportional fashion. Furthermore, the data suggest that dosing every 12 weeks may be insufficient to maintain these improvements, and that more frequent dosing may be required. Visual acuity results from the Phase II studies were more variable, and as a whole the data suggest no additional benefit of the 4 mg dose over a 2 mg dose. There is minimal systemic exposure to VEGF Trap following intravitreal administration, making systemic pharmacodynamic effects or interactions unlikely.

2.4.5. Conclusions on clinical pharmacology

The CHMP considers the following measures necessary to address the issues related to pharmacology:

The CHMP considered that, systemic side effect on blood pressure should not be ruled out and need to be further monitored even if the product is locally administered. This measure is included in the RMP.

2.5. Clinical efficacy

2.5.1. Dose response study(ies)

Dose-response studies in patients suffering from neovascular age-related macular degeneration:

In the early development programme, IV injections of VEGF Trap (0.3, 1 and 3 mg/kg) were compared to placebo in Study VGTF OD 305 over an 8-week duration. These preliminary results suggested that the highest dose of 3.0 mg/kg provided the best improvements in visual acuity, retinal thickness and macular volume.

A direct head-to-head comparison of the two formulations of VEGF Trap (ITV-1, the first formulation and ITV-2, the new formulation used in pivotal clinical studies VIEW 1 and VIEW 2) at the same dose was provided in Study VGFT-OD-0603. The results suggested that the ITV-2 formulation (used in pivotal studies VIEW 1 and 2) would at least provide a similar effect level regarding reduction in retinal thickness or improvements in visual acuity than that observed for the VEGF Trap administered in the ITV-1 formulation (used for dose escalating studies VGFT-OD-502 and 508).

IVT route: Study VGFT-OD-0502 was the first study initiated for a clinical development of intravitreally (IVT) administered VEGF Trap in patients suffering from wet AMD. This was an open label, single escalating doses study (0.05 mg, 0.15 mg, 0.5 mg, 1.0 mg, 2.0 mg and 4.0 mg). The small sample size/group only allowed preliminary conclusions suggesting that better effects on visual acuity or on morphologic endpoints may be provided by higher doses (2, 4 mg) and that they may last until week 43.

IVT route: Study VGFT-OD-0508 was a Phase-2 dose-ranging study which comprised a 12-week fixed-dosing phase followed by a flexible-dosing phase up to week 52, designed to assess the efficacy in AMD patients of repeated IVT administration of VEGF Trap at different doses and dosing intervals.

In this study subjects who received monthly injections at the start of the study (in the 0.5 and 2 mg groups) generally had better outcomes at Week 52, supporting the proposal to administer 3 initial monthly injections of VEGF Trap prior to dosing every 8 weeks. An initial monthly dosing up to 12 weeks was therefore chosen for the design of pivotal VIEW 1 and VIEW 2 studies.

2.5.2. Main study(ies)

Studies VIEW 1 and VIEW 2: in patients suffering from neovascular age-related macular degeneration:

This application is supported by two pivotal trials of two-year duration and of identical design.

- Study VIEW 1 (Study VEGF-OD-605) was conducted from 02 August 2007 to 14 September 2010 (year 1 cut-off) at 154 sites in United States [US] and Canada.

- Study VIEW 2 (Study A36355) was conducted at 186 sites in Asia/Pacific, Europe, and South/Latin America (first patient 11 April 2008 – 16 September 2010 (year 1 cut-off).

The Study period covered from start of enrolment and last subject's last visit was from 31 Jul 2007 to 22 Jul 2011 (VIEW 1) and to 11 Aug 2011 (VIEW 2).

Both studies were multi-center, randomized, double-masked, active controlled (ranibizumab) non-inferiority designed, phase III studies.

The design of both studies is described below.

Methods

Study Participants

The inclusion/exclusion criteria were identical in the two Phase III studies.

Subjects eligible were Men and women ≥ 50 years of age had to have subfoveal CNV secondary to AMD. "Subfoveal" CNV was defined as the presence of subfoveal neovascularization, including juxtafoveal lesions that affect the fovea, documented through confirmed FA by an independent reading

center. Only one eye was designated as the study eye. For subjects who met eligibility criteria in both eyes, the eye with the worse visual acuity (VA) was selected as the study eye.

The Main exclusion Criteria included prior ocular or systemic treatment or surgery for neovascular AMD; total lesion size >12 disc areas (30.5 mm2, including blood, scars and neovascularization); any history of ocular retinal disease history other than AMD, Any intraocular or periocular surgery within 3 months of Day 1 on the study eye, prior trabeculectomy; Previous therapeutic radiation in the region of the study eye; history of corneal transplant or corneal dystrophy in the study eye; significant media opacities, including cataract; history or clinical evidence of diabetic retinopathy, diabetic macular edema or any retinal vascular disease other than AMD in either eye. Exclusions criteria were conventional and as expected for this class of product. Contra-indications for Lucentis as reported in the EU SPC were listed as exclusion criteria.

Treatments

Year-1: Fixed dose/fixed schedule regimens for the first year of the studies were chosen fairly in accordance to the results from phase I and II dose-finding studies. Subjects were randomised to one of the following regimen: 0.5Q4=0.5 mg VEGF Trap-Eye every 4 weeks; 2Q4=2 mg VEGF Trap-Eye every 4 weeks; 2Q8=2 mg VEGF Trap-Eye every 8 weeks after three initial monthly doses and compared to RQ4=ranibizumab 0.5 mg every 4 weeks. This posology corresponds to the original dosing regimen used in the pivotal studies Marina and Anchor for ranibizumab registration either in Europe or in the US. An aseptic procedure for IVT injection was recommended by the Applicant. Nevertheless, a degree of freedom was permitted to take into account the different practices that vary considerably among practitioners or countries.

Year-2: During the second year of the study, the subjects received IVT injection of study drug or comparator at intervals determined by the specific criteria for redosing at the same dose level as originally assigned. They were evaluated every 4 weeks. Injections could be given as frequently as every 4 weeks, but no less frequently than every 12 weeks (modified quarterly dosing schedule), according to the following re-dosing criteria, which were assessed by the investigator:

i) Increase in CRT ≥100 µm compared to the lowest previous value (OCT), or ii) A loss of ≥5 ETDRS letters from the best previous letter score in conjunction with recurrent fluid as indicated by OCT, or iii) New or persistent fluid as indicated by OCT, or iv)New onset classic neovascularization, or v) New or persistent leak on fluorescence angiography (FA), or vi) New macular hemorrhage, or vii) 12 weeks have elapsed since the previous injection.

Subjects and study personnel remained double masked with regard to the dose level but no sham injections were given in the second year for prolonged interval dosing.

Objectives

Objectives were identical across both phase-3 pivotal studies: VIEW 1 and VIEW 2

Primary Objective
The primary objective was to assess the efficacy of IVT administered VEGF Trap-Eye compared to ranibizumab, in a non-inferiority design, in preventing moderate vision loss (defined as a loss < 15 letters/3 lines of vision on the ETDRS chart at a distance of 4 meters) in subjects with all subtypes of neovascular AMD.

Secondary Objective(s)
The secondary objectives were:

1/to assess the safety and tolerability of repeated IVT administration of VEGF Trap-Eye in subjects with all sub-types of neovascular AMD for periods up to 2 years.

2/to assess the effect of repeated IVT administration of VEGF Trap-Eye on Vision-Related Quality of Life (QoL) in subjects with all subtypes of neovascular AMD, as assessed using the NEI VFQ-25 questionnaire.

Outcomes/endpoints

Primary and secondary efficacy criteria were identical in the two Phase-3 studies: VIEW 1 and VIEW 2

Three categories of end points were analysed: Visual, Quality of life and Morphologic

Primary Endpoint

• The primary efficacy variable was the proportion of subjects who maintained vision (ie, loss of fewer than 15 letters on the ETDRS chart compared to Baseline) at Week 52 as assessed in the PPS.

Visual function of the study eye was assessed using the ETDRS chart at 4 meters and a subject was classified as maintaining vision if the subject has lost fewer than 15 letters in ETDRS letter score compared to baseline.

Secondary Endpoints

• Mean change from baseline in BCVA as measured by ETDRS letter score at Week 52.

• Proportion of subjects who gain at least 15 letters of vision from baseline at Week 52 on the ETDRS chart.

Quality of life

• Mean change in total NEI VFQ-25 score from baseline to Week 52.

(Vision-related Quality Of Life is assessed using the National Eye Institute 25-Item Visual Function Questionnaire (NEI VFQ-25).

Morphologic end points

• Mean change in CNV area from baseline to Week 52 as assessed by fluorescein angiography (FA).

Sample size

Assuming that 90% of subjects treated with 0.5 mg ranibizumab and any VEGF Trap-Eye dose would maintain vision (defined as losing fewer than 15 letters of visual acuity) at Week 52 compared to Baseline, a one-sided alpha level of 0.025, a power of 90% and defining **the non-**

inferiority margin to be 10%, the sample size estimation resulted in 191 (VIEW1) / 190 (VIEW 2) subjects per treatment group. Assuming a dropout rate of 30% (a high dropout rate was assumed because of the availability of competing, approved therapies), enrolment of 300 subjects per group was determined to provide adequate power to achieve the study's objectives under the stated assumptions.

Randomisation

Subjects were randomly assigned in a 1:1:1:1 ratio to one of the four treatment groups.

Blinding (masking)

Studies were presented as double masked clinical trial, however a strict blinding was not readily feasible:all VEGF Trap-Eye study medication and sham treatments were packaged in identical packaging with identical labeling, except for the kit number. The comparator was supplied in commercial packaging with over labeling for local languages where necessary.

Study drug injection was to be performed by an unmasked physician. The unmasked physician did not play any role in the study beyond the receipt, tracking, preparation, destruction and administration of study drug, as well as assessing safety at 30-60 minutes post IVT injection.

A separate masked physician was assigned to 1) assess AEs and 2) supervise the masked assessment of efficacy. Visual acuity assessments were always masked to treatment assignment.

Statistical methods

The predefined non-inferiority margin was set at 10% and was justified by reference to the results of pivotal studies for ranibizumab. A conditional sequence of statistical evaluation of non-inferiority was used to control multiplicity (1) 2Q4; 2) 0.5Q4; 3) 2Q8 versus RQ4). A predefined test for superiority on secondary criteria was planned using again a conditional sequence of hypothesis to control multiplicity.

The following methods were used for sensitivity analyses: analysis repeated in FAS using LOCF and in FAS and PPS using Observed case analysis, Worst observed carried forward, Discontinued counted as non-responder, or Treatment failure counted as non-responder.

Results

Patient disposition (all randomized subjects):

Study VIEW 1	RQ4	2Q4	0.5Q4	2Q8	VEGF Trap-Eye Combined	Total
Screened*						2063
Randomized	306 (100)	304 (100)	304 (100)	303 (100)	911 (100)	1217 (100)
Treated[2] (safety set)	304 (99.3)	304 (100)	304 (100)	303 (100)	911 (100)	1215 (99.8)
FAS[1]	304 (99.3)	304 (100)	301 (99.0)	301 (99.3)	906	1210
PPS	269 (87.9)	285 (93.8)	270 (88.8)	265 (87.5)	820	1089
Completed Year 1	284 (92.8)	293 (96.4)	277 (91.1)	276 (91.1)	846 (92.9)	1130 (92.9)
Premature discontinuation within first year						
Total	22 (7.2)	11 (3.6)	27 (8.9)	27 (8.9)	65 (7.1)	87 (7.1)
Subject withdrawal	10 (3.3)	5 (1.6)	7 (2.3)	8 (2.6)	20 (2.2)	30 (2.5)
Adverse event	4 (1.3)	3 (1.0)	5 (1.6)	4 (1.3)	12 (1.3)	16 (1.3)
Death[a]	3 (1.0)	1 (0.3)	2 (0.7)	7 (2.3)	10 (1.1)	13 (1.1)
Lost to follow-up	1 (0.3)	2 (0.7)	4 (1.3)	4 (1.3)	10 (1.1)	11 (0.9)
Protocol deviation*	3 (1.0)	0	3 (1.0)	1 (0.3)	4 (0.4)	7 (0.6)
Treatment failure	0	0	2 (0.7)	2 (0.7)	4 (0.4)	4 (0.3)
Other	1 (0.3)	0	4 (1.3)	1 (0.3)	5 (0.5)	6 (0.5)
Completed study medication	279 91.2)	288 (94.7)	274 (90.1)	273 (90.1)	911 (100)	1114 (91.51)
Prematurely discontinued study medication	27 (8.8)	16 (5.3)	30 (9.9)	30 (9.9)	76 (8.3)	103 (8.5)
Withdrawal by Subject	12 (3.9)	8 (2.6)	9 (3.0)	9 (3.0)	_	38 (3.1)
Adverse event	4 (1.3)	3 (1.0)	5 (1.6)	6 (2.0)	14 (1.5)	18 (1.5)
Lost to follow-up	2 (0.7)	4 (1.3)	4 (1.3)	5 (1.7)	13 (1.4)	15 (1.2)
Death	3 (1.0)	1 (0.3)	2 (0.7)	6 (2.0)	9 (1.0)	12 (1.0)
Protocol deviation*	3 (1.0)	0 (0.0)	3 (1.0)	1 (0.3)	4 (0.4)	7 (0.6)
Treatment failure	1 (0.3)	0 (0.0)	2 (0.7)	2 (0.7)	4 (0.4)	5 (0.4)
Other	2 (0.7)	0 (0.0)	5 (1.6)	1 (0.3)	6 (0.7)	8 (0.7)

[a] An additional four deaths were reported during the study but not captured in the database as a reason for premature discontinuation.
[1] FAS :
RQ4 : 2 subjects excluded from FAS : 144-003 (no leakage) & 227-003 (no baseline value) and 1 subject maintained in FAS 195-001 (treated accidentally by 0.5Q4).
0.5Q4 : 3 subject excluded from FAS : 180-002 (not treated by investigator decision) and 227-006 and 171-005 (no post-baseline value). [2] SAS : 195-001 included.
2Q8 : 2 subject excluded from FAS : 152-003 and 171-004 (no post-baseline value).
*Protocol deviation i.e violation and Screened i.e. enrolled
RQ4=ranibizumab 0.5 mg every 4 weeks; 0.5Q4=0.5 mg VEGF Trap-Eye every 4 weeks; 2Q4=2 mg VEGF Trap-Eye every 4 weeks; 2Q8=2 mg VEGF Trap-Eye every 8 weeks after three initial monthly doses.

Recruitment

Study VIEW 1 was conducted from 2 August 2007 up to 14 September 2010.

Conduct of the study

Up to the database lock for the year-1 data, there were 3 amendments to the original study protocol in response to regulatory agency feedback.

Baseline data

Baseline demographics were balanced across the treatment groups except for sex that shown a more accentuated difference in the 2Q4 group (63.8% vs 58.8% for the total population); most patients were white, non Hispanic or Latino, there were more female (58.8 %) than male and the mean age was 78.1 years (range :from 49 to 99 years). The overall mean BMI was 27.40 kg/m2, the mean weight was 75.39 kg, and the mean height was 165.60 cm.

Disease characteristics were well balanced among groups. Mean BVCA score was 55.1 letters; retinal thickness was 266.6 microns; area of CNV 6.6 mm^2, lesion size 6.95 mm^2 and NEI VQF 25 total score 70.7. Lesion subtypes were also balanced across study groups as reported above with a predominance of occult lesions in all groups.

Numbers analysed

Disposition/Reason	Ranibizumab 0.5Q4 (N = 306)	VEGF Trap-Eye 2Q4 (N = 304)	0.5Q4 (N = 304)	2Q8 (N = 303)
Subjects Randomized	306 (100%)	304 (100%)	304 (100%)	303 (100%)
Safety Analysis Set [a]	304 (99.3%)	304 (100%)	304 (100%)	303 (100%)
Full Analysis Set [b]	304 (99.3%)	304 (100%)	301 (99.0%)	301 (99.3%)
Per Protocol Set [c]	269 (87.9%)	285 (93.8%)	270 (88.8%)	265 (87.5%)

Outcomes and estimation

One-year efficacy results

VIEW 1 Study: One-year efficacy results

All three hypothesis analyses met non-inferiority criteria in favour of the three VEGF Trap-Eye regimens showing upper limits of the 95.1% CI of the difference between each of the three tested dosing regimens and the comparator ≤ 3.1%.

VIEW 1 -Primary efficacy analysis-Proportion of Subjects who Maintained Vision at Week 52

Closed test procedure	Treatment Group[a]	Subjects who Maintained Vision at Wk 52; n (%)	Difference % (95.1% CI)[b]	Statistical Interpretation (LOCF, PPS)
First hypothesis	2Q4 (n=285) RQ4 (n=269)	271 (95.1) 254 (94.4)	**-0.7 (-4.4, 3.1)**	Non-inferiority of 2Q4 to RQ4 is statistically proven, test procedure can be continued as confirmatory analysis
Second hypothesis	0.5Q4 (n=270) RQ4 (n=269)	259 (95.9) 254 (94.4)	**-1.5 (-5.1, 2.1)**	Non-inferiority of 0.5Q4 to RQ4 is statistically proven, test procedure can be continued as confirmatory analysis
Third hypothesis	2Q8 (n=265) RQ4 (n=269)	252 (95.1) 254 (94.4)	**-0.7 (-4.5, 3.1)**	Non-inferiority of 2Q8 to RQ4 is statistically proven, test procedure can be continued as confirmatory analysis

a: RQ4=ranibizumab 0.5 mg every 4 weeks; 0.5Q4=0.5 mg VEGF Trap-Eye every 4 weeks; 2Q4=2 mg VEGF Trap-Eye every 4 weeks; 2Q8=2 mg VEGF Trap-Eye every 8 weeks after three initial monthly doses
b: Difference is ranibizumab minus VEGF Trap-Eye. Negative values favour VEGF Trap-Eye. CI=Confidence interval calculated using normal approximation.

The different methods used as sensitivity analyses provided consistent results with the primary analysis (upper limits ≤ 4.6% and 5.3% for the analyses in the PPS and in the FAS, respectively) although these values were less stringent than observed in the primary analysis.

All values stayed well below the pre-specified CI upper bound of 10% but also well below the 7% margin discussed with CHMP.

Secondary criteria related to visual acuity:

Since non-inferiority to ranibizumab was met for all VEGF Trap-Eye regimens, a test for superiority was authorized for secondary criteria in the FAS. The comparison of the change from baseline to Week 52 in BCVA letter score in the 2Q4 and RQ4 groups demonstrated a superior improvement from baseline for the 2Q4 regimen (mean =10.9 letters; LS mean =10.97 letters versus mean =8.1 letters; LS mean 7.82 letters; LS mean difference = 3.15; 95.1% CI = 0.92 to 5.37; p = 0.0054).

The second conditional sequence of superiority was interrupted at the second authorized comparison (2Q4 versus RQ4 with respect to the proportion of patients' group gaining ≥ 15 letters) as analyses were no longer statistically significant.

The 0.5Q4 and 2Q8 regimens did not show difference with the RQ4 regimen (6.9 letters; p=0.479 and 7.9 letters; p=0.818, respectively).

VIEW 1 - Change from Baseline to Week 52 in ETDRS Letter Score (LOCF) (FAS)

Study View 1	RQ4	2Q4	0.5Q4	2Q8
n	304	304	301	301
Week 52 (change from baseline)				
Mean (SD)	8.1 (15.25)	**10.9 (13.77)**	6.9 (13.41)	7.9 (15.00)
Point estimate for the contrast[a]		**3.15**	-0.80	0.26
95.1% CI for difference		(0.92, 5.37)	(-3.03, 1.43)	(-1.97, 2.49)
p-value vs RQ4[b]		**0.0054**	0.4793	0.8179

a: Difference is VEGF Trap-Eye minus ranibizumab using least-square means (LSMeans). Positive values are in favour of VEGF Trap-Eye. CI=confidence interval calculated using normal approximation.
b: ANCOVA, main effect model using LSMeans.

The best result for the change in letter score from baseline, was observed with the VEGF Trap-Eye dosed monthly (2Q4 regimen) compared to ranibizumab dosed monthly. The 2Q4 regimen showed a superior improvement from baseline in the ETDRS letter score compared to the RQ4 group (a mean of 10.9 letters; LS mean 10.97 letters versus a mean of 8.1 letters; LS mean 7.82 letters; LS mean difference = 3.15; 95.1% CI = 0.92 to 5.37; p = 0.0054).

The analysis of the proportion of subjects gaining ≥ 15 letters from baseline showed numeric trend in favour of the 2Q4 regimen while the 2Q8 and RQ4 regimens were of similar pattern. All sensitivity analyses showed a similar picture.

VIEW 1 – Analysis of the Proportion of subjects gaining ≥ 15 letters from baseline to Week 52 (LOCF/FAS)

Treatment Group	RQ4	2Q4	0.5Q4	2Q8
n	304	304	301	301
Subjects [n (%)] gaining ≥ 15 letters	94 (30.9)	**114 (37.5)**	75 (24.9)	92 (30.6)
Difference [a] (95.1% CI) p-value vs. RQ4 [2]	—	**6.6** (-1, 14.1) 0.1042	-6.0 (-13.2, 1.2) 0.1037	-0.4 (-7.7, 7.0) 0.93

a: Mantel-Haenszel estimate for difference ranibizumab minus VEGF Trap-Eye (positive values are in favour of VEGF Trap- Eye); CI=Confidence interval calculated using normal approximation; [2] Pearson's Chi-Square Test (2-Sided)

Other secondary criteria (Visual Quality of life, CNV area)
By Week 52 in the FAS (LOCF), the improvement in visual quality of life (as assessed by the NEI VFQ-25 total score) was numerically larger in the 2Q4 group (mean change 6.7 points) than in the RQ4 group (mean change 4.9 points). Sensitivity analyses showed a similar trend of results.

By week 52, mean CNV area decreased in all treatment groups while better numeric results were observed again with the 2Q4 regimen (-4.6 mm^2) than with the RQ4 regimen (-4.2 mm^2).

Additional Efficacy Endpoints

By week 12, the greatest improvement in BCVA was seen in the 2Q4 group (a mean of 8.7 letters), while the RQ4 group reached a mean of 7.3 letters.

The proportion of subjects who gained ≥ 0, 10, or 30 letters was numerically higher and the proportion of subjects who lost ≥ 15 or 30 letters was lower in the 2Q4 group than in the RQ4, 0.5Q4, and 2Q8 groups.

The proportions of subjects with severe vision loss ≥ 30 letters were higher in the RQ4 and 2Q8 groups (3%) than in the 0.5Q4 and 2Q4 groups (1%).

VIEW 2 Study: One-year efficacy results

Similarly to VIEW 1 Study, primary criteria analysis met the non-inferiority for all VEGF Trap-eye regimens (all upper limits of the 95% CIs <2.6%). All the nine sensitivity analyses provided consistent results with the primary analysis showing upper limits of the 95% CI of the difference between all VEGF Trap-eye regimens and the comparator ≤ 3.65% and ≤ 8.5% for the analyses in the PPS and in the FAS, respectively.

VIEW 2 -Primary efficacy analysis-Proportion of Subjects who Maintained Vision at Week 52

Closed test procedure	Treatment Group[a]	Subjects who Maintained Vision at Wk 52; n (%)	Difference % (95% CI)[b]	Statistical Interpretation (LOCF, PPS)
First hypothesis	2Q4 (n=274) RQ4 (n=269)	262 (95.62) 254 (94.42)	-1.20 (-4.86, 2.46)	Non-inferiority of 2Q4 to RQ4 is statistically proven, test procedure can be continued
Second hypothesis	0.5Q4 (n=268) RQ4 (n=269)	258 (96.27) 254 (94.42)	-1.84 (-5.40, 1.71)	Non-inferiority of 0.5Q4 to RQ4 is statistically proven, test procedure can be continued
Third hypothesis	2Q8 (n=270) RQ4 (n=269)	258 (95.56) 254 (94.42)	-1.13 (-4.81, 2.55)	Non-inferiority of 2Q8 to RQ4 is statistically proven, test procedure can be continued

a: RQ4=ranibizumab 0.5 mg every 4 weeks; 0.5Q4=0.5 mg VEGF Trap-Eye every 4 weeks; 2Q4= 2 mg VEGF Trap-Eye every 4 weeks; 2Q8=2 mg VEGF Trap-Eye every 8 weeks after three initial monthly doses
b: Difference is ranibizumab minus VEGF Trap-Eye. Negative values favour VEGF Trap-Eye. CI=Confidence interval calculated using normal approximation.

The 0.5Q4 regimen showed the best numeric result according to proportion of patients who maintained vision (96.27%) in the primary analysis. It should be noted that the proportion of patients who maintained vision in the ranibizumab group was similar to that seen in VIEW 1 Study (94.4%) which is in good accordance with the results of Marina Study (by 12 months, 94.6%).

Numeric results for either the 2Q4 or the 2Q8 regimens were very similar (95.62 and 95.56).

In contrast to VIEW 1 results, no superiority was found in VIEW 2 Study for the first step of comparison, which failed to show a statistically significant treatment difference between the 2Q4 and the RQ4 groups (p=0.076).

Secondary criteria related to visual acuity:

VIEW 2 - Change from Baseline to Week 52 in ETDRS Letter Score (LOCF) (FAS)

Study View 2	**RQ4**	**2Q4**	**0.5Q4**	**2Q8**
Week 52 (change from baseline)				
n	291	309	296	306
Mean (SD)	9.4 (13.5)	7.6 (12.6)	**9.7 (14.1)**	8.9 (14.4)
Point estimate for the contrast[a]		-1.95	-0.06	-0.90
95% CI for difference		(-4.10; 0.20)	(-2.24; 2.12)	(-3.06; 1.26)
p-value vs RQ4[b]		0.076	0.956	0.413

a: Difference is VEGF Trap-Eye minus ranibizumab using LSMeans. CI=confidence interval calculated using normal approximation.
b: ANCOVA, main effect model using LSMeans.

Only one comparison was numerically in favour of VEGF Trap-Eye (0.5Q4 group: 9.7 letters versus RQ4 group: 9.4 letters); differences between the three VEGF Trap-Eye groups and the ranibizumab group were numerically slightly in favour of the ranibizumab group with a maximum difference observed in the comparison of 2Q4 vs RQ4 (-1.95 letters) but the 95% CIs for the treatment differences remained consistently included zero and all p-values were > 0.05. The PPS followed the

same trends. Overall, the results of the sensitivity analyses were consistent with the main analysis, except for the following comparisons which were in favour of ranibizumab were point estimate for the difference were (OV: 2Q4 – RQ4::-2.38 (95% CI: -4.61 to -0.14); p=0.0373 and WOCF: 2Q4 – RQ4: point estimate for the difference: -2.60 (95% CI: -4.78 to -0.42); p=0.0193).

VIEW 2 – Analysis of the Proportion of subjects gaining ≥ 15 letters from baseline to Week 52 (LOCF/FAS)

Treatment Group[a]	**RQ4**	**2Q4**	**0.5Q4**	**2Q8**
N	291	309	296	306
Subjects [n (%)] gaining 15 letters	99 (34.02)	91 (29.45)	**103 (34.80)**	96 (31.37)
Difference (95% CI)[b]	—	-4.57 (-12.02, 2.88)	**0.78** (-6.91, 8.46)	-2.65 (-10.18, 4.88)

a: RQ4=ranibizumab 0.5 mg every 4 weeks; 0.5Q4=0.5 mg VEGF Trap-Eye every 4 weeks; 2Q4= 2 mg VEGF Trap-Eye every 4 weeks; 2Q8=2 mg VEGF Trap-Eye every 8 weeks after three initial monthly doses

b: Mantel-Haenszel estimate for difference ranibizumab minus VEGF Trap-Eye; CI=Confidence interval calculated using normal approximation

At Week 52, 103 subjects (34.8%) in the 0.5Q4 group and 96 subjects (31.4%) in the 2Q8 group had gained ≥ 15 letters. In the PPS, results were consistent.

Other secondary endpoints: Overall, at Week 52, in the FAS/LOCF, the results for the NEI VFQ-25 total score numerically favoured ranibizumab and when using the LSmeans from the ANCOVA main effect model, a significant difference was observed in favour of the RQ4 regimen over the 2Q4 regimen, p=0.010). All baseline differences nonetheless, remained in the range (≥4-6) of clinical relevance as identified from Marina and Anchor published studies while ranibizumab provided the higher difference. The results of the sensitivity analyses supported these results.

The results for the change from Baseline to Week 52 in CNV Area numerically slightly favoured all VEGF Trap-eye regimens. The lowest mean decrease was observed in the RQ4 group (-4.16 mm2), the highest in the 2Q4 group (-5.95 mm2) followed by the 2Q8 (-5.16 mm2). When using the LSmeans from the ANCOVA main effect model, a significant difference was observed in favour of the 2Q4 regimen over the RQ4 regimen, p=0.004). The results of the sensitivity analyses (observed cases and WOCF) were consistent with the results obtained in the main analysis applying the LOCF method.

In conclusion, the primary criteria analysis met the non-inferiority for all VEGF Trap-eye regimens and all secondary endpoint analyses supported the comparability of the efficacy of ranibizumab with the three VEGF Trap-Eye treatment regimens. Sensitivity analyses in the FAS and in the PPS of primary and secondary endpoints also supported the main analyses.

Nevertheless, results in favour of the 2Q4 regimen observed in Study VIEW 1 were not replicated in Study VIEW 2. In contrast to the findings observed in VIEW 1 Study, no superiority was evidenced from the first conditional ordered test hypothesis. In addition, while results based on visual acuity measurements seemed to rather favour the 0.5Q4 regimen, results based on morphologic endpoints seemed in favour of the 2Q4 regimen and, to a lesser extent, in favour of the 2Q8 regimen showing the greatest mean decrease in classic CNV area.

Therefore, there were no clear tendencies of results in VIEW 2 Study to favour one dosing regimen of VEGF Trap-Eye over the others, apart the number of injections that is reduced in the 2Q8 regimen.

Ancillary analyses

Since all three VEGF Trap-Eye groups were shown to be non-inferior to ranibizumab on the primary endpoint, additional comparisons were authorized with respect to secondary endpoints, and these have been described above.

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Summary of Efficacy for trial VIEW1

Title: **A randomized, double masked, active controlled, phase 3 study of the efficacy, safety, and tolerability of repeated doses of intravitreal VEGF Trap-Eye in subjects with neovascular age-related macular degeneration**			
Study identifier	14393 (Bayer study ID); VGFT-OD-0605 (Regeneron study ID)		
Design	Multicenter, double-masked, randomized (1:1:1:1), active-controlled, parallel-group study		
	Duration of main phase:		52 weeks for primary efficacy
	Duration of Run-in phase:		21 day maximum screening period
	Duration of Extension phase:		1 year after week 52
Hypothesis	Non-inferiority (primary); superiority (secondary)		
Treatments groups	RQ4		During 1st year: Ranibizumab 0.5 mg every 4 weeks, 306 subjects randomized
	2Q4		During 1st year: VEGF Trap-Eye 2.0 mg every 4 weeks, 304 subjects randomized
	0.5Q4		During 1st year: VEGF Trap-Eye 0.5 mg every 4 weeks, 304 subjects randomized
	2Q8		During 1st year: VEGF Trap-Eye 2.0 mg every 8 weeks, 303 subjects randomized
Endpoints and definitions	Primary endpoint	Maintenance of vision	Proportion of subjects who maintained vision at Week 52, where a subject was classified as maintaining vision if the subject had lost fewer than 15 letters in the Early Treatment Diabetic Retinopathy Study (ETDRS) letter score compared to baseline
	Secondary endpoints	ETDRS change	Change from baseline in best corrected visual acuity (BCVA) as measured by ETDRS letter score at Week 52
		15-letter gain	Proportion of subjects who gained at least 15 letters of vision from baseline to Week 52
		NEI VFQ-25 change	Change in total NEI VFQ-25 score from baseline to Week 52
		CNV change	Change in choroidal neovascularization (CNV) area from baseline to Week 52
Database lock	10 Nov. 2010 (for 1-year database)		

Results and Analysis						
Analysis description	**Primary Analysis**					
Analysis population and time point description	Per protocol set (PPS): All subjects in the full analysis set (see below) who received at least nine injections of study drug or sham and attended at least nine scheduled visits during the first year, except for those who were excluded because of major protocol violations, where a major protocol violation is one that may affect the interpretation of study results. The PPS also included subjects without major protocol deviations who discontinued due to treatment failure at any time during the first 52 weeks of the study. Full analysis set (FAS): All randomized subjects who received any study drug and had a baseline and at least one post-baseline BCVA assessment. At week 52 using last-observation-carried–forward (LOCF) principle for missing week 52 values					
Descriptive statistics and estimate variability	Treatment group	**RQ4**	**2Q4**	**0.5Q4**	**2Q8**	
	Number of subject (PPS)	269	285	270	265	
	Maintenance of vision [no. (%) of subjects]	254 (94.4%)	271 (95.1%)	259 (95.9%)	252 (95.1%)	
Effect estimate per comparison	Primary endpoint **maintenance of vision**	Comparison groups	**2Q4 vs RQ4**			
		RQ4 minus 2Q4	-0.7			
		95.1% CI	-4.4, 3.1			
		P-value	*not applicable*			
		Comparison groups	**0.5Q4 vs RQ4**			
		RQ4 minus 0.5Q4	-1.5			
		95.1% CI	-5.1, 2.1			
		P-value	*not applicable*			
		Comparison groups	**2Q8 vs RQ4**			
		RQ4 minus 2Q8	-0.7			
		95.1% CI	-4.5, 3.1			
		P-value	*not applicable*			
Notes	Confidence intervals (CIs) were calculated using a normal approximation.					
Analysis description	**Analysis of secondary endpoints, pre-specified**					
Analysis population and time point description	Full analysis set (FAS): All randomized subjects who received any study drug and had a baseline and at least one post-baseline BCVA assessment At week 52 using last-observation-carried–forward (LOCF) principle for missing week 52 values					
Descriptive statistics and estimate variability	Treatment group	**RQ4**	**2Q4**	**0.5Q4**	**2Q8**	
	Number of subject	304	304	301	301	
	ETDRS change mean	8.1	10.9	6.9	7.9	
	Standard deviation	15.25	13.77	13.41	15.00	

Effect estimate per comparison	Secondary endpoint **ETDRS change**	Comparison groups	**2Q4 vs RQ4**		
		2Q4 minus RQ4 [LS mean]	3.15		
		95.1% CI	0.92, 5.37		
		P-value (ANCOVA)	0.0054		
		Comparison groups	**0.5Q4 vs RQ4**		
		0.5Q4 minus RQ4 [LS mean]	-0.8		
		95.1% CI	-3.03, 1.43		
		P-value (ANCOVA)	0.4793		
		Comparison groups	**2Q8 vs RQ4**		
		2Q8 minus RQ4 [LS mean]	0.26		
		95.1% CI	-1.97, 2.49		
		P-value (ANCOVA)	0.8179		
Notes	Confidence intervals (CIs) were calculated using a normal approximation. Analysis of covariance (ANCOVA), main effect model. Difference is VEGF Trap-Eye minus Ranibizumab. The pairwise comparison is performed as contrast statement in the ANCOVA model with treatment group as fixed factor (all 4 treatment groups) and the baseline ETDRS letter score as covariate.				
Analysis description	**Analysis of secondary endpoints, pre-specified**				
Analysis population and time point description	Full analysis set (FAS): All randomized subjects who received any study drug and had a baseline and at least one post-baseline BCVA assessment At week 52 using last-observation-carried-forward (LOCF) principle for missing week 52 values				
Descriptive statistics and estimate variability	Treatment group	**RQ4**	**2Q4**	**0.5Q4**	**2Q8**
	Number of subject	304	304	301	301
	15-letter gain [no. (%) of subjects]	94 (30.9%)	114 (37.5%)	75 (24.9%)	92 (30.6%)
Effect estimate per comparison	Secondary endpoint **15-letter gain**	Comparison groups	**2Q4 vs RQ4**		
		2Q4 minus RQ4 [LS mean]	6.6		
		95.1% CI	-1, 14.1		
		P-value (Chi-square)	0.1042		
		Comparison groups	**0.5Q4 vs RQ4**		
		0.5Q4 minus RQ4	-6		
		95.1% CI	-13.2, 1.2		
		P-value (Chi-square)	0.1037		
		Comparison groups	**2Q8 vs RQ4**		
		2Q8 minus RQ4	-0.4		
		95.1% CI	-7.7, 7		
		P-value (Chi-square)	0.93		
Notes	Confidence intervals (CIs) were calculated using a normal approximation.				

Analysis description	**Analysis of secondary endpoints, pre-specified**				
Analysis population and time point description	Full analysis set (FAS): All randomized subjects who received any study drug and had a baseline and at least one post-baseline BCVA assessment At week 52 using last-observation-carried–forward (LOCF) principle for missing week 52 values				
Descriptive statistics and estimate variability	Treatment group	**RQ4**	**2Q4**	**0.5Q4**	**2Q8**
	Number of subject	304	304	301	301
	NEI VFQ-25 change [mean]	4.9	6.7	4.5	5.1
	Standard deviation	14.01	13.50	11.87	14.74

Effect estimate per comparison	Secondary endpoint **NEI VFQ-25 change**	Comparison groups	**2Q4 vs RQ4**
		2Q4 minus RQ4 [LS mean]	1.28
		95.1% CI	-0.73, 3.28
		P-value (ANCOVA)	0.2090
		Comparison groups	**0.5Q4 vs RQ4**
		0.5Q4 minus RQ4 [LS mean]	-0.67
		95.1% CI	-2.69, 1.35
		P-value (ANCOVA)	0.5128
		Comparison groups	**2Q8 vs RQ4**
		2Q8 minus RQ4 [LS mean]	-0.60
		95.1% CI	-2.61, 1.42
		P-value (ANCOVA)	0.5579
Notes	Confidence intervals (CIs) were calculated using a normal approximation. Analysis of covariance (ANCOVA), main effect model. Difference is VEGF Trap-Eye minus Ranibizumab. The pairwise comparison is performed as contrast statement in the ANCOVA model with treatment group as fixed factor (all 4 treatment groups) and the baseline ETDRS letter score as covariate.		

Analysis description	**Analysis of secondary endpoints**				
Analysis population and time point description	**Full analysis set**				
Descriptive statistics and estimate variability	Treatment group	**RQ4**	**2Q4**	**0.5Q4**	**2Q8**
	Number of subject	304	304	301	301
	CNV change [mean]	-4.2	-4.6	-3.5	-3.4
	Standard deviation	5.59	5.47	5.27	6.02

Effect estimate per comparison	Secondary endpoint **CNV change**	Comparison groups	**2Q4 vs RQ4**
		2Q4 minus RQ4 [LS mean]	-0.33
		95.1% CI	-1.04, 0.38
		P-value (ANCOVA)	0.3575
		Comparison groups	**0.5Q4 vs RQ4**
		0.5Q4 minus RQ4 [LS mean]	0.71
		95.1% CI	-0.01, 1.42
		P-value (ANCOVA)	0.0507
		Comparison groups	**2Q8 vs RQ4**
		2Q8 minus RQ4 [LS mean]	0.86
		95.1% CI	0.15, 1.58
		P-value (ANCOVA)	0.0173
Notes	Confidence intervals (CIs) were calculated using a normal approximation. Analysis of covariance (ANCOVA), main effect model. Difference is VEGF Trap-Eye minus Ranibizumab. The pairwise comparison is performed as contrast statement in the ANCOVA model with treatment group as fixed factor (all 4 treatment groups) and the baseline ETDRS letter score as covariate.		

Summary of Efficacy for trial VIEW2

Title: **A randomized, double masked, active controlled, phase 3 study of the efficacy, safety, and tolerability of repeated doses of intravitreal VEGF Trap-Eye in subjects with neovascular age-related macular degeneration (AMD)** **VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD (VIEW 2)**		
Study identifier	311523	
Design	Multicenter, double-masked, randomized (1:1:1:1), active-controlled, parallel-group study	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	52 weeks for primary efficacy 21 day maximum screening period 1 year after week 52
Hypothesis	Non-inferiority (primary); superiority (secondary)	
Treatments groups	RQ4	During 1st year: Ranibizumab 0.5 mg every 4 weeks, 306 subjects randomized
	2Q4	During 1st year: VEGF Trap-Eye 2.0 mg every 4 weeks, 304 subjects randomized
	0.5Q4	During 1st year: VEGF Trap-Eye 0.5 mg every 4 weeks, 304 subjects randomized

PGR2026-00039
Biocon Ex.1065
Page 368 of 595

	2Q8		During 1st year: VEGF Trap-Eye 2.0 mg every 8 weeks, 303 subjects randomized
Endpoints and definitions	Primary endpoint	Maintenance of vision	Proportion of subjects who maintained vision at Week 52, where a subject was classified as maintaining vision if the subject had lost fewer than 15 letters in the Early Treatment Diabetic Retinopathy Study (ETDRS) letter score compared to baseline
	Secondary endpoints	ETDRS change	Change from baseline in best corrected visual acuity (BCVA) as measured by ETDRS letter score at Week 52
		15-letter gain	Proportion of subjects who gained at least 15 letters of vision from baseline to Week 52
		NEI VFQ-25 change	Change in total NEI VFQ-25 score from baseline to Week 52
		CNV change	Change in choroidal neovascularization (CNV) area from baseline to Week 52
Database lock	10 Nov. 2010 (for 1-year database)		

Results and Analysis

Analysis description	**Primary Analysis**				
Analysis population and time point description	Per protocol set (PPS): All subjects in the full analysis set (see below) who received at least nine injections of study drug or sham and attended at least nine scheduled visits during the first year, except for those who were excluded because of major protocol violations, where a major protocol violation is one that may affect the interpretation of study results. The PPS also included subjects without major protocol deviations who discontinued due to treatment failure at any time during the first 52 weeks of the study. Full analysis set (FAS): All randomized subjects who received any study drug and had a baseline and at least one post-baseline BCVA assessment. At week 52 using last-observation-carried–forward (LOCF) principle for missing week 52 values				
Descriptive statistics and estimate variability	Treatment group	**RQ4**	**2Q4**	**0.5Q4**	**2Q8**
	Number of subject (PPS)	269	274	268	270
	Maintenance of vision [no. (%) of subjects]	254 (94.42%)	262 (95.62%)	258 (96.27%)	258 (95.56%)

Effect estimate per comparison	Primary endpoint **maintenance of vision**	Comparison groups	**2Q4 vs RQ4**
		RQ4 minus 2Q4	-1.20
		95% CI	-4.86; 2.46
		P-value	*not applicable*
		Comparison groups	**0.5Q4 vs RQ4**
		RQ4 minus 0.5Q4	-1.84
		95% CI	-5.40; 1.71
		P-value	*not applicable*
		Comparison groups	**2Q8 vs RQ4**
		RQ4 minus 2Q8	-1.13
		95% CI	-4.81; 2.55
		P-value	*not applicable*
Notes	Confidence intervals (CIs) were calculated using a normal approximation.		

Analysis description	**Analysis of secondary endpoints, pre-specified**				
Analysis population and time point description	Full analysis set (FAS): All randomized subjects who received any study drug and had a baseline and at least one post-baseline BCVA assessment At week 52 using last-observation-carried–forward (LOCF) principle for missing week 52 values				
Descriptive statistics and estimate variability	Treatment group	**RQ4**	**2Q4**	**0.5Q4**	**2Q8**
	Number of subject	291	309	296	306
	ETDRS change mean	9.4	7.6	9.7	8.9
	Standard deviation	13.5	12.6	14.1	14.4

Effect estimate per comparison	Secondary endpoint **ETDRS change**	Comparison groups	**2Q4 vs RQ4**
		2Q4 minus RQ4 [LS mean]	-1.95
		95% CI	-4.10; 0.20
		P-value (ANCOVA)	0.076
		Comparison groups	**0.5Q4 vs RQ4**
		0.5Q4 minus RQ4 [LS mean]	-0.06
		95% CI	-2.24; 2.12
		P-value (ANCOVA)	0.956
		Comparison groups	**2Q8 vs RQ4**
		2Q8 minus RQ4 [LS mean]	-0.90
		95% CI	-3.06; 1.26
		P-value (ANCOVA)	0.413

Notes	Confidence intervals (CIs) were calculated using a normal approximation. Analysis of covariance (ANCOVA), main effect model. Difference is VEGF Trap-Eye minus Ranibizumab. The pairwise comparison is performed as contrast statement in the ANCOVA model with treatment group as fixed factor (all 4 treatment groups) and the baseline ETDRS letter score as covariate.

Analysis description	**Analysis of secondary endpoints, pre-specified**				
Analysis population and time point description	Full analysis set (FAS): All randomized subjects who received any study drug and had a baseline and at least one post-baseline BCVA assessment At week 52 using last-observation-carried-forward (LOCF) principle for missing week 52 values				
Descriptive statistics and estimate variability	Treatment group	**RQ4**	**2Q4**	**0.5Q4**	**2Q8**
	Number of subject	291	309	296	306
	15-letter gain [no. (%) of subjects]	99 (34.02%)	91 (29.45%)	103 (34.80%)	96 (31.37%)

Effect estimate per comparison	Secondary endpoint **15-letter gain**	Comparison groups	**2Q4 vs RQ4**
		2Q4 minus RQ4 [LS mean]	-4.57
		95% CI	-12.02; 2.88
		P-value (Chi-square)	0.229

		Comparison groups	**0.5Q4 vs RQ4**
		0.5Q4 minus RQ4	0.78
		95% CI	-6.91; 8.46
		P-value (Chi-square)	0.843
		Comparison groups	**2Q8 vs RQ4**
		2Q8 minus RQ4	-2.65
		95% CI	-10.18; 4.88
		P-value (Chi-square)	0.490
Notes	Confidence intervals (CIs) were calculated using a normal approximation.		
Analysis description	**Analysis of secondary endpoints, pre-specified**		
Analysis population and time point description	Full analysis set (FAS): All randomized subjects who received any study drug and had a baseline and at least one post-baseline BCVA assessment At week 52 using last-observation-carried–forward (LOCF) principle for missing week 52 values		

Descriptive statistics and estimate variability	Treatment group	**RQ4**	**2Q4**	**0.5Q4**	**2Q8**
	Number of subject	291	309	296	306
	NEI VFQ-25 change [mean]	6.3	4.5	5.1	4.9
	Standard deviation	14.8	15.0	13.7	14.7

Effect estimate per comparison	Secondary endpoint **NEI VFQ-25 change**	Comparison groups	**2Q4 vs RQ4**
		2Q4 minus RQ4 [LS mean]	-2.79
		95% CI	-4.90; -0.68
		P-value (ANCOVA)	0.010
		Comparison groups	**0.5Q4 vs RQ4**
		0.5Q4 minus RQ4 [LS mean]	-0.93
		95% CI	-3.07; 1.20
		P-value (ANCOVA)	0.392
		Comparison groups	**2Q8 vs RQ4**
		2Q8 minus RQ4 [LS mean]	-1.95
		95% CI	-4.07; 0.17
		P-value (ANCOVA)	0.072
Notes	Confidence intervals (CIs) were calculated using a normal approximation. Analysis of covariance (ANCOVA), main effect model. Difference is VEGF Trap-Eye minus Ranibizumab. The pairwise comparison is performed as contrast statement in the ANCOVA model with treatment group as fixed factor (all 4 treatment groups) and the baseline ETDRS letter score as covariate.		

Analysis description	**Analysis of secondary endpoints**				
Analysis population and time point description	**Full analysis set**				
Descriptive statistics and estimate variability	Treatment group	**RQ4**	**2Q4**	**0.5Q4**	**2Q8**
	Number of subject	291	309	296	306
	CNV change [mean]	-4.160	-5.950	-4.236	-5.160
	Standard deviation	5.900	6.116	6.129	5.866

Effect estimate per comparison	Secondary endpoint **CNV change**	Comparison groups	**2Q4 vs RQ4**
		2Q4 minus RQ4 [LS mean]	-1.180
		95% CI	-1.979; -0.382
		P-value (ANCOVA)	0.004
		Comparison groups	**0.5Q4 vs RQ4**
		0.5Q4 minus RQ4 [LS mean]	0.170
		95% CI	-0.632; 0.972
		P-value (ANCOVA)	0.678
		Comparison groups	**2Q8 vs RQ4**
		2Q8 minus RQ4 [LS mean]	-0.733
		95% CI	-1.534; 0.068
		P-value (ANCOVA)	0.073

Notes	Confidence intervals (CIs) were calculated using a normal approximation. Analysis of covariance (ANCOVA), main effect model. Difference is VEGF Trap-Eye minus Ranibizumab. The pairwise comparison is performed as contrast statement in the ANCOVA model with treatment group as fixed factor (all 4 treatment groups) and the baseline ETDRS letter score as covariate.

Analysis performed across trials (pooled analyses and meta-analysis)

Due to similar design and inclusion criteria, data from VIEW 1 and VIEW 2 pivotal studies were pooled in accordance with the pre-defined analysis.

Statistical analyses of differences across studies or between treatment groups were not conducted in the integrated analysis data set.

One-year pooled efficacy results (VIEW 1+VIEW 2)

Data set analysed:

The PPS (used for primary efficacy endpoint) comprised 1089, 1081 or 2170 subjects in the VIEW 1, VIEW 2 studies and pooled population, respectively).

The FAS (used for the four main secondary analyses) comprised 1210, 1202 or 2412 subjects in the VIEW 1 and VIEW 2 and pooled population, respectively).

In both analysis sets, subjects were analyzed as randomized. A summary of the pooled results is provided below:

Primary efficacy analysis: Maintenance of vision at Week 52 – PPS Pooled Efficacy results

Integrated Analysis Treatment Group[a]	RQ4	2Q4	0.5Q4	2Q8
N	538	559	538	535
Subjects [n (%)] maintaining vision	508 (94.42)	533 (95.35)	**517 (96.10)**	510 (95.33)
Difference (95% CI)[b]	—	-0.9 (-3.5,1.7)	**-1.7 (-4.2 ,0.9)**	-0.9 (-3.5 ,1.7)

The results of the integrated analysis reflect the findings of the individual studies either for primary or secondary variables. The results of ancillary efficacy endpoints are supportive of the primary and secondary endpoints, showing comparable efficacy for all dosages of VEGF Trap-Eye with ranibizumab. Subgroup analyses showed that subjects who were younger, with poorer baseline vision and smaller lesions were more likely to maintain or gain vision. No important differences were seen between the ranibizumab and VEGF Trap-Eye 2Q8 groups in any subgroup. No geographical variations were observed in VIEW 2 (conducted in Europe, Asia, Australia and Latin America). In no particular group did the efficacy of VEGF Trap-Eye appear to be significantly worse than expected.

Data on certain subgroups are limited, due to the small number of patients: Black race subgroup, and history of hepatic impairment. However, this was not a significant concern. Neovascular AMD has a far higher prevalence in Caucasians than Black patients and there is no reason to suggest that efficacy would differ in the two groups. Systemic exposure to VEGF Trap-Eye following intravitreal injection is minimal, and the liver does not play an important role in the elimination of VEGF Trap, so hepatic impairment should not affect efficacy.

Two-year pooled efficacy results (VIEW 1+VIEW 2)

The applicant submitted results of Year 2 of the pivotal studies in which subjects underwent examinations every 4 weeks and were retreated with Eylea or ranibizumab according to a capped-PRN schedule. Injections could be given as frequently as every 4 weeks, but no less frequently than every 12 weeks. The retreatment criteria included an increase in CRT of ≥100 µm, a loss of ≥5 letters with recurrent fluid on OCT, new or persistent fluid, new onset classic CNV, new or persistent leak on FA, and new macular haemorrhage.

Subjects disposition and analysis sets for subjects entering in year 2

Of the 2457 randomized subjects, 2419 received at least 1 dose of randomized study medication in either VIEW 1 or VIEW 2. In both studies, 2235 (90.0%) of the subjects entered Year 2 (92.0% and 89.9%, in VIEW 1 and 2, respectively) and above 80% completed studies in all treatment groups.

Between randomisation and Week 96/100, the drop-out rate in VIEW 1 study was lower for subjects in the VEGF Trap-Eye 2Q4 arm and in VIEW 2 study, higher in the VEGF Trap-Eye 0.5Q4 arm.

During the 2-year study period, the overall discontinuation rate was 16.0% (394/2457 randomized subjects) and quite similar in both individual studies: 14.7% (179/1217) and 17.3% (215/1240) in VIEW 1 and 2, respectively.

The most frequent primary reasons for premature discontinuation were "withdrawal by subject" (4.9% for VIEW 1 and 6.3% VIEW 2) or "adverse event" (3.1% for VIEW 1 and 4.3% for VIEW 2) showing consistently higher proportions of subjects who discontinued from the study primarily due to adverse events in the VEGF Trap-Eye groups (4.2% - 6.8%) than in the ranibizumab group (1.3%).

In both studies, the treatment groups were well balanced with regard to group sizes, proportions of subjects continuing treatment in Year 2 and demographic baseline. Slight imbalances already present at randomization in VIEW 2 Study persist, in particular poorer baseline anatomical parameters, with greater larger total lesion and CNV areas.

The dosing subgroups were determined post-hoc.

No per-protocol population was defined for the analysis of the data of Year 2.

Efficacy results analysis

The number of injections given in Year 2 and the time between injections are shown in the table below.

When fixed dosing was changed to a capped-PRN schedule in Year 2, a similar mean number of injections (~4), with a similar mean interval duration between injections (~73 days), were observed for the 2Q4 and 2Q8 treatments; these appear also rather similar to ranibizumab (i.e. 4.7 injections and interval of 68 days). Therefore, a prolonged interval of around 10 weeks is observed for the majority of subjects in all treatment groups. This tends to confirm the trend observed in the dose–response study 508.

Integrated analysis: Number of injections in Year 2 (Year 2 completers)				
	R 0.5Q4	VTE		
	N=513	2Q4 N=529	0.5Q4 N=499	2Q8 N=511
Mean Number of Injections (SD) Median Min-max	4.7 (±2.2) 4.0 2-11	4.1 (±1.8) 3.0 2-11	4.6 (±2.2) 4.0 2-11	4.2 (±1.7) 4.0 2-11
Integrated analysis: Mean time between injections (Subjects entering in year 2)				
	0.5Q4 N=557	2Q4 N=571	0.5Q4 N=549	2Q8 N=558
Mean Time between Injections, Days (SD) Median Min-max	67.9 (±20.3) 76.0 27-154	73.7 (±17.4) 82.7 28-125	68.2 (±19.8) 77.0 27-113	73.2 (±21.6) 77.3 28-311*
Integrated analysis: subjects receiving retreatment at least once in a 4-weeks interval in Year 2 (Year 2 completers)				
	0.5Q4 N=557	2Q4 N=571	0.5Q4 N=549	2Q8 N=558
N (%)	231 (41.5%)	166 (29%)	219 (40%)	201 (36%)
Integrated analysis: subjects receiving retreatment at intervals of 8 or 12-weeks in Year 2 (Year 2 completers)				
	0.5Q4 N=557	2Q4 N=571	0.5Q4 N=549	2Q8 N=558
N (%)	291 (52%)	373 (65%)	297 (54%)	326 (58%)
Integrated analysis: subjects receiving retreatment at intervals of 12-weeks in Year 2 (Year 2 completers)				
	0.5Q4 N=557	2Q4 N=571	0.5Q4 N=549	2Q8 N=558
N (%)	218 (39%)	285 (50%)	217 (39.5%)	245 (44%)

311* due to one subject: 440030046

Nevertheless, the VTE 2Q4 regimen shows the lower proportion of patients (29%) receiving retreatment at least once in a 4-weeks interval, and the higher (65%) receiving retreatment at intervals of 8 or 12-weeks in Year 2. This suggests that the 2Q4 regimen administered during the first year of treatment may yield at the end of Year 2 slightly better results than the 2Q8 regimen (36% and 58%) or the competitor ranibizumab (41.5% and 52%).

A similar picture is observed from the Integrated Analysis for post hoc dosing subgroups

(Year 2 study medication completers) as reported in the table below:

Subgroup	Ranibizumab	VEGF Trap-Eye			Total
	0.5Q4 (N = 513) n (%)	2Q4 (N = 529) n (%)	0.5Q4 (N = 499) n (%)	2Q8 (N = 511) n (%)	(N = 2052) n (%)
≤ 3 injections in Year 2	219 (42.7)	288 (54.4)	222 (44.5)	247 (48.3)	976 (47.6)
4-6 injections in Year 2	201 (39.2)	189 (35.7)	195 (39.1)	212 (41.5)	797 (38.8)
≥ 7 injections in Year 2	93 (18.1)	52 (9.8)	82 (16.4)	52 (10.2)	279 (13.6)
Re-treatment always at intervals of 8 or 12 weeks in Year 2 [a]	291 (56.7)	373 (70.5)	297 (59.5)	326 (63.8)	1286 (62.7)

[a] Includes subjects with minimum time between PRN injections of 12 weeks or longer.

Efficacy endpoint (primary endpoint for Year 1):

At week 96 results show a relevant maintenance of therapeutic effect in all treatment groups, although a slight drop off in the proportion of subjects who maintained vision is observed compared to week 52. The proportion of subjects maintaining vision was ≥90% in all treatment groups and comparable between studies. The 95% CIs for the difference in proportions between the VEGF Trap-Eye group and the RQ4 group were consistently well below the boundary of 10%. Results show the same trend when the LOCF method was repeated with the observed values only.

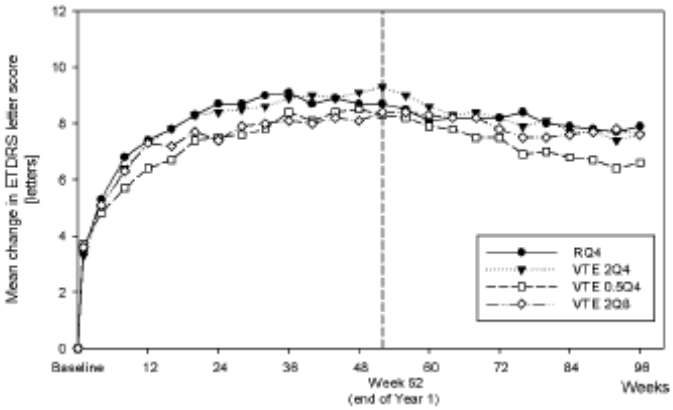
Integrated analysis: Proportion of subjects who maintained vision at Week 52 and 96 (LOCF-FAS)

Treatment Group	RQ4	2Q4	0.5Q4	2Q8
N	595	613	597	607
Subjects [n (%)] maintaining vision (W 52)	561 (94.3)	581 (94.78)	568 (95.14)	576 (94.89)
Difference (95% CI)	—	-0.5 (-3.1, 2.1)	-0.9 (-3.4, 1.7)	-0.6 (-3.2, 2.0)
Subjects [n (%)] maintaining vision (W 96)	545 (91.6)	565 (92.2)	546 (91.5)	561 (92.4)
Difference (95% CI)	—	-0.6 (-3.6, 2.5)	0.2 (-3.0, 3.3)	-0.8 (-3.8, 2.3)
p-value (Breslow-Day test		0.08	0.79	0.67

The largest differences between the two studies at week 96 were the treatment difference of the pairwise comparisons between RQ4 and 2Q4, which was numerically in favour of 2Q4 in VIEW 1 (FAS, LOCF, -3.3 [-7.7; 1.2]), but reversed in VIEW 2 (FAS, LOCF, 2.2 [-2.0; 6.5]). Therefore, the observed variability between VIEW 1 and 2 studies results at Year 1 still persists in Year 2.

Other efficacy endpoints (secondary endpoints for Year 1):

Integrated Analysis: Mean change from Baseline to Week 96 in ETDRS letter score (LOCF, FAS)



Decreases (by 1-2 letters) in mean ETDRS letter score occurred in the second year with a similar pattern in all treatment groups.

W52 mean changes in ETDRS letter score:
RQ4:8.7 (14.4); 2Q4: 9.3 (13.3); 0.5Q4: 8.3 (13.8); 2Q8: 8.4 (14.7)
W96 mean changes in ETDRS letter score:
RQ4:7.9 (16.1); 2Q4: 7.6 (15.5); 0.5Q4: 6.6 (15.3); 2Q8: 7.6 (16.2)
The mean change in visual acuity at W96 remained also similar between groups (increase of 7.6 or 7.9 letters for VTE 2mg and ranibizumab, respectively).

Integrated Analysis: Proportion of subjects who gained at least 15 letters of vision from Baseline to Week 52 and 96 (LOCF, FAS)

Treatment Group[a]	RQ4	2Q4	0.5Q4	2Q8
Integrated Analysis (N)	595	613	597	607
From Baseline to Week 52				
Subjects [n (%)] gaining at least 15 letters	193 (32.44)	205 (33.44)	178 (29.82)	188 (30.97)
Difference (95% CI)[b]	—	1.0 (-4.3, 6.3)	-2.7 (-7.9, 2.6)	-1.5 (-6.8, 3.8)
From Baseline to Week 96				
Subjects [n (%)] gaining at least 15 letters	188 (31.6)	191 (31.2)	168 (28.1)	203 (33.4)
Difference (95% CI)[b]	—	-0.4 (-5.6, 4.8)	-3.5 (-8.7, 1.7)	1.8 (-3.5, 7.1)
p-value (Breslow-Day test		0.04	0.12	0.85

Similarly, a slight decrease occurred in the second year in the proportion of patients who gained ≥ 15 letters.

Change in total NEI VFQ-25 score (0-100) from Baseline to Week 52 and 96 (LOCF, FAS):

During year 2, improvements remained in the same range for each individual studies (4-6 points) or integrated analysis (4-5 points) with nearly identical improvements in all groups.

Change in CNV area (mm^2) from Baseline to Week 52 and 96 (LOCF, FAS):

At the end of year 2, the decreases in mean CNV area observed at Year 1 (W52) were maintained in all groups but no additional improvement was reported.

Therefore, after a second year of treatment, as observed for the primary criteria, all secondary endpoints also show a similar effect for Eylea and ranibizumab, when criteria based re-dosing were applied.

Additional efficacy endpoints results at Week 96

1/Proportion of subjects with vision gain or loss:

According to the results of the integrated analysis at week 96, the proportion of subjects with *vision gains* ≥ 0 letters or ≥ 10 letters or ≥ 30 letters were maintained to approximately 75-77% or 42-51% or 5.2-7.3%. The higher proportion of subjects was observed in the 2Q8 group for gain ≥ 30 letters (7.3%) or ≥ 15 letters (33.4%) (LOCF, FAS).

The proportion of subjects with *vision loss* ≥ 5 letters or ≥ 30 letters were approximately 16-18% or 2.3-3.3% with the highest proportion in the 2Q8 group (3.3%) (LOCF, FAS).

2/Change from Baseline in central retinal thickness (FAS, LOCF):

At Week 52, the results of the pairwise comparisons were all numerically in favour of the VEGF Trap-Eye treatment. By Week 96, the absolute reduction in CRT from Baseline was also most pronounced in the 2Q8 groups (-121 ± 116 µm) compared to the RQ4 group (114 ± 110 µm) in VIEW 1 study and in the 2Q4 and 2Q8 groups (-146 ± 128 µm and 145 ± 118 µm, respectively) compared to the RQ4 group was -121 ± 130 µm. A similar trend was observed in VIEW 2.

Therefore the one year reductions were not completely maintained in all groups over the whole 2-year treatment period. The *largest increase in CRT from Week 52 to Week 96/100* was seen under RQ4 treatment (18.3 ± 76.0 µm) while the mean increase in the combined VEGF Trap-Eye 2 mg groups (2Q4 and 2Q8) was 8.2 ± 63.0 µm.

3/Proportion of subjects without intraretinal cystic edema and/or subretinal fluid (dry retina) on OCT:

In both studies, the proportions of subjects with retinal fluid increased between W52 and W96/100 by about 15-20% or 15% in VIEW 1 and VIEW 2 studies, respectively, showing that, overall, the proportion of subjects with dry retinal fluid status declined from Week 52 to Week 96. At Week 96 retinal fluid remains present in approximately 40-50% of the subjects.

Integrated Analysis: Proportion of subjects with dry retinal fluid status on OCT (W52 and 96 – OV FAS)

At W52: 2Q4, 72%; 2Q8, 68% vs RQ4, 62%

At W96/100: 2Q4, 54%; 2Q8, 50% vs RQ4, 45%

These results may suggest that the disease is progressing more during year 2. Since no fixed regimen was included as comparator arm for treatments through year 2, the link with the change in the schedule of administration (capped-PRN regimen applied in the second year) is not demonstrated.

4/Proportion of subjects receiving re-treatment within the first 12 weeks of the second year (*at Weeks 52 or 56 - subjects entering Year 2)* of the study

The proportion of subjects receiving their first re-treatment injections prior to the mandatory dose after 12 weeks in Year 2 was approximately 10% higher in the RQ4 and 0.5Q4 groups than in the VEGF Trap-Eye 2 mg groups (approximately 40% versus approximately 30%), reinforcing the choice of the 2 mg VTE dosing.

Post hoc dosing subgroup analysis (observed values; Year 2 study completers)

Additional analyses were performed on post-hoc determined dosing subgroups in the group of Year 2 study medication completers with regard to BCVA (changes in ETDRS letter score) and OCT data (changes in CRT and retinal fluid status): i) Subjects with ≤ 3 injections in Year 2; ii) Subjects with 4-6 injections in Year 2; iii) Subjects with ≥ 7 injections in Year 2; iv) Subjects with re-treatment always in the interval of 8 or 12 weeks in Year 2 (this subgroups was considered only in the integrated analysis).

In these dosing subgroups, as observed in the whole population, increases in BCVA from baseline to W96/100 are still observed ranging from 5.5 (2Q4; ≥7 injections) to 10.3 letters (RQ4; 4-6 injections). Although no meaningful differences between groups were identified, numeric BCVA values suggest that subjects receiving ≤ 3 injections or re-treatment every 8 or 12 weeks, in Year 2, may undergo meaningful improvements in vision with less re-treatments than the other dosing groups. The percentage of patients receiving re-treatment every 8 or 12 weeks in Year 2 was > 58%.

Vision gain and loss show a similar picture with more than 70% of patients gaining ≥ 0 letters, approximately 35-60% of patients gaining ≥ 10 letters and 25-40% of patients gaining ≥ 15 letters. Overall, visual gains seem to numerically favoured the 2Q8 regimen (year 1), except for the dosing group 4-6 injections that show numeric gains favouring RQ4 (83%, 60%, 38 %) vs the VEGF trap eye regimens (<76%; 51%; 35%). Less than 9% of subjects underwent vision gain ≥ 30 letters (except for 2Q8, ≥7 injections that reached 15%). Less than 4% of subjects underwent vision loss ≥ 30 letters in all groups.

Changes in CRT: in all treatment groups, subjects who received ≤ 3 injections in Year 2 and subjects who received re-treatment every 8 or 12 weeks in Year 2 had the largest decreases in mean CRT during the study (130-151 microns and 124-147microns, respectively). In both dosing subgroups, the highest decreases in CRT were observed in the 2Q8 treatment groups.

Changes in retinal fluid status: new or persistent fluid as indicated by OCT was the most frequent reason for retreatment (i.e. in approximately 50% of cases). Similarly to what observed for CRT changes, the subgroups of subjects who received ≤ 3 injections in Year 2 and those who received re-treatment always every 8 or 12 weeks in Year 2 also included the highest proportions of subjects without detectable retinal fluid.

Results on dosing subgroups are not surprising since these results may also reflect a more aggressive progression of the disease for these patients who need more frequent re-treatments, independently of the effect of the drug. Therefore, these results should be interpreted with caution.

Clinical studies in special populations

No special populations were formally studied. In the two pivotal studies and the integrated analysis, a number of subgroups were considered for efficacy and safety analyses based on demographics (eg, age, sex, race ..) and baseline disease characteristics (eg, visual acuity, lesion type, lesion size).

The only prognostic factor identified for maintaining vision was "age".

Differences between subgroups were not subjected to formal statistical testing. Overall, no clear tendency was identified among these analyses and no consistent pattern of clinically relevant differences compared to the analyses of the overall population was observed.

Supportive study(ies)

No formal supportive studies were performed.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The design and the conduct of clinical studies submitted for Eylea were in line with the requirement of the scientific advices which were sought by the Applicant and the historical development of previous AMD treatments.

A non-inferiority design with respect to prevention of moderate vision loss (loss < 15 letters of vision on ETDRS chart compared to baseline) versus monthly IVT injection of ranibizumab (Lucentis) was considered appropriate. The primary criterion selected allowed comparing identical study endpoints for VEGF Trap-Eye and ranibizumab since a similar criterion was used in both pivotal trials conducted with ranibizumab for European and US registrations (i.e. Marina and Anchor studies). In addition, this permitted also to compare data to the two other drugs registered in Europe (Macugen and Visudyne) to treat wet AMD. This criterion was also, according to the two pivotal placebo-controlled trials BPD OCR 002 A and B, the historical endpoint which was used for the first medication registered in Europe and the US to treat neovascular AMD (i.e. PDT with verteporfin (Visudyne).

However, this historical endpoint is based on a large vision loss (<15 letters) which doesn't anymore reflect the current expectations of practitioners. From a practitioners' view, a more stringent primary outcome would be the mean change from baseline in visual acuity at 1 year, with a suitable non-inferiority margin chosen and justified by the applicant.

Therefore, importantly, the Applicant integrated as first secondary criteria, the "Mean change from baseline in BCVA" as measured by ETDRS letter score, at Week 52. This criterion was used also as a basis for the first conditional ordered superiority analyses. The second important secondary criteria was the "proportion of subjects who gained ≥ 15 letters of vision" from baseline, at Week 52. Otherwise, "gain ≥ 30 letters or degradation ≥ 30 letters" in visual acuity were additional endpoints of importance.

The complete panel of examinations related to visual acuity or to the morphologic aspect of CNV lesions explored correlates well with the current clinical practice and the procedures used were relevant. The ETDRS procedure is a reliable method for BCVA measurement since it is well standardized (e.g. room lightening, optotype distance (4 meters)…) and was used in previous studies. In addition to the gold standard -fluorescein angiography examination- optical coherence tomography (OCT) is a standard practice of eye specialists to follow the progression of wet AMD and adapt the management of patients' care in case of retinal diseases.

The investigated population and the control treatment in the pivotal studies VIEW 1 and VIEW 2 were appropriate as well as the large number of patients exposed and the endpoints explored.

All deficiencies concerning the protocol or the choice or the management of statistics as identified during the early review of the one year results have been clarified and resolved by the Applicant. In the pivotal studies, the statistical methods used an acceptable ordered sequence of conditional tests. While the use of a non-inferiority design was appropriate, the chosen non-inferiority margin of 10% could have been considered too wide: however the final results were reassuring in showing observed non inferiority margins well below 10%.

The baseline characteristics of subjects in VIEW 2 suggested a slightly more severe disease at the beginning of the study than those in VIEW 1, which was accepted since the severity of disease in participants of both studies falls within the expected clinical scope of untreated AMD. This disparity between VIEW 1 and 2 was attributed by the MAA partly to differences in the methodology used for interpretation of the OCT images by the central reading centres in the assessment of CRT on OCT (readers used in VIEW 1 study a center-point thickness measurement while in VIEW 2, they used a central subfield approach). These appeared to have affected the results, but a reanalysis of VIEW 1 data by the applicant using the methodology utilised in VIEW 2 showed that the results were comparable when analysed with the same methodology.

Both studies demonstrated non-inferiority of Eylea 2Q8 versus ranibizumab, and it was accepted that differences in the baseline characteristics of subjects in the two studies did not preclude an integrated analysis of the results.

Efficacy data and additional analyses

One year results:
One year results from both pivotal studies supported a clinically relevant non-inferiority of all dosages and regimens of VEGF Trap-Eye over ranibizumab, administered monthly. The results were convincing in terms of preservation of visual acuity. Both trials were successful with regard to the primary endpoint using a non-inferiority margin of either 10% or 7%. 95-96% of subjects who received 2 mg VEGF Trap-Eye every 8 weeks maintained vision at Week 52, as compared to 94% of subjects who received ranibizumab.

The applicant provided a short discussion about the variability of results for the primary endpoint across the two pivotal studies, particularly when the most conservative analysis was considered (with all drop-outs counted as non-responders using the full analysis set) and has clarified that inconsistencies observed in the results of the sensitivity analysis in the FAS, counting drop-outs as non-responders, especially in the comparison of the 2Q4 dosing regimen of VEGF and ranibizumab,

are explained by the different drop-out rates of the 2Q4 VEGF Trap-Eye groups and ranibizumab groups between the studies. This was accepted by CHMP.

The clinically relevant result for the primary endpoint was backed up by secondary endpoints, which showed that subjects receiving VEGF Trap-Eye gained an average of 8-9 letters at Week 52, with 30-31% of subjects gaining at least 3 lines of vision. These results were comparable to those for subjects in the active comparator group who received ranibizumab. Visual function questionnaire test scores improved by 5 points for those on VEGF Trap-Eye, and CNV area was reduced by 3-5 mm^2, again comparable to ranibizumab.

The results of ancillary efficacy endpoints were generally supportive of the primary and secondary endpoints, showing comparable efficacy for VEGF Trap-Eye 2Q8, 2Q4 and 0.5Q4 with ranibizumab. The distribution of subjects with varying levels of vision loss and gain were comparable across groups and studies. In the VIEW studies a slightly greater proportion of Eylea 2Q8 subjects experienced a loss of vision from baseline in the first year than those treated with ranibizumab. However, this difference seemed to disappear in Year 2, when PRN treatment was initiated. The difference seen in Year 1 was small (around 4 percentage points at most), and was not considered relevant.

Two year results:
Since neovascular AMD is a chronic disease which requires ongoing treatment, the Year 1 results needed to be confirmed at two years.

The proportion of subjects maintaining vision were ≥ 90% in all treatment groups and was comparable between individual studies, although a slight drop off in the proportion of subjects who maintained vision was observed compared to week 52. Decreases (by 1-2 letters) in mean ETDRS letter score occurred in the second year with a similar picture in all treatment groups. Also, a slight decrease occurred in the second year in the proportion of patients who gained ≥ 15 letters.

Discussion on the number of injections received by patients during year two:
According to the integrated analysis of Year 2 completers, the mean number of injections was approximately similar in all treatments groups (around 4, range: 4.7 for RQ4 vs 4.1-4.2 for 2Q4 or 2Q8) with an interval of around 70 days (range: 67.9 for RQ4 vs 73.7-73.2 for 2Q4 or 2Q8), also approximately similar between groups.

About a third of subjects received at least one injection in Year 2 at an interval of one month from the previous injection. Of these, most patients received ≤ 6 injections while "4-week interval" was only an isolated event for these patients. Nevertheless, it could not be ruled out that a monthly regimen may help to stabilize vision in some patients in the long term. To elucidate this point, the CHMP requested that the applicant commit to a post authorisation study.

2.5.4. Conclusions on the clinical efficacy

The efficacy of Eylea 2 mg in the treatment of wet AMD was demonstrated over the two years data.

The primary endpoint analysis met the non-inferiority margins for all VEGF Trap-eye regimens, and all secondary endpoint analyses support the comparability of the efficacy of ranibizumab with the three VEGF Trap-Eye treatment schedules.

According to study VIEW 1 results, the 2Q4 regimen showed the best results in term of vision, with superior gain in the number of letters read at Week 52; retinal morphology evolution showed also better results with the 2Q4 regimen than with the other regimens. In the VIEW 2 study however, the 52-week numeric results favoured the 0.5Q4 regimen while the 2Q4 and 2Q8 regimens were

very similar and still non inferior to ranibizumab. Wile this result confirmed the efficacy of Eylea in the proposed indication, it left a degree of uncertainty in the selection of the most appropriate dosage regimen. This was also shown by the year 2 data: the possibility of visual improvements with less than 3 injections by year is not excluded. Some patients did require occasional injections on a monthly basis in Year 2, but it is not clear in which circumstances this would be beneficial. As there were no clear tendencies of results to favour one dosing regimen of VEGF Trap-Eye over the others, the 2Q8 regimen was chosen as it reduces the number of injections.

Therefore the CHMP concluded that for the long term (after the first 12 months of treatment), patients should continue to be treated with Eylea every 2 months and that after the first 12 months of treatment with Eylea, the treatment interval could be extended based on visual and anatomic outcomes.

The CHMP also considered that there are still uncertainties regarding the choice of dosing schedule, as it was not demonstrated whether a proactive or a reactive approach was the most beneficial. The SmPC reflects the fact that there is no requirement for monitoring between injections and there is the possibility for the patients to receive monthly injections based on clinician evaluation. The Applicant also committed to submit a clinical study aimed to compare the proactive regimen with injection every 2 months with a reactive regimen based on visual and anatomic outcomes.

The approved indication reads as follows:

The recommended dose for Eylea is 2 mg aflibercept, equivalent to 50 microlitres.

Eylea treatment is initiated with one injection per month for three consecutive doses, followed by one injection every two months. There is no requirement for monitoring between injections.

After the first 12 months of treatment with Eylea, the treatment interval may be extended based on visual and anatomic outcomes. In this case the schedule for monitoring should be determined by the treating physician and may be more frequent than the schedule of injections.

The CHMP considers the following measures necessary to address issues related to efficacy:

To perform a post-authorisation randomised study with the primary objective of comparing the standard regime of injections every 8 weeks with a reactive regimen based on visual and anatomic outcomes, based on a CHMP approved protocol.

The final clinical study report should be submitted by December 31, 2017.

The protocol will be submitted for CHMP agreement by Q1, 2013.

2.6. Clinical safety

Patient exposure

The clinical safety analysis was based on data pooled from two phase 3 studies (VIEW 1 and VIEW 2 constituting pool 1) and phase 1/2 studies (pool 2). Overall, 11 ophthalmology studies were integrated in the safety analysis, including 7 studies in the requested indication of AMD; 3 of these studies are completed (phase 1 and 2) and 4 are still on-going (2 pivotal and 2 extension studies). VEGF Trap-Eye was administered intravitrealy in 3237 patients, including 2647 patients in the requested indication.

PGR2026-00039
Biocon Ex.1065
Page 381 of 595

In pool 1 (pivotal studies), a total of 2457 subjects were distributed as follows: 609 subjects in the RQ4 group, 617 subjects in the 2Q4 group, 615 subjects in the 0.5Q4 group, and 616 subjects in the 2Q8 group. During the first year of treatment in the pool 1 studies, planned exposure to VEGF Trap-Eye in the study eye was 2 mg administered monthly (13 IVT injections, 26 mg/yr) or every 2 months (8 IVT injections, 16 mg/yr), or 0.5 mg administered monthly (13 IVT injections, 6.5 mg/yr), and planned exposure to ranibizumab was 0.5 mg administered monthly (13 IVT injections, 6.5 mg/yr). The mean number of injections administered was similar among the monthly dosing regimens (12.3 in the RQ4, 12.3 in the 2Q4, and 12.2 in the 0.5Q4 groups) and just over half of that in the 2Q8 treatment group (7.5). The total mean exposure was 6.08 mg (RQ4), 24.62 mg (2Q4), 6.08 mg (0.5Q4), and 14.93 mg (2Q8), over a mean duration of 347 to 353 day.

In pool 2, a total of 230 subjects were randomized (159 in VGFT-OD-0508, 51 in VGFT-OD-0502, and 20 in VGFT-OD-0603). A total of 102 subjects from the 3 studies in pool 2 were either randomized to receive VEGF Trap-Eye at a dose of 4 PRN (31 were from VGFT-OD-0508) or were eligible to receive 4 PRN of VEGF Trap-Eye in the extension phase of study VGFT-OD-0502. In addition in study VGFT-OD-0508, 64 subjects were randomized to receive 0.5 PRN and 64 subjects were randomized to receive 2.0 PRN during the first 12 weeks.

The mean number of injections administered to subjects in pool 2 ranged from 2.5 in the 4 mg VGFT-OD-0508 group to 3.6 in the combined 4 mg group, with an overall mean of 3.3 injections. The total mean amount of study medication received increased less than dose proportionally: 1.6 mg (0.5PRN), 6.0 mg (2PRN), 10.1 mg (4PRN) and 14.5 mg in the 4 combined PRN, and 8.1 mg in the pool 2 any dose groups.

Long-term safety data: the 2-Year data have been provided in the Response Document. From VIEW 1: of the 1217 randomized subjects, 1120 (92.0%) entered Year 2 of the study. Eighty-two (7.3%) of these 1120 subjects discontinued the study during the second year. From VIEW 2: of the 1240 randomized subjects, 1115 (89.9%) entered Year 2 of the study. Ninety (8.1%) of these 1115 subjects discontinued the study during the second year.

The long-term extension study VGFT-OD-910 was ongoing at the time of authorisation; safety data on SAEs and deaths have been provided for 202 subjects treated > 2 years; 15 subjects reported 23 SAEs; CIOMS forms have been provided. Final, complete data on this phase 3, long-term extension study will be provided post authorisation.

Adverse events

Pool 1: subjects were evaluated every 4 weeks for safety; safety assessments included ophthalmic examinations, monitoring of clinical treatment-emergent adverse events (TEAEs) (non-ocular, ocular study eye, and ocular fellow eye), and laboratory testing. Adverse event (AE) information were collected up until the termination visit or until 30 days after the last dose of study drug has been administered. Immunological response was monitored through sampling for potential development of anti-VEGF Trap antibodies. ECG and Potential nasomucosal side effects were investigated in a sub-set of subjects participating in the ENT sub-study in VIEW 2 trial only.

Overall, when safety results are pooled from the 2 pivotal studies, the rate of ocular and non-ocular TEAEs appears to be similar between VEGF Trap-Eye and comparator groups.

Overall Summary of Treatment-Emergent Adverse Events, Pool 1 (SafetyAnalysis Set)

	R 0.5 mg Q4 N=595 (100%)	VTE 2.0 mg Q4 N=613 (100%)	VTE 0.5 mg Q4 N=601 (100%)	VTE 2.0 mg Q8 N=610 (100%)	VTE total N=1824 (100%)	TOTAL N=2419 (100%)
Number (%) of subjects with:						
Any TEAE	538 (90.4%)	555 (90.5%)	535 (89.0%)	565 (92.6%)	1655 (90.7%)	2193 (90.7%)
Any non-ocular TEAE	415 (69.7%)	451 (73.6%)	437 (72.7%)	436 (71.5%)	1324 (72.6%)	1739 (71.9%)
Any study drug related TEAE	6 (1.0%)	12 (2.0%)	8 (1.3%)	11 (1.8%)	31 (1.7%)	37 (1.5%)
Any injection related TEAE	0	0	0	0	0	0
Maximum intensity for any non-ocular TEAE						
Mild	191 (32.1%)	229 (37.4%)	225 (37.4%)	217 (35.6%)	671 (36.8%)	862 (35.6%)
Moderate	174 (29.2%)	181 (29.5%)	151 (25.1%)	164 (26.9%)	496 (27.2%)	670 (27.7%)
Severe	50 (8.4%)	40 (6.5%)	59 (9.8%)	55 (9.0%)	154 (8.4%)	204 (8.4%)
Any ocular TEAE (study eye)	433 (72.8%)	419 (68.4%)	408 (67.9%)	436 (71.5%)	1263 (69.2%)	1696 (70.1%)
Any study drug related TEAE	39 (6.6%)	28 (4.6%)	34 (5.7%)	33 (5.4%)	95 (5.2%)	134 (5.5%)
Any injection related TEAE	275 (46.2%)	251 (40.9%)	241 (40.1%)	252 (41.3%)	744 (40.8%)	1019 (42.1%)
Maximum intensity for any ocular TEAE (study eye)						
Mild	280 (47.1%)	274 (44.7%)	283 (47.1%)	286 (46.9%)	843 (46.2%)	1123 (46.4%)
Moderate	134 (22.5%)	123 (20.1%)	98 (16.3%)	133 (21.8%)	354 (19.4%)	488 (20.2%)
Severe	19 (3.2%)	21 (3.4%)	27 (4.5%)	17 (2.8%)	65 (3.6%)	84 (3.5%)
Any ocular TEAE (Fellow Eye)	274 (46.1%)	261 (42.6%)	269 (44.8%)	266 (43.6%)	796 (43.6%)	1070 (44.2%)
Any study drug related TEAE	1 (0.2%)	3 (0.5%)	0	3 (0.5%)	6 (0.3%)	7 (0.3%)
Any injection related TEAE	18 (3.0%)	20 (3.3%)	12 (2.0%)	14 (2.3%)	46 (2.5%)	64 (2.6%)
Maximum intensity for any ocular TEAE (fellow eye)						
Mild	188 (31.6%)	175 (28.5%)	193 (32.1%)	174 (28.5%)	542 (29.7%)	730 (30.2%)
Moderate	71 (11.9%)	76 (12.4%)	64 (10.6%)	86 (14.1%)	226 (12.4%)	297 (12.3%)
Severe	13 (2.2%)	8 (1.3%)	10 (1.7%)	6 (1.0%)	24 (1.3%)	37 (1.5%)
Any TEAE leading to death [1,2]	7 (1.2%)	2 (0.3%)	3 (0.5%)	8 (1.3%)	13 (0.7%)	20 (0.8%)
Any TE SAE	103 (17.3%)	95 (15.5%)	97 (16.1%)	104 (17.0%)	296 (16.2%)	399 (16.5%)
Any non-ocular TE SAE	83 (13.9%)	76 (12.4%)	87 (14.5%)	89 (14.6%)	252 (13.8%)	335 (13.8%)
Any ocular TE SAE (Study Eye)	19 (3.2%)	13 (2.1%)	11 (1.8%)	12 (2.0%)	36 (2.0%)	55 (2.3%)
Any ocular TE SAE (Fellow Eye)	6 (1.0%)	9 (1.5%)	5 (0.8%)	5 (0.8%)	19 (1.0%)	25 (1.0%)
Any TEAE causing disc. of study drug	9 (1.5%)	15 (2.4%)	19 (3.2%)	13 (2.1%)	47 (2.6%)	56 (2.3%)
Any TEAE causing Disc. from the study	0	0	0	0	0	0
Any TEAE of interest	322 (54.1%)	311 (50.7%)	305 (50.7%)	315 (51.6%)	931 (51.0%)	1253 (51.8%)
Any TE SAE of interest	22 (3.7%)	22 (3.6%)	25 (4.2%)	26 (4.3%)	73 (4.0%)	95 (3.9%)
Any non-ocular TE SAE of interest	11 (1.8%)	15 (2.4%)	21 (3.5%)	18 (3.0%)	54 (3.0%)	65 (2.7%)
Any ocular TE SAE of interest (Study Eye) Any	9 (1.5%)	7 (1.1%)	5 (0.8%)	8 (1.3%)	20 (1.1%)	29 (1.2%)
ocular TE SAE of interest (Fellow Eye)	2 (0.3%)	0	2 (0.3%)	0	2 (0.1%)	4 (0.2%)

Note: This table is summarizing all subjects with treatment emergent adverse events starting post first injection
[1] SAEs resulting in death or AEs with fatal outcome.
[2] This table only includes deaths associated with fatal SAEs that began within 30 days of the last administration of study drug. A total of 26 subjects died in the 2 studies combined: 7, 5, 4, and 10 in the RQ4, 2Q4, 0.5Q4, and 2Q8 groups, respectively.

Ocular Treatment-Emergent Adverse Events (TEAEs)

In **pool 1**, 70.1% of subjects overall reported ocular TEAEs in the study eye, the frequency of which was similar across treatment groups: (72.8% [RQ4], 68.4% [2Q4], 67.9% [0.5Q4], and 71.5% [2Q8].

Ocular Treatment-Emergent Adverse Events in the Study Eye, Pool 1 (in 5% of Subjects in Any Treatment Group) (by SOC and PT) (Safety Analysis Set)

Primary system organ class Preferred term MedDRA Version 13.1	R 0.5 mg Q4 N=595 (100%)	VTE 2.0 mg Q4 N=613 (100%)	VTE 0.5 mg Q4 N=601 (100%)	VTE 2.0 mg Q8 N=610 (100%)	VTE total N=1824 (100%)	TOTAL N=2419 (100%)
Eye disorders						
Conjunctival hemorrhage	167 (28.1%)	133 (21.7%)	157 (26.1%)	161 (26.4%)	451 (24.7%)	618 (25.5%)
Eye pain	53 (8.9%)	66 (10.8%)	49 (8.2%)	43 (7.0%)	158 (8.7%)	211 (8.7%)
Macular degeneration	39 (6.6%)	43 (7.0%)	40 (6.7%)	40 (6.6%)	123 (6.7%)	162 (6.7%)
Retinal hemorrhage	48 (8.1%)	36 (5.9%)	47 (7.8%)	50 (8.2%)	133 (7.3%)	181 (7.5%)
Visual acuity reduced	40 (6.7%)	50 (8.2%)	57 (9.5%)	53 (8.7%)	160 (8.8%)	200 (8.3%)
Vitreous detachment	33 (5.5%)	44 (7.2%)	32 (5.3%)	34 (5.6%)	110 (6.0%)	143 (5.9%)
Vitreous floaters	44 (7.4%)	48 (7.8%)	30 (5.0%)	30 (4.9%)	108 (5.9%)	152 (6.3%)
Investigations						
Intraocular pressure increased	41 (6.9%)	38 (6.2%)	27 (4.5%)	30 (4.9%)	95 (5.2%)	136 (5.6%)

Note: At each level of subject summarization, a subject is counted once if the subject reported one or more events. All events reported by at least 5% of subjects are displayed.

TEAEs reported in the supportive phase 1 and phase 2 studies were consistent with those seen in the pivotal phase 3 studies. The most common ocular TEAEs occurring in the study eye for the pool 2 (non pivotal studies) any dose group were conjunctival haemorrhage (47 subjects; 23.2%), reduced VA (31 subjects; 15.3%), and increased IOP (26 subjects; 12.8%).

The 4 combined PRN group had a higher incidence than the other doses for eye pain, foreign body sensation in eyes, and lacrimation increased. The 0.5 PRN group had a higher incidence than the other doses of retinal haemorrhage and VA reduced. Otherwise, the TEAEs were reported with similar frequencies across dose groups.

Ocular Treatment-Emergent Adverse Events in the Study Eye, Pool 2 (in 5% of Subjects in Any Treatment Group) (by SOC and PT) (Safety Analysis Set)

	VGFT-OD-0508			VGFT-OD-0502 VGFT-OD-0508 VGFT-OD-0603	VGFT-OD-0502 VGFT-OD-0508 VGFT-OD-0603
Primary system organ class Preferred term MedDRA Version 13.0	**VTE 0.5 mg PRN N=62 (100%)**	**VTE 2.0 mg PRN N=60 (100%)**	**VTE 4.0 mg PRN N=30 (100%)**	**VTE 4.0 mg PRN TOTAL N=81 (100%)**	**VTE ANY DOSE TOTAL N=203 (100%)**
Eye disorders					
Blepharitis	0	3 (5.0%)	1 (3.3%)	2 (2.5%)	5 (2.5%)
Cataract cortical	0	3 (5.0%)	0	1 (1.2%)	4 (2.0%)
Cataract nuclear	2 (3.2%)	3 (5.0%)	0	1 (1.2%)	6 (3.0%)
Conjunctival hemorrhage	13 (21.0%)	16 (26.7%)	5 (16.7%)	18 (22.2%)	47 (23.2%)
Dry eye	2 (3.2%)	3 (5.0%)	0	1 (1.2%)	6 (3.0%)
Eye pain	2 (3.2%)	1 (1.7%)	1 (3.3%)	8 (9.9%)	11 (5.4%)
Foreign body sensation in eyes	1 (1.6%)	0	0	5 (6.2%)	6 (3.0%)
Lacrimation increased Photopsia	1 (1.6%)	0	1 (3.3%)	5 (6.2%)	6 (3.0%)
Punctate keratitis	1 (1.6%)	2 (3.3%)	2 (6.7%)	3 (3.7%)	6 (3.0%)
Retinal hemorrhage	0	3 (5.0%)	2 (6.7%)	2 (2.5%)	5 (2.5%)
Retinal edema	10 (16.1%)	3 (5.0%)	2 (6.7%)	3 (3.7%)	16 (7.9%)
Visual acuity reduced	4 (6.5%)	3 (5.0%)	0	1 (1.2%)	8 (3.9%)
Visual impairment	14 (22.6%)	6 (10.0%)	5 (16.7%)	11 (13.6%)	31 (15.3%)
Vitreous detachment	2 (3.2%)	0	2 (6.7%)	3 (3.7%)	5 (2.5%)
Vitreous floaters	2 (3.2%)	7 (11.7%)	0	3 (3.7%)	12 (5.9%)
General disorders and administration site conditions	4 (6.5%)	3 (5.0%)	0	3 (3.7%)	10 (4.9%)
Injections site hemorrhage	4 (6.5%)	0	0	3 (3.7%)	7 (3.4%)
Injection site pain	1 (1.6%)	1 (1.7%)	1 (3.3%)	5 (6.2%)	7 (3.4%)
Sensation of foreign vbody	0	0	1 (3.3%)	6 (7.4%)	6 (3.0%)
Investigations					
Intraocular pressure increased	9 (14.5%)	6 (10.0%)	4 (13.3%)	11 (13.6%)	26 (12.8%)

Note: At each level of subject summarization, a subject is counted once if the subject reported one or more events. All events reported by at least 5% of subjects are displayed.

In Pool 1, the number of *ocular drug-related TEAEs* was rather low (5.5% in total) and similar between treatment groups (6.6% ranibizumab vs 5.2% VTE). The most common drug-related TEAEs were vitreous floaters, visual acuity reduced and IOP increased with maximum of 1.2% of

rate. The majority of cases were sporadic with a rate < 1%. Of note, macular degeneration was observed in 11 (0.5%) patients in VEGF Trap-eye group compared to no case in ranibizumab group.

In pool 2, only 14 subjects reported *drug-related ocular treatment-emergent AEs* (6.9%) including 3% of IOP increased.

Non-ocular Treatment-Emergent Adverse Events

In Pool 1, 71.8% of subjects overall reported non-ocular TEAEs; the frequency of which was similar among treatment groups: (69.7% [RQ4], 73.4% [2Q4], 72.7% [O.5Q4], and 71.5% [2Q8].

The most common non-ocular TEAEs in pool 1 were nasopharyngitis (7.8% overall), hypertension (6.8% overall) headache (4.2% overall), bronchitis (3.9% overall), and urinary tract infection (3.6% overall]). Treatment-emergent adverse events occurred with similar frequency across all treatment groups, and were generally characteristic of patients in the age range studied.

Non-ocular TEAEs reported in pool 2 were consistent with those seen in pool 1. The most common non-ocular TEAEs observed in subjects in pool 2 were nasopharyngitis (14 subjects; 6.9%), urinary tract infection (13 subjects; 6.4%), bronchitis (11 subjects; 5.4%), and hypertension (10 subjects; 4.9%).

Cardiovascular Events:
(a) Arterial thromboembolic events (ATEs): the incidence of APTC ATEs was similar in the pivotal studies: 1.7% in ranibizumab group vs 1.8 in VEGF Trap-eye groups. In the long-term safety study (VGFT-OD-0702), 13 patients (8.3%) reported arterial thromboembolic events.

Arterial thromboembolic events, as defined by ApTC criteria, include nonfatal myocardial infarction, nonfatal stroke, or vascular death including deaths of unknown cause).

When TEAEs are analysed as TEAEs of interest in pool 1 (SOC and PT), the global rate of arterial thromboembolic events (refer to table 69 of Summary of Clinical Safety), was higher in VEGF Trap-eye groups (3.2%) when compared to the ranibizumab (1.8%) group. The CHMP listed arterial thromboembolic events as an important potential risk in the RMP and covered in section 4.8 of the SmPC.

(b) Hypertension. In pool 1, hypertension was frequently reported non-ocular TEAE, observed in 7.9% of patients in ranibizumab group and 6.5% in VEGF Trap-eye groups. In addition, hypertension has been reported in 23 (14.6%) patients in pool 2.

Taking into account the potential role of VEGF in the systemic cardiovascular events and the fact that almost 20% of drug substance goes through the systemic circulation, systemic effects of VEGF Trap-eye cannot be excluded.

2-Year Data

A similar number of subjects with any study drug-related adverse event, with any injection-related AE and any AE of interest has been reported in the study groups. However, more subjects discontinued the study due to adverse event in the VEGF Trap-Eye groups (2Q4 4.2%, 0.5Q4 6.5%, 2Q8 4.9%) compared to ranibizumab (3.5%). These AEs were in majority mild and moderate with however about 20% of severe AEs (21.7% in ranibizumab, 20.3% in VEGF Trap-Eye groups).

Table 67. Integrated analysis: Treatment-emergent adverse events during the entire study period from Baseline to Week 96/100 (SAF)

Number of subjects with:	Ranibizumab 0.5Q4 (N = 595) n (%)	VEGF Trap-Eye 2Q4 (N = 613) n (%)	VEGF Trap-Eye 0.5Q4 (N = 601) n (%)	VEGF Trap-Eye 2Q8 (N = 610) n (%)	VEGF Trap-Eye Combined (N = 1824) n (%)
Any TEAE	567 (95.3)	587 (95.8)	566 94.2)	591 (96.9)	1744 (95.6)
Any study drug-related AE	52 (8.7)	51 (8.3)	51 (8.5)	55 (9.0)	157 (8.6)
Any injection-related AE	297 (49.9)	276 (45.0)	276 (45.9)	287 (47.0)	839 (46.0)
Any AE of interest	353 (59.3)	354 (57.7)	333 (55.4)	354 (58.0)	1041 (57.1)
Any AE causing treatment discontinuation	21 (3.5)	26 (4.2)	39 (6.5)	30 (4.9)	95 (5.2)
Maximum intensity for any AE					
Missing	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (<0.1)
Mild	152 (25.5)	163 (26.6)	168 (28.0)	163 (26.7)	494 (27.1)
Moderate	286 (48.1)	313 (51.1)	266 (44.3)	299 (49.0)	878 (48.1)
Severe	129 (21.7)	111 (18.1)	131 (21.8)	129 (21.1)	371 (20.3)
Maximum intensity for any study drug related AE					
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Mild	33 (5.5)	30 (4.9)	38 (6.3)	32 (5.2)	100 (5.5)
Moderate	17 (2.9)	18 (2.9)	10 (1.7)	16 (2.6)	44 (2.4)
Severe	2 (0.3)	3 (0.5)	3 (0.5)	7 (1.1)	13 (0.7)
Any Death	15 (2.5)	12 (2.0)	16 (2.7)	18 (3.0)	46 (2.5)
Any SAE	170 (28.6)	158 (25.8)	168 (28.0)	177 (29.0)	503 (27.6)
Any study drug related SAE	3 (0.5)	7 (1.1)	1 (0.2)	7 (1.1)	15 (0.8)
Any injection related SAE	12 (2.0)	8 (1.3)	3 (0.5)	3 (0.5)	14 (0.8)
Any SAE of interest	40 (6.7)	34 (5.5)	34 (5.7)	42 (6.9)	110 (6.0)
Any SAE causing Discontinuation of study drug	18 (3.0)	19 (3.1)	30 (5.0)	26 (4.3)	75 (4.1)

Source: Annex 3, Post-text table 14.3.1/3a

Table 70. Integrated analysis: Ocular TEAEs in the study eye occurring in ≥5.0% of the subjects at preferred term level in any treatment group during the entire study period from Baseline to Week 96/100 (SAF)

MedDRA preferred term	Ranibizumab 0.5Q4 (N = 595) n (%)	VEGF Trap-Eye 2Q4 (N = 613) n (%)	VEGF Trap-Eye 0.5Q4 (N = 601) n (%)	VEGF Trap-Eye 2Q8 (N = 610) n (%)	VEGF Trap-Eye Combined (N = 1824) n (%)
Any ocular TEAE (study eye)	486 (81.7)	475 (77.5)	467 (77.7)	483 (79.2)	1425 (78.1)
Conjunctival haemorrhage	178 (29.9)	145 (23.7)	171 (28.5)	171 (28.0)	487 (26.7)
Retinal haemorrhage	85 (14.3)	85 (13.9)	82 (13.6)	99 (16.2)	266 (14.6)
Visual acuity reduced	67 (11.3)	76 (12.4)	76 (12.6)	79 (13.0)	231 (12.7)
Eye pain	62 (10.4)	74 (12.1)	60 (10.0)	54 (8.9)	188 (10.3)
Macular degeneration	49 (8.2)	54 (8.8)	52 (8.7)	57 (9.3)	163 (8.9)
Vitreous detachment	48 (8.1)	61 (10.0)	46 (7.7)	47 (7.7)	154 (8.4)
Cataract	37 (6.2)	53 (8.6)	51 (8.5)	40 (6.6)	144 (7.9)
Vitreous floaters	58 (9.7)	59 (9.6)	40 (6.7)	39 (6.4)	138 (7.6)
Intraocular pressure increased	64 (10.8)	48 (7.8)	37 (6.2)	47 (7.7)	132 (7.2)
Retinal oedema	23 (3.9)	21 (3.4)	27 (4.5)	42 (6.9)	90 (4.9)
Retinal degeneration	27 (4.5)	32 (5.2)	26 (4.3)	23 (3.8)	81 (4.4)
Maculopathy	32 (5.4)	23 (3.8)	37 (6.2)	19 (3.1)	79 (4.3)
Ocular hyperaemia	31 (5.2)	24 (3.9)	23 (3.8)	14 (2.3)	61 (3.3)

Note: Preferred terms are sorted in descending order by frequency in the VEGF Trap-Eye combined group.
Source: Annex 3, post-text table 14.3.1/5a

With regards to ocular AEs, a similar number of events has been reported between the study groups. Conjunctival haemorrhage, retinal haemorrhage, visual acuity reduced and eye pain were very frequently reported in all groups. There were some slight differences between the recommended dose group (2Q8) and the comparator ranibizumab group in the rate of retinal

haemorrhage (16.2% vs 14.3%), visual acuity reduced (13% vs 11.3%) and eye pain (8.9% vs 10.4%).

Few of ocular AEs were considered as related to study treatment, 7.4% in ranibizumab group vs 6.7% in the VEGF Trap-Eye groups and the differences in the percentage are not significant.

The incidence of injection-related TEAEs was significantly higher in VIEW 1 when compared to VIEW 2 study. The applicant explained that this was due to the mode of peri-procedural anaesthesia that was different between the two studies.

Serious adverse event/deaths/other significant events

Severe ocular TEAEs

Pool 1: the number of severe ocular TEAEs is low and similar between the treated groups. However, more eye disorders were reported in VEGF Trap-eye groups (3%) compared to ranibizumab group (2%).

Endophtalmitis was reported in 0.5% of patients in ranibizumab and 2Q4 group, as well as IOP increased, retinal haemorrhage and conjunctival haemorrhage. Three cases of cataract were reported in VEGF Trap-eye groups and none in ranibizumab group. Severe eye pain occurred more frequently in VEGF treated groups (0.5%) compared to comparator group (0.3%).

Pool 2: Only 2 subjects reported severe ocular TEAEs in the study eye: in study VGFT-OD-0508, 1 subject in the 0.5 PRN group had severe uveitis and 1 subject in the combined 4 PRN group had severe retinal vascular disorder.

Severe non-ocular TEAEs

Pool 1: 204 (8.4%) subjects experienced severe non-ocular TEAEs: 50 (8.4%) subjects in the RQ4 group, 40 (6.5%) subjects in the 2Q4 group, 59 (9.8%) subjects in the 0.5Q4 group, and 55 (9.0%) subjects in the 2Q8 group. The percentage of subjects in each treatment group reporting severe non-ocular TEAEs was similar across the treatment groups.

The most common severe non-ocular TEAEs was myocardial infarction, and this occurred in 0.5% (12/2419) of subjects, overall. All other severe non-ocular TEAEs occurred in 0.3% of subjects.

One case of transient ischemic attack (TIA) was considered to be related to study drug in the 2Q4 group. In total, TIA was observed in 10 patients treated with VEGF Trap-eye while no cases occurred in comparator group.

Pool 2*:* Severe non-ocular TEAEs were reported in 7.4% (15) of subjects.The most commonly reported severe non-ocular TEAE was congestive cardiac failure (in 2 subjects; 1%). All other severe non-ocular TEAEs occurred in only 1 subject each.

Deaths. A total of 26 subjects died in Pool 1 during year 1 (7 subjects in the RQ4 group, 5 subjects in the 2Q4 group, 4 subjects in the 0.5Q4 group, and 10 subjects in the 2Q8 group) (cut-off date of 10 November 2010). None of the deaths was considered related to study drug.

The reported causes of death were consistent with what would be expected in the elderly population with AMD: cardiac disorders (cardiac arrest, myocardial infarction, cardiopulmonary failure), neoplasm (hepatic neoplasm malignant, leukaemia, lung cancer), cerebral haemorrhage.

Most cases of death occurred in the 2Q8 group (10). Slightly more deaths have been reported in 2Q8 group (1.5%) when compared to 2Q4 (0.7%) and 0.5Q4 (0.5%) groups during the

development programme. As cause of death, 2 cases of vascular disorders were observed in 2Q8 group, and none in other groups.

A total of 2 subjects died in Pool 2. One subject (in the 4 combined PRN group) with a pre-existing condition of pulmonary hypertension died 85 days after the last dose of study drug due to cardiac arrest. The other subject (in the 2PRN group) died due to pancreatic carcinoma diagnosed 112 days after receiving the last dose of study drug.

Long-term study (VGFT-OD-0702): 8 subjects died during the period from baseline of this study to the cut-off date. Two of the deaths occurred after the subjects had completed the initial study but before they had received study treatment in the long-term safety study.

A total of 3 deaths were reported during the first 6 months of **VGFT-OD-0706**, 1 subject each in the 0.5Q4 (multi-organ failure), 2Q4 (sudden death), and 2Q8 (convulsion) groups. None of the events that led to death in these subjects were judged by the investigator to be related to study drug.

2-Year Data

Deaths. Full 2-year data showed a total of 68 deaths (2.8%) reported in the 2 studies, including 20 deaths (3.3%) in 2Q8, 19 (3.2%), 13 (2.1%) and 16 (2.7%) in ranibizumab group. The trend in difference in number of deaths was not confirmed during the second year of treatment. Also, the total number in Eylea groups is comparable with the ranibizumab group.

Ocular serious TEAEs. In the integrated analysis, 91 study subjects (3.8%) were documented to have ocular SAEs in the study eye by the end of Year 2. As seen in the single studies, many of these events were likely procedure-related or AMD-related, with "visual acuity reduced" (19 study pool subjects [0.8%]), "retinal hemorrhage" (17 study pool subjects [0.7%])), and "cataract" (12 study pool subjects [0.5%]) being the prevailing events.

Five cases of endophtalmitis, including one case of pseudoendophtalmitis have been reported, 4 in VIEW 1 and one in VIEW 2 study. Two cases have been observed in the VEGF Trap-Eye groups (0.5Q4 and 2Q4) and 3 cases in ranibizumab group. All cases of endophtalmitis were considered related to the study drug procedure. This event is covered in sections 4.4. and 4.8. of the SmPC and is mentioned as an important identified risk in the RMP.

Non-ocular serious TEAEs. Non-ocular, drug-related treatment-emergent SAEs occurred at a higher frequency in Eylea-treated subjects, though the absolute numbers were low; 7 cerebrovascular events (0.8%) in Eylea-treated subjects (mostly in VIEW 2), none in ranibizumab-treated subjects. Furthermore, a higher frequency of TIAs was detected in Eylea-treated subjects in VIEW 1 than for ranibizumab: 18 events (2%) versus 1 (0.3%). This trend was not observed in VIEW 2, nor is a trend observed when arterial thromboembolic events are analysed according to the APTC criteria.

Laboratory findings

Chemistry

The incidences of pre-defined laboratory abnormalities were low and balanced among treatment groups for all clinical chemistry test parameters.

Hypercholesterolaemia was reported as a TEAE in 34 (1.4%) subjects in pool 1 during the first year of the studies (RQ4 1.3%; 2Q4 1.0%; 0.5Q4 1.5%; 2Q8 1.8%) and in 51 (2.1%) subjects in the 2nd year of treatment (RQ4 2.2%; 2Q4 1.5%; 0.5Q4 2.0%; 2Q8 2.8%). The occurrence of hypercholesterolemia is expected in this elderly population and its rate remains low.

PGR2026-00039
Biocon Ex.1065
Page 388 of 595

No safety signal emerged from haematology and vital signs data.

The majority of the treated subjects (1371 and 131 subjects, respectively), had a medical history of hypertension. Blood pressure changes were presented as the mean and median values, showing no apparent trend over time in pool 1 and 2. No increases in SBP and DBP have been observed in the sub-group of patients with medical history of hypertension up to 2 years of treatment. However, according to the results of the PK studies, there is a possibility that aflibercept might increase blood pressure. As part of the pharmacovigilance activities, it is requested that the post-marketing and study reports which indicate hypertension should be followed up with a targeted questionnaire.

Safety in special populations

Intrinsic Factors

Subgroup analyses were conducted on the following safety variables for subjects in pool 1: gender; age (< 65 years, ≥ 65 years to < 75 years, ≥ 75 years); race (white, black or African American, Asian, American Indian or Alaska native, Native Hawaiian or other Pacific Islander, or other); ethnicity (Hispanic or Latino [no / yes]); renal status (CLCR > 80 mL/min [normal], > 50 – 80 mL/min [mild impairment], > 30 - 50 mL/min [moderate impairment], 2 30 mL/min or requiring dialysis [severe impairment]), history of diabetes mellitus, cataracts, hypertension, CVA/stroke, and myocardial infarction.

The number of subjects in the following subgroups within pool 1 were too small to allow meaningful comparisons: race (other); renal impairment (severe impairment); hepatic impairment, and proteinuria; although there were few subjects in the subgroup of CVA/stroke, analyses were conducted as this is an adverse event of interest.

Overall, the results of the subgroup analyses of all TEAEs were similar to those seen in the entire study population. No clinically relevant imbalances or trends were seen among the treatment groups.

Extrinsic Factors

Pre-filled syringes vs. Vials

Although there where differences in the incidence of events comparing the vial to the PFS group, they appeared random and a pattern was not discerned between the 2 groups.

Pregnancy, Lactation and Fertility

Aflibercept produced embryo-foetal toxicity in rabbit and effects on male and female fertility in monkey after intravenous administration. However, there are large safety margins when compared to corresponding values observed in humans after an intravitreal therapeutic dose. Therefore, systemic effects are unlikely in patients, including pregnant women. In addition, exposure of a woman of childbearing potential to Aflibercept seems to be unlikely given the indication.

It is noted that products of the same therapeutic class are already marketed (Lucentis® and Macugen®), whose SmPCs indicate they should not be used during pregnancy unless there is a clear benefit. Similar recommendations regarding pregnancy, fertility and lactation were inserted in the Product Information.

Overdose

In clinical studies with VEGF Trap-Eye, isolated cases of overdose of up to 10-fold were generally well tolerated. One subject received a single dose of 20 mg VGFT Trap-Eye in 500 µL

volume (instead of the planned 2 mg in 50 µL), which was associated with increased injection volume and subsequently with a transient increase in IOP lasting 1 day. No other TEAE were observed. As of January 2011, all overdosed subjects recovered without sequelae.

The concentration of bound VEGF Trap in plasma following IVT administration of up to 4 mg/eye was about 20-fold lower than those following IV administration of 1 to 4 mg/kg. Since IV administration of VEGF Trap at doses ≥1 mg/kg every 2 weeks was required to completely saturate endogenous VEGF synthesized over the dosing interval, the IVT doses being investigated in this development programme did not appear to be able to saturate systemic VEGF. This conclusion is supported by the observation that the peak concentration of bound VEGF Trap continued to increase in a dose-dependent manner with increasing IVT doses.

Recommended treatment: overdoses of up to 20 mg/eye were generally well tolerated. Overdosing was associated with increased injection volume and subsequently with increased IOP. Therefore, when overdose is associated with increased volume, IOP should be monitored and if deemed necessary by the treating physician, adequate treatment should be initiated.

Drug Abuse

VEGF Trap-Eye will be administered by a qualified physician. The drug will not be prescribed for self-administration In addition, the method of VEGF Trap-Eye administration, IVT injection, is not conductive to drug abuse.

There has been no evidence of psychotropic properties associated with the study drug. Post-intraocular-injection, VEGF-Trap binds with VEGF-A to form a complex. As a protein molecule, VEGF-Trap and its complex are too large to cross the blood-brain barrier, which limits any possibility for centrally-mediated effects associated with drug abuse.

Withdrawal and Rebound

Age-related macular degeneration requires lifelong treatment. Cessation of treatment with VEGF Trap-Eye does not mean that the disease will not recur; VA may again decline over time, consistent with the disease process. There is a large variability in patient presentation, course of treatment, and need for re-treatment in cases of wet AMD.

Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

VEGF Trap-Eye is an ophthalmologic preparation intended to treat visually impaired patients. Subjects may experience temporary visual disturbances after an IVT injection with VEGF Trap- Eye and the associated eye examinations. As a result, they should not drive or use machinery until visual function has sufficiently recovered.

Elderly population

Table 3: Number of subjects with non-ocular treatment-emergent adverse event in the elderly population grouped by age (Year 1 data) - Amended

Age Group	< 65 years		≥ 65 – < 75 years		≥ 75 – < 85 years		≥ 85 years	
	Ranibizumab N=71 (100%)	VEGF Trap-Eye (Total) N=202 (100%)	Ranibizumab N=163 (100%)	VEGF Trap-Eye (Total) N=478 (100%)	Ranibizumab (N=274 (100%)	VEGF Trap-Eye (Total) N=861 (100%)	Ranibizumab N=87 (100%)	VEGF Trap-Eye (Total) N=283 (100%)
Any non-ocular TEAEs	**43 (60.6%)**	**144 (71.3%)**	**105 (64.4%)**	**335 (70.1%)**	**200 (73.0%)**	**623 (72.4%)**	**67 (77.0%)**	**222 (78.4%)**
Fatal (ie, deaths)	0	0	1 (0.6%)	1 (0.2%)	3 (1.1%)	5 (0.6%)	3 (3.4%)	7 (2.5%)
Serious	1 (1.4%)	15 (7.4%)	19 (11.7%)	48 (10.0%)	44 (16.1%)	117 (13.6%)	19 (21.8%)	72 (25.4%)
Withdrawals or discontinuations	0	4 (2.0%)	1 (0.6%)	6 (1.3%)	3 (1.1%)	14 (1.6%)	1 (1.1%)	9 (3.2%)
Any non-ocular TEAEs by AE grouping								
CNS (confusion/extrapyramidal)	1 (1.4%)	5 (2.5%)	6 (3.7%)	3 (0.6%)	5 (1.8%)	14 (1.6%)	1 (1.1%)	10 (3.5%)
AE related to falling	0	2 (1.0%)	5 (3.1%)	4 (0.8%)	16 (5.8%)	24 (2.8%)	5 (5.7%)	25 (8.8%)
Cardiovascular events	0	6 (3.0%)	1 (0.6%)	12 (2.5%)	11 (4.0%)	26 (3.0%)	8 (9.2%)	8 (2.8%)
Cerebrovascular events	0	0	0	5 (1.0%)	1 (0.4%)	10 (1.2%)	1 (1.1%)	20 (7.1%)
Infections and Infestations	23 (32.4%)	49 (24.3%)	54 (33.1%)	140 (29.3%)	96 (35.0%)	239 (27.8%)	27 (31.0%)	86 (30.4%)

Table 7: Number of subjects with non-ocular treatment-emergent adverse event in the elderly population grouped by age (2 Year data)

Age Group	< 65 years		≥ 65 – < 75 years		≥ 75 – < 85 years		≥ 85 years	
	Ranibizumab N= 71 (100%)	VEGF Trap-Eye (Total) N=202(100%)	Ranibizumab N= 163(100%)	VEGF Trap-Eye (Total) N= 478 (100%)	Ranibizumab (N= 274 (100%)	VEGF Trap-Eye (Total) N= 861(100%)	Ranibizumab N= 87 (100%)	VEGF Trap-Eye (Total) N= 283 (100%)
Any non-ocular TEAEs	**51 (71.8%)**	**166 (82.2%)**	**129 (79.1%)**	**393 (82.2%)**	**235 (85.8%)**	**732 (85.0%)**	**79 (90.8%)**	**251 (88.7%)**
Fatal ie, deaths	0	1 (0.5%)	2 (1.2%)	8 (1.7%)	6 (2.2%)	20 (2.3%)	7 (8.0%)	17 (6.0%)
Serious	5 (7.0%)	21 (10.4%)	29 (17.8%)	83 (17.4%)	80 (29.2%)	221 (25.7%)	32 (36.8%)	112 (39.6%)
Withdrawals or discontinuations	0	5 (2.5%)	2 (1.2%)	11 (2.3%)	7 (2.6%)	32 (3.7%)	4 (4.6%)	25 (8.8%)
Any non-ocular TEAEs by AE grouping								
CNS (confusion/extrapyramidal)	2 (2.8%)	8 (4.0%)	9 (5.5%)	8 (1.7%)	9 (3.3%)	26 (3.0%)	2 (2.3%)	15 (5.3%)
AE related to falling	0	6 (3.0%)	6 (3.7%)	8 (1.7%)	24 (8.8%)	49 (5.7%)	9 (10.3%)	47 (16.6%)
Cardiovascular events	3 (4.2%)	6 (3.0%)	8 (4.9%)	21 (4.4%)	18 (6.6%)	41 (4.8%)	9 (10.3%)	21 (7.4%)
Cerebrovascular events	0	2 (1.0%)	0	6 (1.3%)	9 (3.3%)	20 (2.3%)	3 (3.4%)	27 (9.5%)
Infections and Infestations	28 (39.4%)	63 (31.2%)	70 (42.9%)	182 (38.1%)	134 (48.9%)	360 (41.8%)	40 (46.0%)	123 (43.5%)
APTC events	1 (1.4%)	2 (1.0%)	2 (1.2%)	11 (2.3%)	11 (4.0%)	24 (2.8%)	5 (5.7%)	23 (8.1%)

Several tables on number of subjects with TEAEs, ocular TEAEs and non-ocular TEAEs in the elderly population grouped by age and including year 1 and 2-year data have been provided by the applicant.

No deaths related to ocular TEAEs have been reported in the elderly during 2 years. The rate of deaths from non-ocular TEAEs was comparable between the treatment groups during the first and the second year of treatment and increased with age.

Ocular TEAEs were related to the infections; in addition, 3 cases of blepharospasm have been observed in the VEGF Trap-Eye groups.

The number of cerebrovascular events was higher in the VEGF Trap-Eye groups (35) compared with ranibizumab (2 cases) in elderly, especially in the sub-group ≥ 85 years (20 vs 1 case), during the first year of treatment. Two-year data showed also the increased number of cerebrovascular events in the VEGF Trap-Eye groups vs ranibizumab: 53 vs 12 (27 vs 3 in the sub-group ≥ 85 years). One death due to CVA in the 0.5Q4 group and one death due to ischemic stroke in the 2Q8 group were considered as treatment related.

Immunological events

As with all therapeutic proteins, there is a potential to develop immunogenicity towards VEGF Trap-Eye, and this is mentioned in section 4.4 of the SmPC. In order to monitor subjects for the potential appearance of anti-VEGF Trap antibodies, serum samples were collected at study-specific time points during each of the VEGF Trap clinical studies and examined for the presence of ADA (Anti-drug antibodies).

The resulting immunogenicity data reflects the percentage of subjects whose test results were considered positive for ADA in immunoassays and are highly dependent on the sensitivity and specificity of the assays. Early studies (pool 2) used a validated, direct ADA enzyme-linked immunosorbent assay (ELISA) to assess immunogenicity; no samples from these studies were confirmed positive for ADA. For the phase 3 studies (VIEW 1 and 2), a validated, titer-based, bridging ADA immunoassay, which is approximately 40-fold more sensitive than the original ADA ELISA, was used to assess immunogenicity. In these phase 3 studies the pre-treatment incidence of immunoreactivity to VEGF Trap-Eye was 1% to 3% across treatment groups. After dosing with VEGF Trap-Eye for 52 weeks, treatment-emergent positive responses in the assay were detected in a similar percentage range of subjects across treatment groups.

The observed low level of positive assay responses in subjects treated with ranibizumab was similar to the levels in subjects treated with VEGF Trap-Eye, suggesting that a majority of these positive assay responses may be due to pre-existing immunoreactivity in these subjects and, therefore, not due to an immune response to VEGF Trap-Eye.

The tables on proportion of subjects with maintained vision at week 52 and week 96 by negative or positive ADA results have been provided. These 2-year data showed that the majority of subjects with positive ADA results maintained their vision.

However, the analysis was based on the small number of subjects having positive ADA, especially during the first year of treatment (41 subjects in VIEW 1 and 38 in VIEW 2). At week 96, 86 subjects had positive ADA and the majority maintained the vision status (87% to 100%).

Safety related to drug-drug interactions and other interactions

No formal drug interaction studies have been performed with VEGF-Trap Eye.

Individuals with AMD are generally older and often have concomitant diseases that are characteristic of an older population. Study subjects in the VEGF Trap-Eye clinical development programme had a mean age of 76.0 years and a medical history characteristic of individuals in the target AMD population.The mean age of the population in the VEGF Trap-Eye clinical development programme is similar to that found in the MARINA study range = 52 – 95 years) (Rosenfeld 2006) and in the ANCHOR study (age=76.0, range = 53-97) (Brown 2006).

Concomitant topical medications (topical anesthetic and antibiotic) given during the injection of VEGF Trap-Eye do not penetrate the sclera and are not expected to interact with Eylea.

Free VEGF Trap binds VEGF to form a stable, inert complex. As with other large proteins, both free and bound VEGF are expected to be cleared by proteolytic catabolism. Hepatic and renal impairment do not impact clearance of the drug, nor does VEGF Trap-Eye interfere with drugs metabolized through the hepatic and renal systems.

Discontinuation due to adverse events

A total of 212 (8.6%) subjects discontinued from their study within the first year; the most common reason for discontinuation was withdrawal by subject (84 subjects [3.4%]). A total of 255 (10.4%) subjects prematurely discontinued the study medication within the first year; the most common reason was "withdrawal by subject" (94 [3.8%]).

Adverse events leading to withdrawal were generally consistent with events associated with disease progression or with the expected consequences of the IVT injection procedure, and were characteristic of AEs observed in the overall AMD subject population.

In **pool 1**, the most common TEAEs leading to withdrawal were retinal haemorrhage, reduced VA, retinal detachment, CVA, angina pectoris, and myocardial infarction, and were similar among the treatment groups.

In **pool 2**, the TEAEs leading to withdrawal were retinal detachment, abscess in a limb, osteomyelitis, sinusitis, constipation, colon cancer, and cutis laxa.

The AEs leading to withdrawal in the long-term safety study **VGFT-OD-0702** were comparable with those reported in pools 1 and 2 (macular degeneration, reduced VA, and metastatic non-small cell lung cancer). None of the AEs that led to permanent withdrawal of study drug was judged by the investigator to be related to study drug.

The incidence of TEAEs leading to premature treatment discontinuation in the integrated analysis over the entire study period of 2 years (116 [4.8%] of the 2419 study subjects) was 3.5% in the RQ4 group, 4.2% in the 2Q4 group, 6.5% in the 0.5Q4 group, 4.9% in the 2Q8 group, and 5.2% in the VEGF Trap-Eye combined group. Thus, the rate of subjects discontinuing treatment because of AEs over 2 years in the integrated analysis was slightly higher with VEGF Trap-Eye than on treatment with ranibizumab. However, the overall discontinuation rate and discontinuations due to an AE remain low in all study groups.

Post marketing experience

Not applicable

2.6.1. Discussion on clinical safety

The exposure and safety database size are considered sufficient to allow the safety evaluation.

The safety assessment conducted by the applicant in the 2 pivotal studies is appropriate. When safety results are pooled from these studies, the rate of ocular and non-ocular TEAEs seems similar between VEGF Trap-Eye and comparator groups.

In term of ocular TEAEs, the rate of conjunctival hemorrhage, vitreous floaters and IOP increase was slightly higher in the comparator group in pool 1, while Visual acuity was more reduced in VEGF Trap Eye groups. The number of severe ocular TEAEs is low and similar between the treated groups in pool 1. Three cases of cataract were reported in VEGF Trap-eye groups and none in ranibizumab group.

Five cases of endophtalmitis, 2 for VEGF Trap-Eye and 3 for ranibizumab, have been observed. All were considered related to the study drug. This event is covered by sections 4.4. and 4.8. of the SmPC and is mentioned as an important identified risk in the RMP.

For vascular disorders, hypertension appeared with similar rates between the ranibizumab and VEGF Trap-eye groups (7.9% vs 6.5%). In pool 1 (SOC and PT), the overall rate of arterial thromboembolic events was higher in VEGF Trap-eye groups (3.2%) compared to 1.8% in ranibizumab group.

Taking into account the fact that almost 20% of drug substance goes through the systemic circulation, systemic effects of VEGF Trap-eye on the circulation cannot be excluded, and appropriate monitoring is foreseen in the RMP.

The number of cerebrovascular events was higher in the VEGF Trap-Eye groups (35) compared with ranibizumab (2 cases) in the elderly, especially in the sub-group ≥ 85 years (20 vs 1 case), during the first year of treatment. Two-year data showed also the increased number of cerebrovascular events in the VEGF Trap-Eye groups vs ranibizumab: 53 vs 12 (27 vs 3 in the sub-group ≥ 85 years). One death due to CVA in the 0.5Q4 group and one death due to ischemic stroke in the 2Q8 group were considered as treatment related.

Among severe non-ocular TEAEs, TIA (transient ischemic attack) was observed in 10 patients treated with VEGF Trap-eye, while no cases occurred in comparator group. The majority of these subjects had pre-existing risk factors for cardiovascular disease. No subject had a positive anti-drug antibody status. Since subjects were randomised to treatment, it is reasonable to assume that there would be an equal prevalence of risk factors in those assigned to ranibizumab.

Arterial thromboembolic events are listed as an important potential risk in the RMP and covered in sections 4.4 and 4.8 of the SmPC. The higher proportion of TIAs and cerebrovascular events reported within the pooled data is of concern and will be carefully considered within further assessments of ATEs during routine pharmacovigilance procedures and PSURs.

No specific studies have been provided in renal and hepatic insufficiency; nor specific interaction studies have been performed.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

Overall, the safety profile of aflibercept appears to be similar to the already marketed comparator drug, ranibizumab. No dose related effect was observed.

Concerns were raised on potential role of aflibercept on the arterial thromboembolic events, cerebrovascular events and TIAs. As routine pharmacovigilance, these events will be subject to m monitoring and safety evaluation in each PSUR. A targeted questionnaire will be used to follow-up on any post-marketing or study reports suspicious for ATEs.

The CHMP has also requested additional pharmacovigilance activities in the form of a non-interventional study to assess the safety and real-life treatment practice with aflibercept.

Further long term data are expected at the conclusion of extension study VGFT-OD-0910.

Educational material for physicians and patients to allow correct use of the product will be prepared. The Applicant has submitted a detailed outline in the RMP, but a study protocol should be designed to assess the knowledge and understanding of the key messages by physicians and patients, and submitted to the CHMP before study initiation (see Pharmacovigilance section).

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The applicant submitted a risk management plan (version 7)

The applicant submitted a risk management plan, which included a risk minimisation plan.

PGR2026-00039
Biocon Ex.1065
Page 395 of 595

SUMMARY OF THE RISK MANAGEMENT PLAN

Safety Concern	Proposed pharmaco-vigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
Important identified risks		
Endophthalmitis	Routine pharmacovigilance: Ongoing monitoring and safety evaluation in each PSUR A targeted questionnaire will be used to follow-up on any post-marketing or study reports suspicious for an intraocular infection (see Annex 9).	Routine risk minimization: Labeling (Undesirable effects, section 4.8): Serious adverse reactions related to the injection procedure included endophthalmitis. Uncommon: endophthalmitis Labeling (Special warnings and precautions for use, section 4.4): Intravitreal injections, including those with Eylea®, have been associated with endophthalmitis (see section 4.8 Undesirable effects). Proper aseptic injection techniques must always be used when administering Eylea®. Patients should be instructed to report any symptoms suggestive of endophthalmitis without delay and these should be managed appropriately. Labeling (Method of administration): ***Method of administration*** Intravitreal injections must be carried out according to medical standards and applicable guidelines by a qualified physician experienced in administering intravitreal injections. In general, adequate anesthesia and asepsis, including topical broad spectrum microbicide (e.g. povidone iodine applied to the periocular skin, eyelid and ocular surface) have to be ensured. Surgical hand disinfection, sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent) are recommended. Additional risk minimization: Educational program (Physician information pack including prescriber guide, intravitreal injection procedure video, patient information audio-CD and patient information booklet)
Transient intraocular pressure increase	Routine pharmacovigilance: Ongoing monitoring and safety evaluation in each PSUR	Routine risk minimization: Labeling (Undesirable effects, section 4.8) Serious adverse reactions related to

Safety Concern	Proposed pharmaco-vigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
		the injection procedure have occurred in less than 1 in 1,000 intravitreal injections with Eylea and included endophthalmitis, traumatic cataract and transient increased intraocular pressure IOP increase labeled as ADR (frequency category: common) Labeling (Special warnings and precautions for use, section 4.4): ***Increase in intraocular pressure*** Increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including those with Eylea® (see section 4.8). Special precaution is needed in patients with poorly controlled glaucoma (do not inject Eylea® while the intraocular pressure is ≥ 30 mmHg). In all cases both intraocular pressure and the perfusion of the optic nerve head must therefore be monitored and managed appropriately. Additional risk minimization: Educational program (Physician information pack including prescriber guide, intravitreal injection procedure video, patient information audio-CD and patient information booklet)
Conjunctival hemorrhage	Routine pharmacovigilance: Ongoing monitoring and safety evaluation in each PSUR	Routine risk minimization: Labeling (Undesirable effects, section 4.8): Labeled as ADR (frequency category: very common) Additional risk minimization: Educational program (Physician information pack including prescriber guide, intravitreal injection procedure video, patient information audio-CD and patient information booklet)
Eye pain	Routine pharmacovigilance: Ongoing monitoring and safety evaluation in each PSUR	Routine risk minimization: Labeling (Undesirable effects, section 4.8): Labeled as ADR (frequency category: very common) Additional risk minimization: Educational program (Physician information pack including prescriber guide, intravitreal

Safety Concern	Proposed pharmaco-vigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
		injection procedure video, patient information audio-CD and patient information booklet)
Vitreous detachment	Routine pharmacovigilance: Ongoing monitoring and safety evaluation in each PSUR	Routine risk minimization: Labeling (Undesirable effects, section 4.8): Labeled as ADR (frequency category: common) Additional risk minimization: Educational program (Physician information pack including prescriber guide, intravitreal injection procedure video, patient information audio-CD and patient information booklet)
Vitreous floaters	Routine pharmacovigilance: Ongoing monitoring and safety evaluation in each PSUR	Routine risk minimization: Labeling (Undesirable effects, section 4.8): Labeled as ADR (frequency category: common) Additional risk minimization: Educational program (Physician information pack including prescriber guide, intravitreal injection procedure video, patient information audio-CD and patient information booklet)
Retinal pigment epithelium tears	Routine pharmacovigilance: Ongoing monitoring and safety evaluation in each PSUR	Routine risk minimization: Labeling (Undesirable effects, section 4.8) Labeled as ADR (frequency category: common) Labeling (Special warnings and precautions for use, section 4.4): ***Retinal pigment epithelial tears*** Risk factors associated with the development of a retinal pigment epithelial tear after anti-VEGF therapy for wet AMD, include a large and/or high pigment epithelial retinal detachment. When initiating Eylea® therapy, caution should be used in patients with these risk factors for retinal pigment epithelial tears. Additional risk minimization: Educational program (Physician information pack including prescriber guide, intravitreal injection procedure video, patient

Safety Concern	Proposed pharmaco-vigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
		information audio-CD and patient information booklet)
Important potential risks		
Hypersensitivity and immunogenicity	Routine pharmacovigilance: Ongoing monitoring and safety evaluation in each PSUR	Routine risk minimization: Labelling (Special warnings and precautions for use, section 4.4): ***Immunogenicity*** As this is a therapeutic protein, there is a potential for immunogenicity with Eylea® (see section 4.8). Patients should be instructed to report any signs or symptoms of intraocular inflammation, e.g. pain, photophobia, or redness, which may be a clinical sign attributable to hypersensitivity.
Traumatic cataract	Routine pharmacovigilance: Ongoing monitoring and safety evaluation in each PSUR.	Routine risk minimization: Labeling (Undesirable effects, section 4.8): Serious adverse reactions related to the injection procedure have occurred in less than 1 in 1,000 intravitreal injections with Eylea® and included endophthalmitis, traumatic cataract and transient increased intraocular pressure (see section 4.4). Cataract labeled as ADR (frequency category: common) Additional risk minimization: Educational program (Physician information pack including prescriber guide, intravitreal injection procedure video, patient information audio-CD and patient information booklet)
Arterial thromboembolic events (ATEs) including non-MI ATEs (cerebrovascular events and TIAs) and cardiovascular ischemic events	Routine pharmacovigilance: Ongoing monitoring and safety evaluation in each PSUR. A targeted questionnaire will be used to follow-up on any post-marketing or study reports suspicious for ATEs (see Annex 9). Additional pharmacovigilance: Registry/PASS for Eylea® use in clinical practice (A non-interventional study to assess the safety and real-life treatment practice with	Routine risk minimization: Labeling (Undesirable effects, section 4.8): Arterial thromboembolic events (ATEs) are adverse events potentially related to systemic VEGF inhibition. There is a theoretical risk of arterial thromboembolic events following intravitreal use of VEGF inhibitors. ATEs, as defined by Antiplatelet Trialists' Collaboration (APTC) criteria, include nonfatal myocardial infarction, nonfatal stroke, or

PGR2026-00039
Biocon Ex.1065
Page 399 of 595

Safety Concern	Proposed pharmaco-vigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
	aflibercept in patients with wet age-related macular degeneration (AMD))	vascular death (including deaths of unknown cause). The incidence in the phase 3 wet AMD studies (VIEW1 and VIEW2) during the 96 weeks study duration was 3.3% (60 out of 1,824) in the combined group of patients treated with Eylea® compared with 3.2% (19 out of 595) in patients treated with ranibizumab (see section 5.1). Labeling (Special warnings and precautions for use, section 4.4): There is a potential risk of arterial thromboembolic events following intravitreal use of VEGF (vascular endothelial growth factor) inhibitors (see section 4.8).
Venous thromboembolic events	Routine pharmacovigilance: Ongoing monitoring and safety evaluation in each PSUR	Routine risk minimization: No activities currently planned.
Hypertension	Routine pharmacovigilance: Ongoing monitoring and safety evaluation in each PSUR A targeted questionnaire will be used to follow-up on any post-marketing or study reports suspicious for hypertension (see Annex 9).	Routine risk minimization: No activities currently planned.
Proteinuria	Routine pharmacovigilance: Ongoing monitoring and safety evaluation in each PSUR	Routine risk minimization: No activities currently planned.
Bleeding due to altered wound angiogenesis	Routine pharmacovigilance: Ongoing monitoring and safety evaluation in each PSUR	Routine risk minimization: No activities currently planned.
Medication error	Routine pharmacovigilance: Ongoing monitoring and safety evaluation in each PSUR	Routine risk minimization: No activities currently planned.
Off label use	Routine pharmacovigilance: Ongoing monitoring and safety evaluation in each PSUR	Routine risk minimization: No activities currently planned.
Embryo-fetotoxicity	Routine pharmacovigilance: Ongoing monitoring and safety evaluation in each PSUR	Routine risk minimization: Labeling (Pregnancy and lactation): ***Pregnancy:*** There are no data on the use of aflibercept in pregnant women.

Safety Concern	Proposed pharmaco-vigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
		Studies in animals have shown embryo-fetal toxicity after high systemic exposure (see section 5.3). Although the systemic exposure after ocular administration is very low, Eylea® is not recommended during pregnancy unless the potential benefit outweighs the potential risk to the fetus.
Retinal hemorrhage	Routine pharmacovigilance: Ongoing monitoring and safety evaluation in each PSUR	Routine risk minimization: No activities currently planned.
Important missing information		
Use of Eylea® in patients with uncontrolled glaucoma	Routine pharmacovigilance: Ongoing monitoring and safety evaluation in each PSUR	Routine risk minimization: Labeling (Special warnings and precautions for use, section 4.4): Special precaution is needed in patients with poorly controlled glaucoma
Concomitant use of different anti-VEGF therapies and other therapies for wet AMD	Routine pharmacovigilance: Ongoing monitoring, safety evaluation in each PSUR, provide safety results of ongoing clinical studies Additional pharmacovigilance: Registry/PASS for Eylea® use in clinical practice (A non-interventional study to assess the safety and real-life treatment practice with aflibercept in patients with wet age-related macular degeneration (AMD))	Routine risk minimization: No activities currently planned.
Long term safety beyond 2 years	Routine pharmacovigilance: Ongoing monitoring, safety evaluation in each PSUR, safety results of ongoing clinical studies Additional pharmacovigilance: Registry/PASS for Eylea® use in clinical practice (A non-interventional study to assess the safety and real-life treatment practice with aflibercept in patients with wet age-related macular degeneration (AMD)) Safety data from the extension	Routine risk minimization: No activities currently planned

Safety Concern	Proposed pharmaco-vigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
	study VGFT-OD-0910	
Posology utilized in marketed use	Routine pharmacovigilance: Ongoing monitoring Additional pharmacovigilance: Registry/PASS for Eylea® use in clinical practice (A non-interventional study to assess the safety and real-life treatment practice with aflibercept in patients with wet age-related macular degeneration (AMD)) Additional activity: Post authorization efficacy study: clinical trial to compare the proactive dosing regimen with injection every 2 months with a reactive regimen based on visual and anatomic outcomes.	Routine risk minimization: No activities currently planned.

The Applicant reconsidered its position and now agrees to conduct a post-authorisation safety study to assess the risk of arterial thromboembolic and cerebrovascular events including TIAs. A full study protocol should be submitted to the CHMP before study initiation.

To answer to the remaining issue regarding the optimal dosing frequency, the Applicant should commit to submit a post-authorisation randomised study with primary objective to compare the proactive 8-weekly injections to a reactive regimen based on visual and anatomic outcomes.

The Applicant has agreed to provide educational material for physicians and patients and has submitted a detailed outline of the requested educational materials in Annex 8 with the revised RMP.

Moreover, the final cross-sectional observational study protocol to assess the knowledge and understanding of physicians and patients of the key messages in the educational material should be provided to the CHMP before study initiation.

The CHMP, having considered the data submitted, was of the opinion that the below pharmacovigilance activity(ies) in addition to the use of routine pharmacovigilance are needed to investigate further some of the safety concerns:

Description	Due date
A non-interventional study to assess the safety and real-life treatment practice with aflibercept in patients with wet age-related macular degeneration (AMD). (Included in RMP- Final study protocol: February 2013)	Final study report 31 December 2018
Long-term safety extension study VGFT-OD-0910 (Included in RMP)	Final study report: April 2015
A post-authorisation safety study to evaluate physician and patient knowledge	Final study

Description	Due date
of information on safety and safe use for Eylea in Europe. (Included in RMP - Final study protocol Feb 2013)	report 31 December 2014

The following additional risk minimisation activities were required:

All ophthalmological clinics where EYLEA is expected to be used are provided with a physician information pack containing physician information which includes the Summary of Product Characteristics, an intravitreal injection procedure video and -pictogram as well as patient information packs. The patient information packs include the patient information leaflet, a patient information booklet and an audio-CD. The key safety messages of the educational materials are outlined in chapter 4, conditions or restrictions with regard to the safe and effective use of the medicinal product.

2.8. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

Neovascular age-related macular degeneration is a chronic, progressive, degenerative condition affecting the eye, which, left untreated, results in moderate to severe visual loss. Potential benefits of therapies in this area are prevention of progression of vision loss, and improvement of reduced vision.

Anti-angiogenic therapy with the vascular endothelial growth factor inhibitor ranibizumab is currently the treatment of choice for neovascular AMD. Monthly injections of ranibizumab have been shown to prevent moderate vision loss in over 90% of patients, and improve vision by an average of at least 7 letters after 1 year of treatment, with over 30% of patients gaining at least 15 letters of vision.

The sought indication of "treatment of neovascular (wet) age-related macular degeneration (AMD) for adults" implies a disease modifying effect, in that inhibition of VEGF reduces neovascularisation and vessel leakage, and is accompanied by an improvement in clinical signs and symptoms (macular thickness and vision). This is not a first-in-class product and the development program has been designed to demonstrate non-inferiority against an existing VEGF inhibitor. As such the clinical trials were designed to provide long-term (2-year) data.

The development plan of the anti-VEGF treatment Eylea is satisfactory and in agreement with the historical development of other treatments for Wet AMD. As Ranibizumab (Lucentis) is currently the gold standard therapy for patients suffering from wet AMD, it was selected as comparator in the pivotal non-inferiority studies.

A total of 1217 and 1098 patients were respectively randomized in two pivotal studies, VIEW 1 and VIEW 2. The choice of the primary criteria was discussed and agreed through scientific advices. All criteria or methods used for assessment are well validated for the pathology.

The primary endpoint, i.e. proportion of subjects maintaining vision at Week 52, was met for all VEGF Trap-Eye treatment regimens and established the non-inferiority of VEGF Trap-Eye to ranibizumab (at a pre-specified 10% margin). The statistical test sequence showed confirmatory results with narrow confidence intervals (i.e. ≤ 3.1% and ≤ 2.6 %, in VIEW 1 and in VIEW 2, respectively). These intervals were well below the more stringent non-inferiority margin of 7% which was recommended by the Scientific Advice in 2007 specifically for the pooled analysis, with respect to the more modest difference with placebo observed for pegaptanib (i.e. 14%).

Data from the two pivotal studies show that injections of VEGF Trap-Eye every 8 weeks (initiated with three monthly injections) were non-inferior to monthly injections of ranibizumab, with 95% of patients maintaining vision (ie, losing <15 letters) at Year 1. Results for the secondary endpoints show further benefits and support the comparable efficacy of the two therapies; subjects gained an average of 8 letters of vision, with 31% gaining at least 15 letters; choroidal neovascularisation area decreased by an average of 4 mm^2, and visual function questionnaire test scores improved by an average of 5 points. These benefits were evident across all subgroups and regions.

The analysis of the change from baseline in ETDRS letter score in the 2Q4 group vs RQ4 group was the first ordered comparison for testing superiority. Results, in study VIEW 1, showed superiority of VEGF Trap 2Q4 regimen over ranibizumab (p=0.0054) however, no superiority was found in Study VIEW 2. Therefore no superiority of Eylea over ranibizumab could be demonstrated. The 2Q8 regimen was chosen as it reduces the number of injections.

The two year results show that the efficacy is maintained over the second year of treatment despite a slight drop in vision (1-2 letters of ETDRS Chart) and stagnation or slight decrease in improvements of the morphologic criteria based on OCT examinations.

Two Year data from the two pivotal studies show that capped-PRN injections of VEGF Trap-Eye given 8-weekly at entry in Year 1 (2Q8) were non-inferior to capped-PRN injections of ranibizumab, with respectively, 92.4% vs 91.6% of patients maintaining vision at Year 2. Results for the secondary endpoints show that meaningful benefits were also maintained and support the comparable efficacy of the two therapies.

Uncertainty in the knowledge about the beneficial effects.

The non inferiority over ranibizumab monthly administered was demonstrated by 1-year for all fixed proposed dosages and regimens, i.e. 0.5Q4, 2Q4 and 2Q8, and these results have been further confirmed at two years. But, as no fixed regimen was maintained as comparator in the second year, uncertainties remain whether the proposed fixed 2Q8 regimen offers the best long-term benefit. Provision of further long term data at the conclusion of study VGFT-OD-0910 should help to elucidate this point.

The results of Year 2 of the studies failed in appropriately providing guidance to clinicians in the optimal dosing regimen required to maintain initial improvement in vision. Indeed, it is presently not totally clarified whether a rigid dosing schedule with a maximum dosing interval of 8 weeks or retreatment on a capped-PRN basis, are required to maintain the optimal efficacy of VEGF Trap-Eye beyond Year 1. The results submitted for the second year using reactive dosing (PRN), instead of proactive dosing in Year 1, suggest that a part of patients may benefit from less or more frequent dosing than the 2Q8 dosings. This is of importance, since the main benefit of this product over the existing standard of care would be the reduced frequency of injections required to produce a

similar effect. Therefore, the CHMP recommended that this point be further investigated through a post-marketing study.

Risks

Unfavourable effects

The safety database for VEGF Trap-Eye has not highlighted any major safety concerns. Several of the commonly reported adverse events are associated with the injection procedure and may be considered non-serious or easily manageable (conjunctival haemorrhage, eye pain, transient rise in intraocular pressure). Rates of more serious events such as endophthalmitis were low, and there does not appear to be any significant risk of intraocular inflammation.

The risk of clinically significant decrease in visual acuity appeared to be slightly higher in the VEGF Trap-Eye groups than in the ranibizumab control group.

The most common ocular adverse reactions (in at least 5% of patients treated with Eylea) were conjunctival haemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters and increased intraocular pressure.

In addition, cases of endophtalmitis have been associated with intravitreal injections of aflibercept as well as retinal detachment, retinal haemorrhage and retinal tear.

As with all therapeutic proteins, there is a potential for immunogenicity with aflibercept. The number of positive anti-drug antibodies (ADA) was similar between the treatment groups in the pivotal studies.

Hypertension was a very common non-ocular adverse event. Hypersensitivity as well as Arterial thromboembolic events (ATEs) were commonly reported. One case of transient ischemic attack (TIA) was considered to be related to study drug. TEAEs of myocardial infarction, congestive cardiac failure were reported in low rate. These events will specifically be monitored post-marketing.

Uncertainty in the knowledge about the unfavourable effects

Aflibercept is a recombinant protein consisting of portions of human VEGF receptors, and acts as a soluble decoy receptor that binds VEGF-A and PlGF with higher affinity than their natural receptors, leading to endothelial cell proliferation and neovascularization. With regards to the fact that almost 20% of drug substance goes through the systemic circulation and given the potential role of VEGF in the systemic adverse events, systemic effects of VEGF Trap-eye cannot be excluded. Adverse reactions related to this inhibition: *hypertension, arterial thromboembolic events, haemorrhage* have been reported during the safety review of study data. It has been postulated that a link exists between use of intravitreal VEGF inhibitors and an increased risk of arterial thromboembolic events.

The global rate of arterial thromboembolic events was higher in VEGF Trap-eye groups (3.2%) compared to 1.8% in ranibizumab group. The number of cerebrovascular events was significantly higher in the VEGF Trap-Eye groups compared with ranibizumab, especially in the sub-group ≥ 85 years, during the first year of treatment. Two-year data showed also the increased number of cerebrovascular events and TIAs in the VEGF Trap-Eye groups vs ranibizumab. Two deaths (CVA, ischemic stroke) were considered as treatment related. The applicant agreed to conduct a non-interventional postmarketing study addressing the risk of ATEs, CVAs, and TIAs.

Balance

Importance of favourable and unfavourable effects

Data from the two pivotal studies demonstrate that injections of VEGF Trap-Eye every 8 weeks (initiated three early monthly injections) were non-inferior to monthly injections of ranibizumab, with 95% of patients maintaining vision (ie, losing <15 letters) and established the non-inferiority of VEGF Trap-Eye to ranibizumab (at a pre-specified 10% margin).

Results for the secondary endpoints show further benefits and support the comparable efficacy of the two therapies. These benefits were evident across all subgroups and regions.

The results of Year 2 of the studies failed in appropriately elucidating the optimal dosing regimen required to maintain initial improvement in vision. This is the subject of a post-authorisation measure.

The safety database for VEGF Trap-Eye has not evidenced any unexpected or major safety concerns. Several of the commonly reported adverse events are associated with the injection procedure and may be considered non-serious or easily manageable (conjunctival haemorrhage, eye pain, transient rise in intraocular pressure). Rates of more serious events such as endophthalmitis were low, and there does not appear to be any significant risk of intraocular inflammation.

The applicant agreed to conduct a non-interventional postmarketing study to elucidate the risk of ATEs, CVAs, and TIAs.

Benefit-risk balance

Discussion on the benefit-risk assessment

The two pivotal studies demonstrated that injections of VEGF Trap-Eye every 8 weeks (initiated with three monthly injections) were non-inferior to monthly injections of ranibizumab, with 95% of patients maintaining vision (ie, losing <15 letters) at Year 1. Results for the secondary endpoints support the comparable efficacy of the two therapies.

Results, in study VIEW 1, showed superiority of VEGF Trap 2Q4 regimen over ranibizumab (p=0.0054) however, no superiority was found in Study VIEW 2. Therefore no superiority for the 2Q8 regimen over ranizumab was demonstrated.

The CHMP would like to further elucidate the optimal dosing to be used beyond one year of treatment, as uncertainties remain. A post-marketing study will be performed by the Applicant. (Please refer to efficacy conclusions).

No major or unexpected safety concerns arise from the safety database for VEGF Trap-Eye.

Further elucidation on long term safety and the risk of arterial thromboembolic events, including cerebrovascular events and TIAs, will be provided by post-marketing studies.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Eylea in the

treatment of neovascular (wet) age-related macular degeneration (AMD) (see section 5.1)

is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

Risk Management System

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the marketing authorisation, is in place and functioning before and whilst the product is on the market.

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 7 of the Risk Management Plan presented in Module 1.8.2. of the Marketing Authorisation and any subsequent updates of the RMP agreed by the Committee for Medicinal Products for Human Use (CHMP).

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).
In addition, an updated RMP should be submitted

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the European Medicines Agency.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Prior to launch in each Member State the Marketing Authorisation Holder (MAH) shall agree the final educational material with the National Competent Authority.

The MAH shall ensure that, following discussions and agreement with the National Competent Authorities in each Member State where EYLEA is marketed, at launch and after launch all ophthalmological clinics where EYLEA is expected to be used are provided with a physician information pack containing the following elements:

- Physician information
- Intravitreal injection procedure video
- Intravitreal injection procedure pictogram
- Patient information packs

The physician information should contain the following key elements:

- The Summary of Product Characteristics
- Sterile techniques, including periocular and ocular disinfection to minimise the risk of infection
- Use of antibiotics
- Use of povidone iodine or equivalent
- Techniques for the intravitreal injection

- Patient monitoring after intravitreal injection
- Key signs and symptoms of intravitreal injection related adverse events including endophthalmitis, increased intraocular pressure, conjunctival hemorrhage, eye pain, vitreous detachment, vitreous floaters, retinal pigment epithelium tear and traumatic cataract
- Management of intravitreal injection related adverse events

The patient information pack should be provided in both the form of a patient information booklet and an audio-CD that contain following key elements:

- Patient information leaflet
- How to prepare for EYLEA treatment
- What are the steps following treatment with EYLEA
- Key signs and symptoms of serious adverse events including endophthalmitis, increased intraocular pressure, conjunctival hemorrhage, eye pain, vitreous detachment, vitreous floaters, retinal pigment epithelium tear and traumatic cataract
- When to seek urgent attention from their health care provider

Obligation to complete post-authorisation measures

The MAH shall complete, within the stated timeframe, the following measures:

Description	**Due date**
To perform a post-authorisation randomised study with the primary objective of comparing the standard regime of injections every 8 weeks with a reactive regimen based on visual and anatomic outcomes, based on a CHMP approved protocol.	Final study report submission: 31 December 2017

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that Aflibercept is qualified as a new active substance.

APPENDIX FDA10

https://web.archive.org/web/20170601000000*/http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/125387Orig1s000PharmR.pdf September 13, 2025

INTERNET ARCHIVE WEB TEXTS VIDEO AUDIO SOFTWARE IMAGES SIGN UP | LOG IN UPLOAD Search

ABOUT BLOG PROJECTS HELP DONATE CONTACT JOBS VOLUNTEER PEOPLE

DONATE

INTERNET ARCHIVE WaybackMachine

Explore more than 946 billion web pages saved over time

http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/12538

Calendar · Collections · Changes · Summary · Site Map · URLs

Saved **15 times** between January 18, 2017 and July 10, 2025.

002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 **2017** 2018 2019 2020 2021 2022 2023 2024 2025

JAN

1	2	3	4	5	6	7
8	9	10	11	12	13	14
15	16	17	18	19	20	21
22	23	24	25	26	27	28
29	30	31				

FEB

			1	2	3	4
5	6	7	8	9	10	11
12	13	14	15	16	17	18
19	20	21	22	23	24	25
26	27	28				

MAR

			1	2	3	4
5	6	7	8	9	10	11
12	13	14	15	16	17	18
19	20	21	22	23	24	25
26	27	28	29	30	31	

APR

						1
2	3	4	5	6	7	8
9	10	11	12	13	14	15
16	17	18	19	20	21	22
23	24	25	26	27	28	29
30						

MAY

	1	2	3	4	5	6
7	8	9	10	11	12	13
14	15	16	17	18	19	20
21	22	23	24	25	26	27
28	29	30	31			

JUN

				1	2	3
4	5	6	7	8	9	10
11	12	13	14	15	16	17
18	19	20	21	22	23	24
25	26	27	28	29	30	

JUL

						1
2	3	4	5	6	7	8
9	10	11	12	13	14	15
16	17	18	19	20	21	22
23	24	25	26	27	28	29
30	31					

AUG

		1	2	3	4	5
6	7	8	9	10	11	12
13	14	15	16	17	18	19
20	21	22	23	24	25	26
27	28	29	30	31		

SEP

					1	2
3	4	5	6	7	8	9
10	11	12	13	14	15	16
17	18	19	20	21	22	23
24	25	26	27	28	29	30

OCT

1	2	3	4	5	6	7
8	9	10	11	12	13	14
15	16	17	18	19	20	21
22	23	24	25	26	27	28
29	30	31				

NOV

			1	2	3	4
5	6	7	8	9	10	11
12	13	14	15	16	17	18
19	20	21	22	23	24	25
26	27	28	29	30		

DEC

					1	2
3	4	5	6	7	8	9
10	11	12	13	14	15	16
17	18	19	20	21	22	23
24	25	26	27	28	29	30
31						

Note

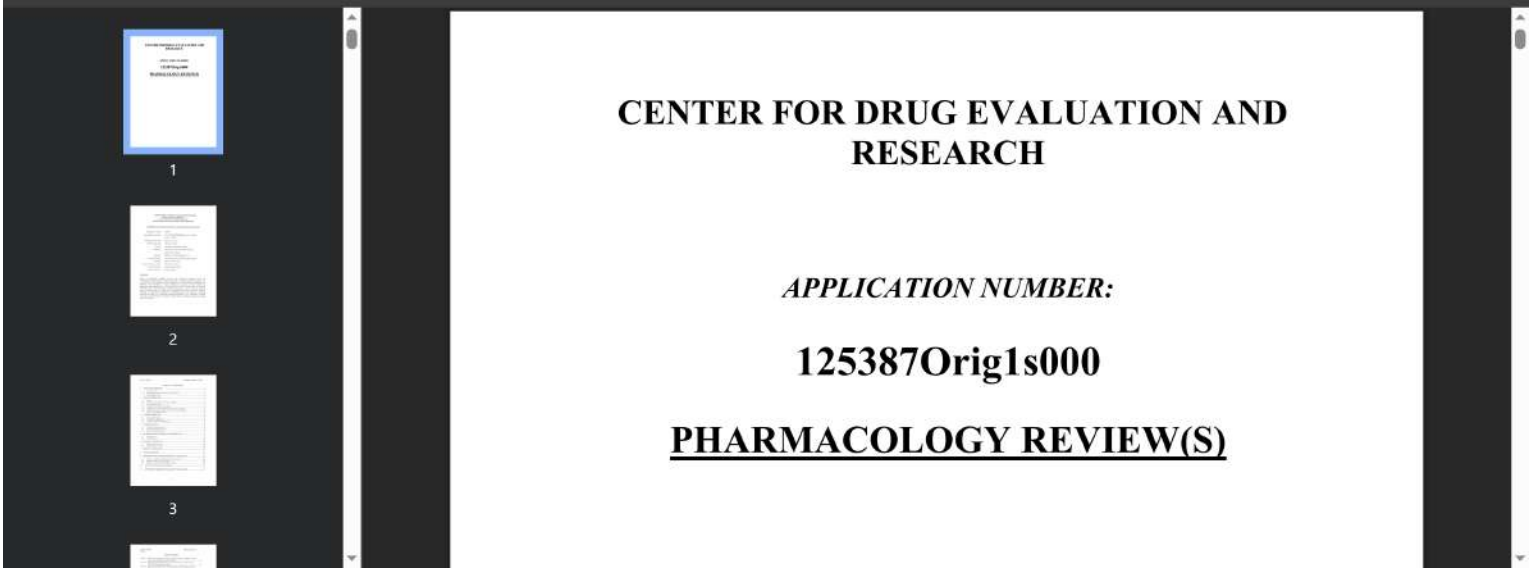
This calendar view maps the number of times **http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/125387Orig1s000PharmR.pdf** was crawled by the Wayback Machine, *not* how many times the site was actually updated. More info in the FAQ.

FAQ | Contact Us | Terms of Service (Dec 31, 2014)

The Wayback Machine is an initiative of the Internet Archive, a 501(c)(3) non-profit, building a digital library of Internet sites and other cultural artifacts in digital form. Other projects include Open Library & archive-it.org.

Your use of the Wayback Machine is subject to the Internet Archive's Terms of Use.

https://web.archive.org/web/20170118195257/http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/125387Orig1s000PharmR.pdf September 13, 2025
INTERNET ARCHIVE Wayback Machine http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/125387Orig1s000PharmR.pdf Go DEC JAN FEB
15 captures 18 Jan 2017 - 10 Jul 2025 2016 18 2017 2020 About this capture
125387Orig1s000PharmR.pdf 1 / 82 100%



1

2

3

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125387Orig1s000

PHARMACOLOGY REVIEW(S)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125387Orig1s000

PHARMACOLOGY REVIEW(S)

PGR2026-00039
Biocon Ex.1065
Page 412 of 595

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY BLA REVIEW AND EVALUATION

Application number:	125387
Supporting document/s:	IND 12462 [redacted] (b) (4) Memo to File dated June 17, 2009
Applicant's letter date:	February 17, 2011
CDER stamp date:	February 18, 2011
Product:	Aflibercept Ophthalmic Solution
Indication:	Neovascular "wet" age-related macular degeneration (AMD)
Applicant:	Regeneron Pharmaceuticals, Inc.
Review Division:	Anti-infective and Ophthalmology Products
Reviewer:	María I. Rivera, Ph.D.
Supervisor/Team Leader:	William Taylor, Ph.D.
Division Director:	Renata Albrecht, M.D.
Project Manager:	Michael Puglisi

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of BLA 125387 are owned by Regeneron Pharmaceuticals, Inc. or are data for which Regeneron Pharmaceuticals, Inc. has obtained a written right of reference. Any information or data necessary for approval of BLA 125387 that Regeneron Pharmaceuticals, Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of BLA 125387. Applicant material has been used in this review.

PGR2026-00039
Biocon Ex.1065
Page 413 of 595

TABLE OF CONTENTS

1 EXECUTIVE SUMMARY 5
1.1 INTRODUCTION 5
1.2 BRIEF DISCUSSION OF NONCLINICAL FINDINGS 5
1.3 RECOMMENDATIONS 6
2 DRUG INFORMATION 8
2.1 DRUG 8
2.2 RELEVANT INDS, NDAS, BLAS AND DMFS 9
2.3 DRUG FORMULATION 9
2.4 COMMENTS ON NOVEL EXCIPIENTS 9
2.5 COMMENTS ON IMPURITIES/DEGRADANTS OF CONCERN 9
2.6 PROPOSED CLINICAL POPULATION AND DOSING REGIMEN 10
2.7 REGULATORY BACKGROUND 10
3 STUDIES SUBMITTED 10
3.1 STUDIES REVIEWED 10
3.2 STUDIES NOT REVIEWED 13
3.3 PREVIOUS REVIEWS REFERENCED 13
4 PHARMACOLOGY 13
4.1 PRIMARY PHARMACOLOGY 13
4.2 SECONDARY PHARMACOLOGY 16
4.3 SAFETY PHARMACOLOGY 17
5 PHARMACOKINETICS/ADME/TOXICOKINETICS 17
5.1 PK/ADME 17
5.2 TOXICOKINETICS 20
6 GENERAL TOXICOLOGY 20
6.1 SINGLE-DOSE TOXICITY 20
6.2 REPEAT-DOSE TOXICITY 20
7 GENETIC TOXICOLOGY 64
8 CARCINOGENICITY 64
9 REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY 64
9.1 FERTILITY AND EARLY EMBRYONIC DEVELOPMENT 64
9.2 EMBRYONIC FETAL DEVELOPMENT 65
9.3 PRENATAL AND POSTNATAL DEVELOPMENT 70
10 SPECIAL TOXICOLOGY STUDIES 71
11 INTEGRATED SUMMARY AND SAFETY EVALUATION 71

PGR2026-00039
Biocon Ex.1065
Page 414 of 595

Table of Tables

Table 1: Binding Parameters (Range) for the Interaction of Different VEGF Trap Lots with VEGF-A_{165} and PIGF-2 14
Table 2: Binding Parameters (Mean) for the Interaction of VEGF Trap to VEGF Family Related Ligands 14
Table 3: Mean PK Parameters for Free and Bound VEGF Trap in Rabbits after a Single 500 µg/eye Intravitreal Injection of VEGF Trap 18
Table 4: Mean PK Parameters of Free VEGF Trap in Monkey Serum after a Single IV or SC Dose 19
Table 5: Incidence and Severity of Microscopic Findings in the Nasal Turbinates following ITV Dosing of VEGF Trap to Cynomolgus Monkey Monthly for 8 Months 26
Table 6: Mean Plasma and Vitreous Free VEGF Trap and Plasma Bound VEGF Trap Concentrations in Monkeys 7 Days after the Last of 9 ITV Doses Administered Every 4 Weeks 29
Table 7: Mean Plasma and Vitreous Free VEGF Trap and Plasma Bound VEGF Trap Concentrations in Monkeys 7 Days after the Last of 4 ITV Doses Administered Every 4 Weeks 34
Table 8: Intravitreal Doses Used in Study # VGFT-TX-03053 35
Table 9: Placebo and VEGF Trap Formulations Evaluated in a 13-Week (4 Doses) Ocular Toxicity Study in Monkeys (Study # VGFT-TX-05015) 36
Table 10: Mean Plasma Concentrations for Free, Adjusted Bound, Total VEGF Trap Concentrations in Monkeys, 3 Days after the 4th ITV Administration of VEGF Trap 2 mg/eye Every 4 Weeks 38
Table 11: Main Findings Observed in Rat Systemic Toxicity Studies following Subcutaneous Administration of VEGF Trap 40
Table 12: Main Findings Observed in Mouse Systemic Toxicity Studies following Subcutaneous Administration of VEGF Trap 42
Table 13: Incidence of VEGF Trap-related Macroscopic Findings in Bones and Nasal Cavities in the 6-Month Intravenous Toxicity Study in Cynomolgus Monkeys 47
Table 14: Incidence and Severity of VEGF Trap-related Histopathological Findings in Nasal Cavities in the 6-Month Intravenous Toxicity Study in Monkeys 50
Table 15: Incidence and Severity of VEGF Trap-related Histolopathological Findings in the Female Reproductive System in the 6-Month Intravenous Toxicity Study in Monkeys 53
Table 16: Bone Abnormalities Detected by Digital Radiographs in the 6-Month Intravenous Toxicity Study in Monkeys 59
Table 17: Mean Plasma Concentrations of Free and Bound VEGF Trap in Pregnant Rabbits in the IV Embryofetal Toxicity Study 68
Table 18: Safety Margins for Systemic Toxicities Based on the Animal and Human Free VEGF Exposures 77

PGR2026-00039
Biocon Ex.1065
Page 415 of 595

Table of Figures

Figure 1 Secondary and Tertiary Structure of Aflibercept.....9

PGR2026-00039
Biocon Ex.1065
Page 416 of 595

1 Executive Summary

1.1 Introduction

VEGF Trap is a recombinant protein that is composed of two domains of the human VEGF cell surface receptors (VEGF R1 and VEGF R2) fused to the Fc region of human IgG. This recombinant molecule binds with high affinity to VEGF-A (K_D=0.36-0.76 pM) along with the related Placental Growth Factor (PlGF; K_D=29-392 pM). VEGF Trap has demonstrated anti-angiogenic activity in several preclinical animal models. In this BLA, this molecule is intended for the treatment of neovascular (wet) age-related macular degeneration (AMD) by intravitreal (ITV) injection of a 2 mg dose once every 2 months, following 3 initial 2 mg monthly injections.

1.2 Brief Discussion of Nonclinical Findings

The monkey was selected as the relevant species. Findings observed in ocular toxicity studies following ITV administration of VEGF Trap included mild and transient increases in anterior segment and vitreous cellularity (interpreted as a mild inflammation) that was not associated with other ocular abnormalities. These findings occurred at doses 0.5 times the intended clinical dose when correcting for vitreous volume (i.e., assuming a vitreous volume of 2 mL in monkeys and 4 mL in humans). However, the mild and transient nature of the finding does not represent a major clinical concern.

Epithelial erosion/ulceration of the nasal turbinates accompanied with chronic-active inflammation was noted in the ocular toxicity studies following ITV administration of VEGF Trap. Partial recovery was observed. Similar, albeit more severe lesions in the nasal cavity were noted in systemic toxicity studies in monkeys following repeated, IV administration. These findings occurred at exposures 42 and 56 times higher those observed after ITV administration in humans based on C_{max} and AUC, respectively. The reviewer is not aware of the observation of similar nasal findings with any other approved VEGF inhibitor following ITV injection. The applicant monitored for this finding in a subset of patients in the clinical trials. The finding is acknowledged in the proposed label.

Systemic toxicity studies in monkeys identified toxicities mostly related to the pharmacology of VEGF Trap. The main target organs included the bone, kidney, adrenals, ovary and, as noted above, nasal cavity. Other microscopic findings included vascular alterations in the brain choroid plexus and digestive tract (duodenum, stomach, gallbladder, pancreas), vascular degeneration and fibrosis in several tissues including the heart, and hepatic portal inflammation and periportal necrosis. Findings in the bone, nasal cavities, digestive system, liver, and brain (choroid plexus) were still present at recovery. A NOAEL was not established but these systemic adverse effects occurred at systemic exposures well in excess of the exposure observed in humans.

VEGF Trap adversely affected the female and male reproductive systems. Absent or irregular menses associated with alterations in female reproductive hormone levels,

PGR2026-00039
Biocon Ex.1065
Page 417 of 595

decreases in ovarian and uterus weights, ovarian and uterine microscopic alterations, reduction in sperm motility, and sperm morphological abnormalities were observed at all dose levels. All changes were reversible. A NOAEL was not established but these systemic adverse effects occurred at systemic exposures over 1500 times higher than the exposure observed in humans. These findings are well known class effects.

As expected, given the role of VEGF in organogenesis, VEGF Trap was embryotoxic and teratogenic in rabbits. Dose-related increases in fetal resorptions, abortions, and numerous fetal (external, visceral and skeletal) malformations were observed. A developmental NOAEL was not identified but systemic exposures were at least 600 times higher than those in humans. Free VEGF Trap was detected in amniotic fluid samples in the dose range-finding study in rabbits.

VEGF inhibitors, as a class, are known to increase blood pressure. Elevations in blood pressure were primarily observed in rats and mice after systemic administration. No effects were noted after ITV administration in monkeys. The blood pressure remained elevated above pre-treatment baseline values until circulating VEGF Trap levels fell below ~ 1 µg/mL in both rats and mice. The mean C_{max} observed in humans is ~50 times lower than the identified threshold in rodents. The applicant monitored for changes in blood pressure in the clinical trials.

1.3 Recommendations

1.3.1 Approvability

Approval is recommended from the nonclinical perspective.

1.3.2 Additional Non Clinical Recommendations

None

1.3.3 Labeling

8.1 Pregnancy

Pregnancy Category C

(b) (4)

[redacted]

PGR2026-00039
Biocon Ex.1065
Page 418 of 595

Reviewer's recommendations (2nd paragraph): Aflibercept produced embryo-fetal toxicity (b) (4) *when administered during organogenesis in pregnant rabbits* (b) (4) at intravenous (b) (4) doses of (3 to 60 mg/kg). *A series of external, visceral, and skeletal malformations were observed in the fetuses.* The maternal No Observed Adverse Effect Level (NOAEL) was (b) (4) 3 mg/kg, *whereas the fetal NOAEL was below 3 mg/kg.* At this dose, the systemic exposures based on C_{max} and AUC for free aflibercept were approximately 2900 and 600 (b) (4) *times* higher, respectively, than corresponding values observed in humans after an intravitreal dose of 2 mg.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

(b) (4)

Reviewer's recommendations: No studies have been conducted on the mutagenic or carcinogenic potential of aflibercept. Effects on male and female fertility were assessed as part of a 6-month study in monkeys with intravenous administration of aflibercept at doses ranging from 3 to 30 mg/kg. Absent or irregular menses associated with alterations in female reproductive hormone levels and changes in sperm morphology and motility were observed at all dose levels. *In addition, females showed decreased ovarian and uterine weight accompanied by compromised luteal development and reduction of maturing follicles. These changes correlated with uterine and vaginal atrophy.* A No Observed Adverse Effect Level (NOAEL) was not identified. Based on C_{max} and AUC for free aflibercept observed at the *lowest dose used of* 3 mg/kg (b) (4) the systemic exposures were approximately 4900 (b) (4) *times* and 1500 (b) (4) *times* higher, respectively, than the exposure observed in humans after an intravitreal dose of 2 mg. All changes were reversible.

13.2 Animal Toxicology and/or Pharmacology

(b) (4)

PGR2026-00039
Biocon Ex.1065
Page 419 of 595

Similar effects were not seen in clinical studies [*see Clinical Studies (14)*].

Reviewer's recommendations: Erosions and ulcerations of the respiratory epithelium in nasal turbinates in monkeys treated with aflibercept intravitreally were observed at (b) (4) *intravitreal doses of 2 or 4 mg/eye.* (b) (4) At the No Observed Adverse Effect Level (NOAEL) *of 0.5 mg/eye*, the systemic exposure was 42 and 56 (b) (4) *times* higher based on C_{max} and AUC, respectively, *than the exposure observed in humans after an intravitreal dose of 2 mg.*

Similar effects were not seen in clinical studies [*see Clinical Studies (14)*].

2 Drug Information

2.1 Drug

CAS Registry Number: 862111-32-8

Generic Name: Aflibercept

Code Name: VEGF Trap-Eye; BAY 86-5321

Chemical Name: Des-432-lysine-[human vascular endothelial growth factor receptor 1-(103-204)-peptide (containing Ig-like C2-type 2 domain) fusion protein with human vascular endothelial growth factor receptor 2-(206-308)-peptide (containing Ig-like C2-type 3 domain fragment) fusion protein with human immunoglobulin G1-(227 C-terminal residues)-peptide (Fc fragment)], (211-211':214-214')-bisdisulfide dimer

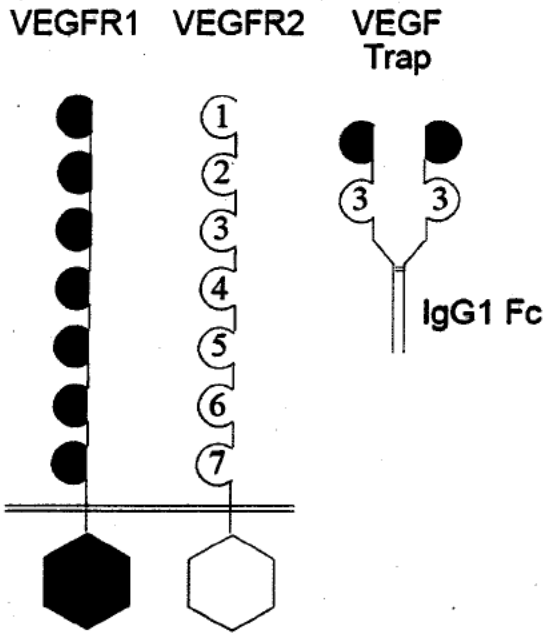
Molecular Formula/Molecular Weight: Aflibercept is a dimeric glycoprotein with a protein molecular weight of 96.9 kDa. It contains approximately 15 % glycosylation to give a total molecular weight of 115 kDa. Its molecular formula (without glycosylation) is $C_{4318}H_{6788}N_{1164}O_{1304}S_{32}$.

Structure or Biochemical Description: Aflibercept is a recombinant protein consisting of sequences derived from human vascular endothelial growth factor (VEGF) receptor extracellular domains fused to the Fc portion of human immunoglobulin G1 (IgG1). (b) (4) (b) (4) The presumptive Ig domain structure of aflibercept is

PGR2026-00039
Biocon Ex.1065
Page 420 of 595

provided in Figure 1. The amino acid sequence of the protein was provided in Module 3.2.S.1.2 Structure of the CTD.

Figure 1 Secondary and Tertiary Structure of Aflibercept



Pharmacologic Class: Vascular endothelial growth factor (VEGF) inhibitor

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 12462 (b) (4)

2.3 Drug Formulation

VEGF Trap-Eye drug product, (b) (4) 40 mg/mL, is a sterile solution for intravitreal (ITV) injection. The drug product is produced by formulating aflibercept drug substance in an aqueous (b) (4) solution at pH 6.2, containing 10 mM sodium phosphate, 40 mM sodium chloride, 5% (w/v) sucrose, and 0.03% (w/v) polysorbate 20 (PS20). The drug product is manufactured in single-dose vials (b) (4)

2.4 Comments on Novel Excipients

None

2.5 Comments on Impurities/Degradants of Concern

Refer to the product quality and CMC reviews.

PGR2026-00039
Biocon Ex.1065
Page 421 of 595

2.6 Proposed Clinical Population and Dosing Regimen

Aflibercept Ophthalmic Solution is indicated for the treatment of patients with neovascular (wet) age-related macular degeneration (AMD). The recommended dose is 2 mg (50 µL) administered by ITV injection once every 2 months, following 3 initial monthly injections of 2 mg (50 µL). Aflibercept Ophthalmic Solution may be dosed as frequently as 2 mg once per month.

2.7 Regulatory Background

(b) (4)

In an applicant meeting held on June 1, 2009 (See Memo to File IND 12462 and (b) (4) dated June 17, 2009), DAIOP concurred that the pharmacology/ toxicology program appeared sufficient for the indications of AMD and (b) (4) as long as there were no findings which warranted further studies. The applicant was asked to justify the use of a single species in the chronic toxicology studies. It was agreed in this meeting that pre- and post-natal development studies were not required for the current indication. Based on ICH S6 recommendations, the Division agreed that conducting genotoxicity and carcinogenicity studies for VEGF Trap were considered inappropriate in this case.

3 Studies Submitted

3.1 Studies Reviewed

Primary Pharmacology

- Determination of Equilibrium Binding Constants for the Interaction of Human VEGF-A165 and Human PlGF-2 with Aflibercept Conformance and Production Lots (Study # VGFT-MX-08021)
- Determination of Equilibrium Binding Constants for the Interaction of Aflibercept with VEGF-Family Related Ligands (Study # VGFT-MX-08022)
- VEGFR2 Bioassays of Aflibercept: Blocking of VEGFR2 Phosphorylation and Calcium Mobilization in HUVE Cells (Study # VGFT-MX-08016)
- VEGFR2 Bioassays of Aflibercept: Blocking of VEGFR2 Phosphorylation and Calcium Mobilization in HUVE Cells (Study # VGFT-MX-08016)

PGR2026-00039
Biocon Ex.1065
Page 422 of 595

- A Study to Evaluate the Safety and Efficacy of VEGF Trap Administered by Intravitreal Injection and Intravenous Infusion in a Cynomolgus Monkey Choroidal Neovascularization (CNV) Model of Age-Related Macular Degeneration (Study # VGFT-TX-03027)
- Intravitreal Injection of VEGF Trap Reverses Breakdown of Blood-Retinal Barrier in Diabetes (Study # VGT-NC-007)
- VEGF Trap Reverses Breakdown of Blood-Retinal Barrier in Diabetes (Study # VGT-NC-008)
- Intravitreal Administration of VEGF Trap Inhibits Pathological Retinal Neovascularization in a Mouse Model of Oxygen-Induced Retinopathy (Study # VGT-NC-013)

Secondary Pharmacology

- Blood Pressure Effects of VEGF Trap (AVE0005) in Telemetered Mice and Rats (Study # VGFT-MX-08018)
- Complement-Dependent Cytotoxicity (CDC) and Antibody-Dependent Cell-Mediated Cytotoxicity (ADCC) Activities of Aflibercept (AVE0005, VEGF Trap) (Study # VGFT-MX-07014)

Safety Pharmacology

- Effect on the Respiratory Function after a Single 30-Minute Intravenous Infusion in Unrestrained Conscious Rats using Whole Body Plethysmography (Study # VGFT-TX-06009)

PK/ADME

- Collection of Samples for a Pharmacokinetic Study of VEGF Trap and Mini-VEGF Trap After Intravitreal Injection in Pigmented Rabbits (Study # VGFT-PK-03028)
- A Single-Dose Intravenous and Subcutaneous Pharmacokinetic Study of VEGF Trap in Cynomolgus Monkeys (Study # VGFT-PK-01012)
- Biodistribution of VEGF Trap in Normal Sprague-Dawley Female Rats (Study # VGFT-PK-01005.2)
- Pharmacokinetics of VEGF Trap Following Intravenous Administration to Sham-Operated and Nephrectomized Sprague Dawley Rats (Study # VGFT-PK-01004.2)
- Pharmacokinetics of VEGF Trap following Intravenous Administration to Sprague Dawley Rat: Correlation between Pharmacokinetic Parameters and Sialic Acid Levels (Study # PK06005-9-SA-01V1)

Single-Dose Toxicity

- Summary Report AVE0005: Exploratory Single-Dose Intravenous (30-Minute Infusion) Toxicity Study in Rats with 2-Week Observation Period (Study # VGFT-TX-06007)
- AVE0005: Exploratory Single-Dose Intravenous (30-Minute Infusion) Toxicity Study in Rats with 2-Week Observation Period (Study VGFT-TX-06008)

Repeat-Dose Toxicity

PGR2026-00039
Biocon Ex.1065
Page 423 of 595

- 8-Month Intravitreal Toxicity and Toxicokinetic Study in VEGF Trap in Cynomolgus Monkeys with a 4-Month Recovery (Study # VGFT-TX-05011)
- 13-Week Intravitreal Toxicity and Toxicokinetic Study with VEGF Trap in Cynomolgus Monkeys with a 10-Week Recovery (Study # VGFT-TX-04019)
- 13-Week Exploratory Intravitreal Study of VEGF Trap and Mini-VEGF Trap in Cynomolgus Monkeys (Study # VGFT-TX-03053)
- A 13-Week Exploratory Formulation Intravitreal Toxicity and Toxicokinetic Study of a VEGF Trap in Cynomolgus Monkeys (Study # VGFT-TX-05015)
- An Intravitreal Toxicity and Toxicokinetic Study with VEGF Trap in Cynomolgus Monkeys (Study # VGFT-TX-04025)
- A Non-GLP, Exploratory Study to Determine the Effect of Subcutaneous Administration of VEGF Trap (25 mg/kg) on Nude (T cell deficient) Rats Twice a Week for Four or Eight Weeks (Study # PK01032)
- A non-GLP, Exploratory Study to Determine the Effect of Subcutaneous Administration of VEGF Trap (10 and 15 mg/kg) on Sprague Dawley Rats Three Times per Week for Four Weeks (Study # PK01027)
- A Non-GLP, Exploratory Study to Determine the Effect of Subcutaneous Administration of VEGF Trap (2 and 5 mg/kg) on Sprague Dawley Rats Three Times per week for Four Weeks (Study # PK01034)
- A Non-GLP, Exploratory Study to Determine the Effect of Subcutaneous Administration of VEGF Trap (0.5 and 1 mg/kg) on Sprague Dawley Rats Three Times per Week for Four Weeks (Study # PK01042)
- A 3-Month Toxicity Study of VEGF Trap by Subcutaneous Injection in Rats (Study # VGFT-TX-02006)
- A 6-Month Intravenous Toxicity Study of VEGF Trap in Cynomolgus Monkeys with a 5-Month Recovery Period (Study # VGFT-TX-05009)
- A 4-Week Subcutaneous Toxicity Study of VEGF Trap in Cynomolgus Monkeys Followed by a 4-Week Recovery Period (Module 4.2.3.2, VGFT-TX-03004)
- A 13-Week Subcutaneous Toxicity Study of VEGF Trap in Cynomolgus Monkeys Followed by a 6-Week Recovery Period (Module 4.2.3.2, VGFT-TX-02037)
- A 4-Week Intravenous Toxicity Study of VEGF Trap with a 6-Week Recovery Period in Cynomolgus Monkeys (Module 4.2.3.2, VGFT-TX-02029)
- A 13-Week Repeat-Dose Intravenous Toxicity Study of VEGF Trap in Cynomolgus Monkeys and a 13-Week Recovery Period (Module 4.2.3.2, VGFT-TX-03048)

Embryonic Fetal Development

- AVE005: Intravenous (30-Minute Infusion) Embryo-Fetal Toxicity Study in Rabbits (Study # VGFT-TX-06002)
- AVE0005: Intravenous (30-min Infusion) Range-Finding Toxicity Study in Pregnant Rabbits (Study # VGFT-TX-06001; Module 4.2.3.5.2.1)

Special Toxicology Studies

- Cross-Reactivity of VEGF Trap with Human Tissue *Ex Vivo* (Study # SPS 01-141)
- Evaluation of VEGF Trap to Induce Hemolysis in Monkey Blood and to Induce Flocculation in Monkey Plasma and Serum (Study # Hem#1)

PGR2026-00039
Biocon Ex.1065
Page 424 of 595

- Evaluation of VEGF Trap to Induce Hemolysis in Whole Blood from Humans and to Induce Flocculation in Human Plasma and Serum (Study # Hem#3)
- Evaluation of VEGF Trap to Induce Hemolysis in Whole Blood from Humans and to Induce Flocculation in Human Plasma and Serum (Study # Hem#4)
- Evaluation of VEGF Trap to Induce Hemolysis in Whole Blood from Humans and to Induce Flocculation in Human Plasma and Serum (Study # Hem#5)

3.2 Studies Not Reviewed

- Pharmacokinetics and Bioavailability of VEGF Trap Following Intravenous and Subcutaneous Administration to Sprague Dawley Rats (Study # VGFT-PK-01001.2)
- Pharmacokinetic Dose Ranging Study of VEGF Trap Administered as a Single Subcutaneous Injection to Sprague-Dawley Rats (VGFT-PK-01002.0)
- Pharmacokinetics and Bioavailability of VEGF Trap Following Intravenous and Subcutaneous Administration to CD-I Mice (VGFT-PK-01007.3)
- Pharmacokinetics of VEGF Trap following Intravenous Administration to Sprague Dawley Rat: Correlation Between Pharmacokinetic Parameters and Sialic Acid Levels (Study # PK06005-9-SA-01V1)
- AVE0005: Exploratory 14-Day Intravenous (30-Min Infusion) Toxicity Study in Nonpregnant Female Rabbits (Study # VGFT-TX-05007)
- AVE0005: Single-Dose Local Intravenous, Intramuscular, and Subcutaneous Tolerance Study in Female Rabbits (Study # VGFT-TX-05008)
- A 3-Month Intravenous Toxicity Study of VEGF Trap in Cynomolgus Monkeys with a 5-Month Recovery Period (Study # VGFT-TX-05010)
- All analytical methods and validation reports

3.3 Previous Reviews Referenced

Memo to File: IND 12462 (b) (4) dated 6-17-2009 by James Wild, Ph.D.

4 Pharmacology

4.1 Primary Pharmacology

Determination of Equilibrium Binding Constants for the Interaction of Human VEGF-A165 and Human PlGF-2 with Aflibercept Conformance and Production Lots (Study # VGFT-MX-08021) - The interaction between aflibercept (4 conformance lots and 3 production lots) and human VEGF-A_{165} and PlGF-2 were measured using BiaCore technology. The range for the association rate constant (ka), dissociation rate constant (kd), and equilibrium dissociation constant (KD) are shown in the table below. Similar binding affinities were observed between lots.

PGR2026-00039
Biocon Ex.1065
Page 425 of 595

Table 1: Binding Parameters (Range) for the Interaction of Different VEGF Trap Lots with VEGF-A_{165} and PlGF-2

Ligand	ka ($M^{-1}s^{-1}$)	Kd (s^{-1})	K_D (pM)
VEGF-A_{165}	2.28-5.12 x 10^7	1.41-2.54 x10^{-5}	0.496-0.763
PlGF-2	1.75-3.73 x 10^6	1.05-9.62 x10^{-5}	29.1-42.6

Determination of Equilibrium Binding Constants for the Interaction of Aflibercept with VEGF-Family Related Ligands (Study # VGFT-MX-08022) – The interaction between aflibercept and eleven VEGF family related ligands was measured using BiaCore technology. As shown in the table below, VEGF Trap exhibited high affinity binding to VEGF-A from human, mouse, rat and rabbit (sub-picomolar K_D values). VEGF Trap also exhibited a high affinity for human and mouse PlGF, although lower than that for VEGF-A. Aflibercept did not demonstrate binding to human VEGF-C and human VEGF-D.

Table 2: Binding Parameters (Mean) for the Interaction of VEGF Trap to VEGF Family Related Ligands

Ligand	ka ($M^{-1}s^{-1}$)	kd (s^{-1})	K_D (pM)
Human VEGF-A_{165}	4.05x10^7	2.01x10^{-5}	0.497
Human VEGF-A_{121}	3.75x10^7	1.35x10^{-5}	0.360
Human PlGF-2	1.75x10^6	6.81x10^{-5}	38.8
Human PlGF-1	6.73 x10^6	2.64x10^{-3}	392.0
Murine VEGF-A_{164}	2.80x10^7	1.64x10^{-5}	0.585
Murine VEGF-A_{120}	2.15x10^7	1.23 x10^{-5}	0.571
Murine PlGF-2	1.64x10^7	5.45x10^{-5}	3.33
Rat VEGF-A_{164}	3.67x10^7	1.73x10^{-5}	0.471
Rabbit VEGF -A_{165}	3.39x10^7	2.63 x10^{-5}	0.775
Human VEGF-C	NB[a]	NB	NB
Human VEGF-D	NB	NB	NB
Abbreviations used: ka = Association rate constant, kd = Dissociation rate constant, K_D = Equilibrium dissociation constant.			

[a] NB= no detectable binding

The applicant stated that the binding affinity of VEGF Trap to VEGF-A from cynomolgus monkey was not tested because the monkey VEGF-A protein sequence is identical on the amino acid level to its human counterpart. Thus, the applicant believes that the binding interaction of human and monkey VEGF-A with VEGF Trap should likely be indistinguishable. The fact that the systemic toxicity studies (Section 6.2) showed

PGR2026-00039
Biocon Ex.1065
Page 426 of 595

targets of toxicity known for VEGF inhibitors and efficacy (see below) was observed in a monkey model of choroidal neovascularization (CNV) supports the assertion that VEGF Trap binds to monkey VEGF.

VEGFR2 Bioassays of Aflibercept: Blocking of VEGFR2 Phosphorylation and Calcium Mobilization in HUVE Cells (Study # VGFT-MX-08016) – Complete inhibition of VEGF-dependent VEGF receptor phosphorylation was observed when VEGF Trap (1 nM) was incubated with 1-3 nM VEGF-A_{165}, i.e., at a molar ratio of 1:1 or greater. VEGF Trap effectively inhibited calcium mobilization with an IC_{50} of 1.20-1.73 nM.

A Study to Evaluate the Safety and Efficacy of VEGF Trap Administered by Intravitreal Injection and Intravenous Infusion in a Cynomolgus Monkey Choroidal Neovascularization (CNV) Model of Age-Related Macular Degeneration (Study # VGFT-TX-03027) – Cynomolgus monkeys (3/sex/goup) were administered placebo or VEGF Trap at concentrations of 50-500 µg/eye biweekly by ITV injection for a total of 3 doses beginning ~ 1 week prior to laser treatment. An additional high-dose group received a single ITV injection 15 days postlaser for a CNV regression group. A separate set of animals received placebo, or 3 or 10 mg/kg VEGF Trap weekly via IV infusion for a total of 6 doses ~ 1 week prior to laser treatment. Evaluations included fluorescein angiography, slit lamp biomicroscopy, indirect ophthalmoscopy, and intraocular pressure. At 35 days postlaser treatment, animals were sacrificed, and the eyes were collected and preserved for microscopic evaluation.

Administration of VEGF Trap prevented the development of clinically significant Grade 4 CNV leak following laser injury at all doses tested and by both routes of administration as assessed by fluorescein angiography. Microscopic evaluation of laser areas showed that when VEGF Trap administration (500 µg biweekly ITV; only dose evaluated) was begun prior to laser injury, choroidal fibroplasia and retinal elevation scores were all lower in VEGF Trap-treated animals relative to placebo controls. A single ITV injection of 500 µg induced rapid and complete regression of established, active CNV leak with microscopic evidence for a trend toward decreased CNV.

Similar to the findings in the repeat-dose ocular toxicology studies (Section 6.2), mild (trace to 1+) inflammatory cells were observed in the anterior chamber or vitreous in all VEGF Trap treated animals. IOP increased immediately after dosing in all groups including controls with reversal to baseline values by the next time it was measured. This increased was attributed to the sudden increase in intraocular volume secondary to the injection. A lower injection volume (25 µL *vs.* 50 µL) resulted in a smaller increase in IOP.

Peak plasma concentrations of free VEGF Trap were measured 24 hrs after ITV injection with mean concentrations of < 0.886 and <1.51 µg/mL at 250 and 500 µg/eye, respectively. At 50 µg/mL, plasma levels were BLQ. After IV administration, mean concentrations were < 77.4 and <278 µg/mL at 3 and 10 mg/kg, respectively.

Intravitreal Injection of VEGF Trap Reverses Breakdown of Blood-Retinal Barrier in Diabetes (Study # VGT-NC-007) – Diabetic male Sprague-Dawley rats received a

PGR2026-00039
Biocon Ex.1065
Page 427 of 595

single, ITV injection of VEGF Trap (3 µg/3 µL) in one eye, and an equal amount of control protein, hFc in the contralateral eye. Forty-eight hours after treatment, animals were injected IV with Evans Blue dye (45 mg/kg), and retinal vessel permeability was assessed by measuring dye concentration in the retina 2 hrs later. Evans Blue concentrations in eyes injected with VEGF Trap were significantly reduced compared to those injected ITV with hFc, and were equivalent to the levels seen in non-diabetic controls, indicating that VEGF Trap suppressed the leaking of fluid from the blood vessels in the diabetic eyes.

VEGF Trap Reverses Breakdown of Blood-Retinal Barrier in Diabetes (Study # VGT-NC-008) – Diabetic male Sprague-Dawley rats received a single, IP injection of VEGF Trap (25 mg/kg) and were assessed 24 hrs later for retinal permeability by the extravasation of Evans Blue dye. As noted after ITV injection (Study # VGT-NC-007 above), Evans Blue concentrations in retinas from animals treated with VEGF Trap were significantly reduced compared to those in diabetic eyes, and were equivalent to the levels seen in non-diabetic controls.

Intravitreal Administration of VEGF Trap Inhibits Pathological Retinal Neovascularization in a Mouse Model of Oxygen-Induced Retinopathy (Study # VGT-NC-013) – Seven days old C57/B16 pups subjected to hyperoxia for 5 days exhibited marked pathological angiogenesis in the retina, characterized by the presence of vascular tufts penetrating the inner limiting membrane and chaotic sprouting of vessels on the surface of the retina. VEGF Trap effectively blocked the development of these vascular abnormalities when administered as an ITV dose of 0.5 µg at postnatal day 14 (evaluated at postnatal day 17) or 0.24 µg at postnatal day 15 (evaluated at postnatal day 19).

4.2 Secondary Pharmacology

Blood Pressure Effects of VEGF Trap (AVE0005) in Telemetered Mice and Rats (Study # VGFT-MX-08018) – Single, subcutaneous injections of VEGF Trap (0.5-25 mg/kg) produced relatively rapid increases in blood pressure in Wistar-Kyoto (WKY) rats. No elevations were noted at ≤0.15 mg/kg. Similarly, doses of 2.5 and 25 mg/kg produced rapid increases in blood pressure in C57BL/6 mice. The maximal increases were evident 2-4 days (WKT rats) or 1-2 days postdose (C57BL/6 mice).

The maximal elevation in blood pressure saturated at ≥10 mg/kg (rats). In contrast, the duration of blood pressure elevation was dose proportional throughout the full range of doses tested, in both species. In rats, blood pressure remained above baseline for only 3-4 days in animals receiving 1 mg/kg VEGF Trap, but remained elevated for more than 2 weeks in animals receiving 25 mg/kg VEGF Trap. In mice, the duration of the blood pressure elevation above baseline was ~7 days at 2.5 mg/kg, whereas it was ~ 21 days at 25 mg/kg.

The duration of blood pressure elevation was correlated with the presence of free VEGF Trap in the circulation, such that systolic and diastolic blood pressure remained

PGR2026-00039
Biocon Ex.1065
Page 428 of 595

elevated above pre-treatment baseline values until circulating VEGF Trap levels fell below ~ 1 µg/mL in both species.

In both rats and mice, heart rate tended to transiently decrease below baseline levels at all VEGF Trap doses tested. This drop in heart rate appears to be a reflexive response to the elevation of blood pressure.

The clinical mean C_{max} after a 2 mg ITV dose every 4 weeks was 0.0193 µg/mL. Thus, the threshold of 1 µg/mL is ~50 times the observed human exposure.

Complement-Dependent Cytotoxicity (CDC) and Antibody-Dependent Cell-Mediated Cytotoxicity (ADCC) Activities of Aflibercept (AVE0005, VEGF Trap) (Study # VGFT-MX-07014) - VEGF Trap (0.85 pM-50 nM ± 10 nM $VEGF_{165}$) did not demonstrate ADCC activity in either primary human umbilical vein endothelial cells (HUVECs) or tumor cell lines (lung Calu-6, colon DLD1 and epidermoid A431) incubated with human peripheral blood mononuclear cells (PBMCs). Weak activity was observed on HT1080 cells at the highest drug concentrations used (>1 nM). VEGF Trap (0.85 pM-50 nM ± 10 nM $VEGF_{165}$) was unable to mediate CDC activity in either primary HUVECs or tumor cell lines (fibrosarcoma HT1080, lung Calu6, colon DLD1 and epidermoid A431) incubated with normal human serum (with complement components).

4.3 Safety Pharmacology

Effect on the Respiratory Function after a Single 30-Minute Intravenous Infusion in Unrestrained Conscious Rats using Whole Body Plethysmography (Study # VGFT-TX-06009) – The IV infusion of AVE0005 over 30 minutes at 10, 50 or 250 mg/kg in unrestrained conscious male Sprague-Dawley rats had no significant effects on the respiratory function measured by whole body plethysmography up to 7 days after administration.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Collection of Samples for a Pharmacokinetic Study of VEGF Trap and Mini-VEGF Trap After Intravitreal Injection in Pigmented Rabbits (Study # VGFT-PK-03028) - Male pigmented New Zealand crossbred rabbits received a single ITV injection of VEGF Trap (500 µg/eye) into both eyes. The protein was detected in all ocular tissues examined (vitreous humor, retina and choroid) and plasma. VEGF Trap was eliminated relatively slowly from the vitreous with a half-life ($t_{1/2}$) of ~5 days. The drug penetrated the retina and choroid, though in general never reached more than 10% of the concentrations in the vitreous. The drug was observed in the plasma, though there was a lag in the time of the maximal plasma VEGF Trap concentrations compared to the peak concentration in the eye tissues (see table below). Bound VEGF Trap was measured in both vitreal and plasma samples. In the vitreous humor, free VEGF Trap levels exceeded bound levels for the duration of the study, while in the plasma, bound levels of VEGF

PGR2026-00039
Biocon Ex.1065
Page 429 of 595

Trap exceeded free. As noted by the applicant, these results suggest that there is sufficient free VEGF Trap in the vitreous to reach the choroid and retina, the sites of action. Given that bound VEGF Trap concentrations exceed the levels of free VEGF Trap in the periphery, the applicant hypothesized that there should be limited ability of the free VEGF Trap to bind a substantial percentage of the available endogenous VEGF. The terminal $t_{1/2}$ of bound complex in the vitreous was calculated to be ~130 days. The applicant noted this estimate is likely an overestimation of the intrinsic bound VEGF Trap $t_{1/2}$, due to the continual conversion of free VEGF Trap to the bound form while in the vitreal compartment. The mean PK parameters are summarized below.

Table 3: Mean PK Parameters for Free and Bound VEGF Trap in Rabbits after a Single 500 µg/eye Intravitreal Injection of VEGF Trap

Tissue	C_{max} (µg/mL or µg/g tissue*)	$AUC_{0\text{-}672\ hrs}$ (µg•hr/mL or µg•hr/g tissue*)	T_{max} (hr)	$t_{1/2}$ (hr)
Vitreous				
Free	491	64840	6	115
Bound	0.610	339	240	3199
Retina				
Free	20.8*	3206*	24	132
Choroid				
Free	36.2*	2963	1	115
Plasma				
Free	0.515	199	72	157
Bound	1.26	518	240	171

A Single-Dose Intravenous and Subcutaneous Pharmacokinetic Study of VEGF Trap in Cynomolgus Monkeys (Study # VGFT-PK-01012) – Four groups were dosed once subcutaneously at 0.75, 1.5, 5.0, and 15.0 mg/kg, and one group was dosed once intravenously at 5.0 mg/kg. Three monkeys/sex were assigned to each group. Following SC administration, measures of exposure (C_{max} and AUC) were approximately proportional to the dose at 0.75 and 1.5 mg/kg and at 5 and 15 mg/kg. Group mean terminal $t_{1/2}$ for males and females were ~2 days at 0.75 and 1.5 mg/kg and ~4 - 5 days at 5 and 15 mg/kg. The corresponding free VEGF Trap mean CL/F values were greater and the t1/2 shorter for the lower dose range, as compared to the higher dose range. As noted by the applicant, these observations, in addition to the lack of dose-proportionality, suggest the contribution of a saturable clearance pathway to the total systemic clearance of free VEGF Trap. On the other hand, the nonlinear PK profile could be due to a dose-dependent bioavailability and/or rate of absorption. Absolute bioavailability following SC administration was similar for males and females and averaged 85% at 5 mg/kg (only calculated at this dose).

Following a single 5 mg/kg IV administration, VEGF Trap displayed a multicompartmental PK serum profile. Clearance was slow, the t1/2 was prolonged, and volume of distribution was low compared to total body water (~690 mL/kg for monkeys). In general, no gender differences were distinguished but there was high variability within groups. The mean PK parameters are summarized below.

PGR2026-00039
Biocon Ex.1065
Page 430 of 595

Table 4: Mean PK Parameters of Free VEGF Trap in Monkey Serum after a Single IV or SC Dose

Route		IV	SC	SC	SC	SC
No. of animals[a]		6 (3/3)	6 (3/3)	6 (3/3)	6 (3/3)	6 (3/3)
Dose	[mg/kg]	5	0.75	1.5	5	15
C_{max}	[µg/mL]	181.7 ± 46.4	3.7 ± 2.0	6.5 ± 2.6	36.2 ± 13.0	101 ± 20.8
T_{max}	[h]	n.c.	39 ± 25	64 ± 29	40 ± 28	32 ± 24
$AUC_{0-\infty}$	[µg x h/mL]	10235 ± 1532	511 ± 217	1089 ± 389	8704 ± 2584	24379 ± 5207
$t_{1/2}$	[h]	98 ± 31	55 ± 18	45 ± 10	118 ± 19	101 ± 39
CL	[mL/h/kg]	0.50 ± 0.07	n.c.	n.c.	n.c.	n.c.
Vss	[mL/kg]	62 ± 11	n.c.	n.c.	n.c.	n.c.
CL/F	[mL/h/kg]	n.c.	1.68 ± 0.64	1.61 ± 0.83	0.62 ± 0.17	0.64 ± 0.13
MRT_{0-t}	[h]	99 ± 7	98 ± 19	115 ± 17	137 ± 5	140 ± 10
F[b]	[%]	n.c.	n.c.	n.c.	85	n.c.

[a] number of all animals (male / female)
[b] bioavailability determined from $AUC_{0-\infty}$ ratio
n.c = not calculated

Biodistribution of VEGF Trap in Normal Sprague-Dawley Female Rats (Study # VGFT-PK-01005.2) – Rats received a 1 mg/kg IV dose of ^{125}I-labeled VEGF Trap. Heart, lungs, liver, kidneys, adrenal glands, spleen, small intestine, large intestine, colon, fat pad, thigh muscle, thyroid gland, and serum were analyzed for radioactive counts. At 5 min postdose, the radioactivity followed a rank order (% dose) of serum (75%) > liver (11.4%) > kidney (1.33%) > spleen (0.42%) > lung (0.34%) > heart (0.19%). The remaining tissues had levels of 0.01-0.04% of the dose. By 24 hrs postdose, the levels in the serum had declined to 12% of the dose and by 168 hrs postdose, the levels were down to 0.76%. By 168 hrs postdose, only 0.16% of the dose was detected in the liver. The results suggest that the distribution of VEGF Trap is limited largely to the circulation and the liver is the main organ for elimination.

Pharmacokinetics of VEGF Trap Following Intravenous Administration to Sham-Operated and Nephrectomized Sprague Dawley Rats (Study # VGFT-PK-01004.2) – After administration of a single VEGF Trap IV dose of 1 mg/kg to female rats, there were no substantial differences in the PK parameters between sham-operated (n=7) and functionally nephrectomized (n=10) rats. The mean (± SD) concentration of VEGF Trap at the 1st blood sampling was 27.26 ± 4.82 µg/mL for the sham-operated rats and 26.86 ± 3.52 µg/mL for the nephrectomized rats. $AUC_{0\text{-}10\ hrs}$ was 163.7 ± 14.2 µg•hr/mL and 163.7 ± 17.3 µg•hr/mL for the sham-operated and nephrectomized rats, respectively. These results imply that the kidney does not play a major role in VEGF Trap clearance from the systemic circulation.

PGR2026-00039
Biocon Ex.1065
Page 431 of 595

5.2 Toxicokinetics

The vitreous and plasma concentrations of free VEGF Trap and the plasma concentrations of VEGF Trap complex were determined in 4 separate toxicology studies following repeated ITV dosing to male and female cynomolgus monkeys (VGFT-TX 04019, VGFT-TX-04025, VGFT-TX-05011, and VGFT-TX-05015). Refer to each toxicology study under Section 6.2.

6 General Toxicology

6.1 Single-Dose Toxicity

Summary Report AVE0005: Exploratory Single-Dose Intravenous (30-Minute Infusion) Toxicity Study in Rats with 2-Week Observation Period (Study # VGFT-TX-06007) – According to the summary (full report not submitted), single IV administration of AVE0005 to Sprague Dawley Crl:CD®(SD)IGS BR rats at doses of 150 and 500 mg/kg resulted in transient skin lesions, and at 150 mg/kg only, discoloration of the tail (administration site). A moderate decrease in body weight gain (30-55%) was noted in both male and female rats at both dose levels, associated with a moderate decrease (51-90%) in food consumption in female rats at 500 mg/kg. The applicant concluded that under the conditions of this study, the lethal dose and the MTD were >500 mg/kg. The reviewer concurs.

AVE0005: Exploratory Single-Dose Intravenous (30-Minute Infusion) Toxicity Study in Rats with 2-Week Observation Period (Study VGFT-TX-06008) – A single 30-min IV infusion of AVE0005 to Sprague Dawley Crl:CD®(SD)IGS BR rats at doses of 50, 150 or 500 mg/kg resulted in lesions at the injection site in a few rats at 50 and 500 mg/kg and moderate dose-related decrease in mean body weight gain (38-65%) in males at all dose levels associated with slight decreases in mean food consumption (16-27%). The applicant noted that from Days 8-14 mean body weight gain of males was comparable in all groups. However, although the data showed some recovery, lower body weight gains were still observed at all dose levels (26-43%) compared to controls. The applicant concluded that under the conditions of this study, the lethal dose was above 500 mg/kg and the NOAEL was considered to be 150 mg/kg since at this dose level the effect on body weight gain was reversed by the end of the study and the effect on food consumption at the end of the study was minimal (<10% decrease). However, the reviewer considers that given that there was still a significant decrease in body weight gain even at the low dose (26%) at the end of the study, a NOAEL was not identified in males. In females, the NOAEL was > 500 mg/kg.

6.2 Repeat-Dose Toxicity

Ocular Route Specific Studies

Study title: 8-Month Intravitreal Toxicity and Toxicokinetic Study in VEGF

PGR2026-00039
Biocon Ex.1065
Page 432 of 595

Trap in Cynomolgus Monkeys with a 4-Month Recovery

Study no.:	VGFT-TX-05011
Study report location:	Module 4.2.3.2
Conducting laboratory and location:	(b) (4) 2595
Date of study initiation:	July 6, 2006
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	VEGF Trap (10 mM Sodium Phosphate, 0.03% PS20, 40mM NaCl, 5% Sucrose, pH 6.2) 10 mg/mL, lot # C06002D640X21A, 99.5% pure VEGF Trap (10 mM Sodium Phosphate, 0.03% PS20, 40mM NaCl, 5% Sucrose, pH 6.2) 40 mg/mL, lot # C06002D640N11A, 99.3% pure VEGF Trap (10 mM Sodium Phosphate, 0.03% PS20, 40mM NaCl, 5% Sucrose, pH 6.2) 80 mg/mL, lot # C06002D640X11A, 98.6% pure VEGF Trap (10 mM Sodium Phosphate, 0.03% PS20, (b) (4) NaCl) 40 mg/mL, lot # C06002D640X31A, 99.2% pure ***Note:*** *The (b) (4) 40 mg/mL VEGF Trap formulations (10 mM Sodium Phosphate, 0.03% PS20, 40mM NaCl, 5% Sucrose, pH 6.2) are the intended commercial formulations.*

Key Study Findings

- ITV administration of VEGF Trap to cynomolgus monkeys at 4-week intervals for 9 doses at levels of 500-4000 µg/eye produced a mild and transient anterior segment and vitreous inflammatory response that was not associated with other ocular abnormalities.
- Epithelial erosion/ulceration of the nasal turbinates was noted at ≥ 2000 µg/eye.
- No marked differences in these findings were noted between both formulations evaluated, including the commercial formulation.
- Compared with the free VEGF Trap concentration in the vitreous, the systemic concentration was low (<3%). However, there was substantial systemic exposure of VEGF Trap (free and/or bound) after ITV injection as levels were in the µg/mL

PGR2026-00039
Biocon Ex.1065
Page 433 of 595

range. The applicant acknowledged these levels may be underestimated because of the long storage period of three samples prior to analysis.

- Ten out of 48 animals were positive for the presence of anti-VEGF Trap antibodies. There was no obvious correlation between the appearance of these putative antibodies and any change in either free and/or bound VEGF Trap levels in these animals.

Methods

Doses:

Group	No. of Animals Male	No. of Animals Female	Dose Level (µg/eye)	Dose Concentration (mg/mL)
Formulation: 0.03% PS20, 40mM NaCl, 5% Sucrose				
1 (Control)	6	6	0	0
2 (Low)	6	6	500	10
3 (Mid)	6	6	2000	40
4 (High)	6	6	4000	80
Formulation: 0.03% PS20, (b) (4)				
5 (Control)	6	6	0	0
6 (Mid)	6	6	2000	40

Frequency of dosing: Once every 4 weeks for 8 months (9 doses/eye)

Route of administration: ITV to both eyes

Dose volume: 50 µL/eye using pre-filled 1-mL glass syringes

Formulation/Vehicle: As shown above, two formulations were evaluated: (1) 10 mM Sodium Phosphate, 0.03% PS20, 40 mM NaCl, and 5% sucrose and (2) 10 mM Sodium Phosphate, 0.03% PS20, and (b) (4) NaCl

Note: Formulation (1) is the commercial formulation

Species/Strain: Cynomolgus monkeys (*Macaca fascicularis*)

Number/Sex/Group: 6

Age: 2-4 yrs old

Weight: 2.1-4.0 kg for males and 2.0-2.9 kg for females

Satellite groups: Two animals/sex/group underwent at least 4 months without treatment following the final dose for recovery assessment.

Unique study design: Complement activation was evaluated.

Deviation from study protocol: None that could adversely affect interpretation of the study results.

Observations and Results

Mortality (Twice daily) – One high-dose male was sacrificed on Day 164 due to a sore on the left foot. This was considered unrelated to the test article.

PGR2026-00039
Biocon Ex.1065
Page 434 of 595

Clinical Signs (Once daily cageside observation; at least once during the predose phase, once weekly during the dosing and recovery phases, and on the day of scheduled sacrifice for detailed observations) – No test article-related findings

Body Weights (At least once prior to treatment, on the first day of treatment, and weekly thereafter during the dosing phase; on Day 1 of the recovery phase an weekly thereafter during the recovery phase) – No test article-related effects

Feed Consumption (Once daily qualitatively) – This data was difficult to evaluate as presented. The applicant claims there was no test article-related effect. The lack of an effect in body weights, supports this claim.

Ophthalmoscopy

Ophthalmic Examinations (OE) (During the predose phase, prior to each dose, 2 days after each dose, approximately weekly during the dosing phase during non-dose weeks, every 2 weeks during recovery, and before the terminal and recovery necropsies by slit lamp biomicroscope and indirect ophthalmoscope) – The two VEGF Trap formulations and, to a lesser extent, the two vehicle controls typically resulted in a mild anterior segment/vitreous inflammatory response. The severity was usually trace to 1+ (mild) with some occasions of 2+, 3+, or 4+ (moderate-severe), particularly in the low dose (Group 2) and also at 2000 µg/eye (Group 6) and 4000 µg/eye (Group 4). This finding was not continuous, *i.e*, it was not observed at all dose intervals. It is unclear why the low-dose VEGF Trap group would exhibit anterior chamber cell scores ≥1+ more frequently than groups treated with greater amounts of the test article using either the same or different vehicles. After usually peaking 2 days after each dose, anterior chamber cell scores spontaneously declined in the interval between doses in all six groups. By 1 week after each dose, anterior chamber cell scores usually had returned to 0 values in all six groups. This finding was not present at recovery.

Vitreal cells (generally trace to 1+) were observed in the majority of eyes through the dosing phase in all groups including controls. Some instances of 2-4+ were observed but this was not persistent (lower severity in subsequent injections). This finding was continuous throughout dosing and gradually disappeared during the recovery period.

Intraocular Pressure (IOP) (In conjunction with OE) – There was a ≤5-fold increase in IOP immediately postdose across all groups including controls. This increase could be expected from the sudden increase in intraocular volume after a bolus injection into the vitreous. IOP returned to normal range by the next time point measured.

Electroretinography (ERG) (During the predose phase, during Weeks 5/6, 13/14, 24, and 32 of the dosing phase (~1 week after the 2nd and 4th doses, ~3 weeks after the 6th dose and within 2 weeks before the terminal sacrifice), and during Week 7/8 of the recovery phase and within 2 weeks before the recovery sacrifice) – No test article-related effects

PGR2026-00039
Biocon Ex.1065
Page 435 of 595

Ocular Photographs (OP) (Once during the predose phase and during Weeks 6, 14, 25, and 33 of the dosing phase (~2 weeks after the 2nd and 4th doses, ~1 week after the 7th dose, and within 1 week before the terminal sacrifice), and during Week 8/9 of the recovery phase and within 1 week before the recovery sacrifice) – No test article-related effects

Fluorescein Angiography (FA) (In conjunction with ERG evaluations) - No test article-related effects

Hematology and coagulation (Twice during the predose phase, once during Weeks 5, 13, 26, and 34 of the dosing phase, and during Weeks 9 and 17 of the recovery phase) – No test article related effects

Clinical Chemistry (Twice during the predose phase, once during Weeks 5, 13, 26, and 34 of the dosing phase, and during Weeks 9 and 17 of the recovery phase) – The applicant mentioned that the only statistically significant difference considered potentially test article-related was mildly lower serum chloride concentration observed at Day 176 and 232 of the dosing phase for high dose males treated with the first formulation (0.03% PS20, 40mM sodium chloride, 5% sucrose). The individual animal listings showed the values were within predose and control range on Day 176. At Day 232, only 1/5 monkeys had a value below the range observed in the concurrent control (99 nmol/L at the high-dose compared to control range of 100-112 nmol/L). Therefore, the reviewer believes the decrease was unrelated to treatment.

Urinalysis (Once during the predose phase, once during Weeks 5, 13, 26, and 34 of the dosing phase, and during Weeks 9 and 17 of the recovery phase) - The applicant mentioned that the only statistically significant difference considered potentially test article-related was decreased urine pH and mildly higher urine sodium, potassium, and chloride excretion observed at Day 232 of the dosing phase for males treated with the first formulation (0.03% PS20, 40mM sodium chloride, 5% sucrose) at 4000 µg/eye. The individual animal listings showed a range of values similar to that seen at predose in all groups and/or within the concurrent control, and therefore, these differences were considered incidental.

Gross Pathology (After 8 months of treatment or after 4-months of recovery phase) – No test article-related findings

Organ Weights (Performed in the following organs from all animals) – No test article-related changes

PGR2026-00039
Biocon Ex.1065
Page 436 of 595

adrenal (2)	prostate
brain[a]	seminal vesicles
epididymides (2)	spleen
heart[a]	thyroid (2) with parathyroid[a]
kidney (2)	testis (2)
liver with gallbladder (drained)	thymus[a]
ovary (2)	uterus
pituitary[a]	

a Due to the upper body perfusion, these weights will be considered postfixation weights and will be collected on the day of necropsy.

Histopathology (From control and high-dose groups, eye, eyelids, lacrimal glands, and nonocular tissues (as appropriate) were examined microscopically. The adrenals, brain, femur with marrow (including knee joint), vertebrae and surrounding muscle, heart, duodenum, colon, rectum, kidneys, lesions, nasal turbinates, urinary bladder, ovaries, and uterus of all animals were examined.

Adequate Battery - Yes

Note: Bone marrow smears were prepared but not examined.

Peer Review – Only conducted for ocular tissues.

Histological Findings – At the end of the dosing phase there was a test article-related increased incidence of epithelial erosion/ulceration, often accompanied by chronic-active inflammation of the nasal turbinates in animals given 2000 µg/eye (regardless of formulation) and 4000 µg/eye. At recovery, minimal to slight chronic active inflammation was noted in 1/2 animals in most groups including male controls (except for an incidence of 2 in the low dose females) but the other findings were not present. The incidence (and severity) is given in Table 5.

PGR2026-00039
Biocon Ex.1065
Page 437 of 595

Table 5: Incidence and Severity of Microscopic Findings in the Nasal Turbinates following ITV Dosing of VEGF Trap to Cynomolgus Monkey Monthly for 8 Months

Controls from group(s): 1	Animal sex:	-- Animals Affected -- Males --						-- Females --					
	Dosage group:	Ctls	2	3	4	5	6	Ctls	2	3	4	5	6
Tissues With Diagnoses	No. in group:	4	4	4	3	4	4	4	4	4	4	4	4
Nasal Turbinates ..... Number examined:		4	4	4	3	4	4	4	4	4	4	4	4
Inflammation, Chronic-Active													
	->	4	2	2	2	4	0	3	3	1	2	4	0
	1>	0	2	1	0	0	2	0	0	1	0	0	1
	2>	0	0	0	1	0	2	1	1	2	2	0	3
	3>	0	0	1	0	0	0	0	0	0	0	0	0
..... Total Incidence of Finding Observed:		0	2	2	1	0	4	1	1	3	2	0	4
Erosion/Ulceration, Respiratory Epithelium													
	->	4	4	3	3	4	2	4	4	3	3	4	0
	1>	0	0	0	0	0	0	0	0	0	0	0	2
	2>	0	0	0	0	0	2	0	0	1	1	0	1
	3>	0	0	0	0	0	0	0	0	0	0	0	1
	4>	0	0	1	0	0	0	0	0	0	0	0	0
..... Total Incidence of Finding Observed:		0	0	1	0	0	2	0	0	1	1	0	4
Hyperplasia, Respiratory Epithelium													
	->	4	4	4	3	4	4	4	4	4	4	4	4
..... Total Incidence of Finding Observed:		0	0	0	0	0	0	0	0	0	0	0	0
Hemorrhage													
	->	4	4	4	3	4	4	4	4	4	4	4	3
	2>	0	0	0	0	0	0	0	0	0	0	0	1
..... Total Incidence of Finding Observed:		0	0	0	0	0	0	0	0	0	0	0	1
Squamous metaplasia (conversion from respiratory to -squamous epithelium)													
	->	4	4	4	3	4	3	4	4	4	4	4	4
	2>	0	0	0	0	0	1	0	0	0	0	0	0
..... Total Incidence of Finding Observed:		0	0	0	0	0	1	0	0	0	0	0	0

All Diagnoses; Phases: P2; Death types: Scheduled PS; Date of death range: 06.Mar.07 To 15.Mar.07

One male at 4000 µg/eye (#I08593) had a B-astrocytoma in the brain, one female at 4000 µg/eye µg/eye (#I08629) had a moderate liver granuloma with thick connective tissue capsule. Slight lymphoid hyperplasia in the lung was observed at 4000 µg/eye in one male (#I08593) and one female (#I08632) and in one male at 2000 µg/eye (#I08609). These findings were not observed in the 6-month systemic toxicity study (Study # VGFT-TX-05009) at weekly IV doses up to 30 mg/kg and therefore, they were considered incidental. In addition, the applicant considered the astrocytoma in the brain to be spontaneous and not related to test article treatment for the following reasons:

- Similarly, other marketed drugs of a similar anti-VEGF mechanistic class (Lucentis™, Avastin™, and Macugen™) have not been associated with neoplasia (manufacturer package insert prescribing information).
- While spontaneous central nervous system neoplasia in the nonhuman primate is a rare event, it has been shown to occur.

Special Evaluations

C-reactive protein (Twice once during the predose phase, on Day 5 and once during Weeks 5, 13, 26, and 34 of the dosing phase, and during Weeks 9 and 17 of the recovery phase) - No test article-related effect

PGR2026-00039
Biocon Ex.1065
Page 438 of 595

Complement Analysis (Once during the predose phase and once before dosing on Days 29, 85, 169, 197, and 225 of the dosing phase and during the last week of the recovery phase for C3a, Cd4, and soluble C5b-9) – No test article-related effect

Serum Anti-VEGF Trap Antibody Analysis [Once during the predose phase, once before each dose on Days 1, 29, 57, 85, 113, 141, 169, 197, and 225 of the dosing phase, during Week 26 (from males in Groups 1 through 4), on the day of terminal necropsy (Week 34 of the dosing phase), and during Weeks 9 and 17 (Groups 1 through 4) or 18 (Groups 5 and 6) of the recovery phase] – Ten out of 48 animals had samples collected from the dosing phase that were positive in the anti-VEGF Trap antibody (914-6070 mIU/mL). Of the animals that received VEGF Trap, 2 animals in Group 2 (I08585 and I08617), 1 animal in Group 3 (I08627), 3 animals in Group 4 (I08631, I08632 and I08634), and 4 animals in Group 6 (I08606, I08607, I08608 and I08641) had samples that were positive in the anti-VEGF Trap antibody assay at various time points of the study. There was no obvious correlation between the appearance of these putative antibodies and any change in either free and/or bound VEGF Trap levels in these animals.

Vitreous Fluid Collection (On days of schedule sacrifice; only free VEGF Trap analyzed) – VEGF Trap levels in vitreous humor samples were approximately dose proportional in the highest two dose groups and less than dose proportional at 500 µg/eye. At the end of the 4-month recovery period, there was no detectable free VEGF Trap in the vitreous of any of the animals. No apparent difference was noted in the 2 cohorts receiving the different formulations of VEGF Trap at 2000 µg/eye (Group 3 and Group 6) with respect to the concentration of free VEGF Trap detected in vitreal samples. See Table 6 for mean vitreous levels (both gender combined).

Toxicokinetics (Both free and bound VEGF Trap were analyzed predose and 1 and 3 days postdose on Days 1, 29, 57, 85, 113, 141, 169, 197, and 225 of the dosing phase; weekly during the non-dosing weeks of the dosing phase; and every 2 weeks during the recovery phase, and on the day of terminal necropsy) – Plasma samples were analyzed ~4-24 month after initial sample collection and some samples underwent more than the number of freeze-thaw cycles that the assay was validated for. Therefore, concentrations in the samples may be underestimated.

Free VEGF Trap in plasma –The T_{max} was observed 24 hrs after ITV injection. Free VEGF Trap concentrations at the 24-hr time point were approximately dose proportional in the highest two dose groups and greater than dose proportional at 500 µg/eye when compared with either the 2000 or 4000 µg/eye cohorts. Free VEGF Trap was not detected in the majority of analyzed plasma samples beyond the 1st week postdose in the 500 µg/eye dosing cohort (Group 2). In the two 2000-µg/eye cohorts (Groups 3 and 6), free VEGF Trap was not detected in the majority of analyzed plasma samples beyond the 2nd week postdose. In the 4000-µg/eye cohort (Group 4), free VEGF Trap was detected in most of the Week 3 postdose samples but in only a few animals just prior to the next monthly ITV injection. This suggests that at least some high-dose animals had drug exposure during the entirety of several of the

PGR2026-00039
Biocon Ex.1065
Page 439 of 595

month-long dosing intervals. However, in general, there appears to be little to no accumulation of free drug in the plasma.

Mean free VEGF Trap levels (males and females combined) ranged from 0.802-1.37 µg/mL ($AUC_{0\text{-}28d}$ ≤ 6.66 µg•day/mL) in Group 2 animals receiving 500 µg/eye, from 3.99-6.49 µg/mL ($AUC_{0\text{-}28d}$ ≤ 84.3 µg•day/mL) in Group 3 animals receiving 2000 µg/eye and from 8.36-15.3 µg/mL ($AUC_{0\text{-}28d}$ ≤ 140 µg•day/mL) in the 4000 µg/eye cohort (Group 4) at 24 hrs post each dose administration. The mean systemic levels are shown in Table 6.

In the 2 cohorts receiving the different formulations of VEGF Trap at 2000 µg/eye (Group 3 and Group 6), Group 6 females had slightly higher (1.7-fold) mean free VEGF Trap levels (based on $AUC_{0\text{-}28d}$). Similarly, Group 6 females had higher mean $AUC_{0\text{-}28d}$ values (≤1.7 fold) compared to Group 6 males up to dose # 5.

Free VEGF Trap was detected in plasma samples collected through the 2nd week of recovery in the 4 monkeys at 4000 µg/eye (0.199-0.346 µg/mL), at Day 1 in the 2 of 4 recovery animals at 500 µg/eye (0.221-0.193 µg/mL), at Day 1 in all 8 animals in the two 2000 µg/eye dose groups (0.901-2.52 µg/eye), and at Week 2 in only 1 of the 8 animals at 2000 µg/eye (0.157 µg/mL).

VEGF:VEGF Trap complex (bound VEGF Trap) – Apparent T_{max} was achieved ~1 week post-dose in the 500 µg/eye cohort and ~ 2 weeks postdose in the 2000 and 4000 µg/eye cohorts. There was a less than dose proportional increase in bound VEGF Trap levels. The applicant noted that the low levels of free VEGF Trap observed in circulation after each of these ITV injections is not believed to be sufficient to completely bind all of the endogenous systemic VEGF available *in vivo*. However, the presence of systemically circulating free VEGF Trap for at least 1 week postdose suggests that at least some of the free VEGF Trap can reach systemic circulation via the eye and be detected prior to binding to endogenous VEGF.

Unlike free VEGF Trap, the bound complex has a much slower clearance and elimination rate as it was still detected well into the recovery period. VEGF Trap complex was detected during the recovery period for all VEGF Trap treated cohorts. In the 500 µg/eye dose group (Group 2), bound VEGF Trap was detected in all animals through Week 6 of the recovery period; one monkey in this cohort (#I08585) had detectable complex through recovery Week 14. In the two cohorts administered 2000 µg/eye, complex was measured in all recovery animals through recovery Week 14 for the Group 3 animals and through recovery Week 10 for the Group 6 animals, with 2 of the 4 recovery animals from Group 6 demonstrating bound VEGF Trap at recovery Week 14. In the 4000 µg/eye cohort (Group 4), bound VEGF Trap was measured in all animals through recovery week 10, with 3 out of 4 animals demonstrating measurable complex at recovery Week 14 and 1 of the 4 with detectable complex at the end of the study (recovery Week 18).

PGR2026-00039
Biocon Ex.1065
Page 440 of 595

As noted by the applicant, the results indicate that the majority of the total drug concentration in circulation (Free VEGF Trap + Adjusted Bound VEGF Trap) after each ITV administration of VEGF Trap was the free form directly following administration and the bound form at later time points. Although in general most of the animals may not have been systemically exposed to free VEGF Trap for the entire time period between doses, the monkeys were exposed to VEGF:VEGF Trap complex throughout the study.

The table below shows the mean concentration of free and bound VEGF Trap in the plasma and free VEGF Trap in the vitreous 7 days after the 9th ITV injection.

Table 6: Mean Plasma and Vitreous Free VEGF Trap and Plasma Bound VEGF Trap Concentrations in Monkeys 7 Days after the Last of 9 ITV Doses Administered Every 4 Weeks

Group	Dose (mg/eye)	No. of animals (M/F)	Plasma		Vitreous
			Free VEGF Trap (µg/mL)	Adjusted VEGF Trap Complex (µg/mL)[a]	Free VEGF Trap (µg/mL)
2	0.5[b]	6/6	0.384	1.12	42.0
3	2.0	6/6	4.19	2.74	148
4	4.0	6/6	6.14	3.13	265
6	2.0[c]	6/6	2.15	2.41	129

[a] The bound VEGF Trap concentrations are reported as total complex weight per volume (e.g. µg/mL) and must be normalized for the VEGF Trap portion of the weight alone by multiplying by 0.717 to generate adjusted-bound concentrations.

[b] Formulation ITV-2 (Phase 3 commercial enabling) was: 10 mM sodium phosphate, 40 mM sodium chloride, 0.03% PS20, 5% sucrose, pH 6.2

[c] Formulation 3 was: 10 mM sodium phosphate, [redacted] (b) (4) sodium chloride, 0.03% PS20, pH 6.2

Dosing Solution Analysis – Stability analysis at Time 0 and at End of Study demonstrated dosing solutions were >97% of nominal concentration.

Study title: 13-Week Intravitreal Toxicity and Toxicokinetic Study with VEGF Trap in Cynomolgus Monkeys with a 10-Week Recovery

Study no.:	VGFT-TX-04019
Study report location:	Module 4.2.3.2
Conducting laboratory and location:	[redacted] (b) (4)
Date of study initiation:	August 10, 2004
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	VEGF Trap (1 mg/mL), lot # C04005D620F11A, 99.8% pure VEGF Trap (5 mg/mL), lot # C04005D620E11A, 99.8% pure

PGR2026-00039
Biocon Ex.1065
Page 441 of 595

VEGF Trap (10 mg/mL, lot # C04005D620C11A, 98.6% pure

Key Study Findings

- Mild and reversible ocular inflammation (generally 1+ or less) was observed at all doses in the anterior segment and/or vitreous with a trend for an increased incidence with dose.
- No anti-VEGF Trap antibodies were detected.
- Dose-dependent levels of free VEGF Trap were detected in vitreous humor samples collected 7 days after the last ITV injection. At the end of the 10-week recovery period, there was no detectable free VEGF Trap in the vitreous of any of the animals except for small amounts in 2 high-dose monkeys.
- VEGF-Trap (free and/or bound) was detected systemically after ITV administration at the mid and high doses. Compared with the vitreous concentration of free VEGF Trap, the systemic concentration was low (<1%).

Methods

Doses:	0, 50, 250, or 500 µg/eye
Frequency of dosing:	Once every 4 weeks (4 doses/eye)
Route of administration:	ITV to both eyes
Dose volume:	50 µL/eye
Formulation/Vehicle:	10 mM Sodium phosphate, (b) (4) sodium chloride, and (b) (4)
Species/Strain:	Cynomolgus monkeys (*Macaca fasciculari)*
Number/Sex/Group:	6/sex in control, mid, and high-dose groups; 4/sex in the low dose group
Age:	3-5 yrs old
Weight:	3.8-6.2 kg for males and 2.2-3.2 kg for females
Satellite groups:	Two animals/sex/group in the control, mid and high-dose underwent a 10 week recovery period.
Unique study design:	None
Deviation from study protocol:	None that could adversely affect interpretation of the study results

Observations and Results

Mortality (Twice daily) - None

Clinical Signs (Detailed observations prior to initiation of treatment and weekly during the study; cageside observations daily) – No test article-related effects

Body Weights (Prior to initiation of treatment, on the first day of treatment, and weekly thereafter) - No test article-related effects

PGR2026-00039
Biocon Ex.1065
Page 442 of 595

Feed Consumption (Daily qualitatively) – Apparently, there was no test article-related effects. However, due to the qualitative evaluation, the data is not considered very informative.

Ophthalmoscopy

OE [Once prior to initiation of treatment and predose on each day of dosing (Days 1, 29, 57, and 85; on Days 3, 31, and 87 (2 days after dosing on Days 1, 29, and 85); on Days 8, 34/35, and 64 (~7 days after dosing on Days 1, 29, and 57); on Days 15, 43, 71, and 98/99 (~2 weeks after dosing); and during recovery on Days 112/113, 126/127, 140/141, and on the day of sacrifice (Days 92 and 157/158)] - Mild ocular inflammation (trace or 1+) was observed in the anterior segment and/or vitreous. In the anterior segment, this inflammatory response was apparent at 2 days postdose and diminished with time prior to the next dose. Although observed in all groups including the control group, there was a trend for an increase in the incidence of inflammation with dose. For example, >1+ anterior chamber cell was seen at one or more time points during the study in 4/24 (16.7%), 8/16 (50%), 11/24 (45.8%), and 21/24 (87.5%) eyes at 0, 50, 250, or 500 µg/eye, respectively. During recovery, this finding had resolved.

Inflammatory cells in the vitreous were slower to appear (peak scores typically occurred 1 week postdose) and were slower to leave the viscous vitreal gel than the water-like aqueous humor. The frequency of vitreal cell also exhibited a weak dose response effect. Over the entire study, vitreal cells were seen in 15/24 (62.5%), 12/16 (75%), 20/24 (83.3%), and 24/24 (100%) eyes at 0, 50, 250, or 500 µg/eye, respectively. Overall, however, vitreal cells did not increase in frequency or score between Day 8 (1 week after the first dose) and Day 92 (1 week after the fourth dose) indicating that the 4-week dosing interval does not result in accumulation of inflammatory cells in the vitreous.

Indirect ophthalmoscopy showed focal chorioretinal depigmentation in the right eye in one high dose female beginning on Day 1 and throughout the study. Given the isolated event, a relationship to the test article is not clear.

IOP (In conjunction with OEs) - There was a ≤5.5-fold increase in IOP immediately postdose across all groups including controls. This increase could be expected from the sudden increase in intraocular volume after a bolus injection into the vitreous. IOP returned to normal by the next time point measured (2 days postdose).

ERG [Once before initiation of treatment and during Weeks 6 and 10 and Week 21 (recovery animals)] – No test article-related effects

OP and FA – [Once before initiation of treatment and during Weeks 7 and 13, and Week 22 (recovery animals)] – The applicant stated that there was no test article-related effect (the data was not submitted).

PGR2026-00039
Biocon Ex.1065
Page 443 of 595

Hematology and coagulation [Prior to initiation of treatment and on Day 31/32, Weeks 13 (Day 87) and 18, and on the day of recovery sacrifice (Day 157/158)] – No test article-related effects

Clinical Chemistry [Prior to initiation of treatment and on Day 31/32, Weeks 13 (Day 87) and 18, and on the day of recovery sacrifice (Day 157/158)] – No test article-related effects

Urinalysis (Prior to each schedule sacrifice and Week 17 during the recovery period) - No test article-related effects

Gross Pathology [On Days of schedule necropsy, *i.e.,* Day 92 and after 10 weeks of recovery (Day 157/158)] – Red focus were noted in the cecum of one male and one female each in the mid and high dose groups and in the colon of one female each in the mid and high dose groups. There was no microscopic correlate.

Organ Weights (Performed in the following organs from all animals: adrenals, brain, heart, kidney, liver with gallbladder, spleen, ovary, testis, and thymus) – No test article-related changes

Histopathology (For all animals; full battery) –

Adequate Battery: Yes

Note: Bone marrow smear was collected but not evaluated.

Peer Review: No

Histological Findings - No test article-related effects

Special Evaluation

Vitreous Fluid Collection (On the day of dosing and recovery necropsy) – Dose-dependent levels of VEGF Trap were detected in vitreous humor samples collected 7 days after the last dose. The mean vitreous levels (both genders combined) are shown in Table 7.

At the end of the 10-week recovery phase, VEGF Trap was not detected in the vitreous humor of any animal in the 50 or 250 µg/eye. In vitreous collected from animals in the 500 µg/eye, only two samples from two animals had detectable, although low, VEGF Trap levels (~86 ng/mL).

Serum Antibody Analysis [Before the initiation of treatment and before dosing on Days 1, 29, 57, and 85; on Day 99, during Week 18, and on the day of recovery necropsy (Day 157/158)] – No antibodies were detected

PGR2026-00039
Biocon Ex.1065
Page 444 of 595

Toxicokinetics (On Days 1, 29, 57, and 85 predose, ~1 hr and 1 and 3 days postdose, and approximately weekly throughout the remainder of recovery) -

Free VEGF Trap - Free VEGF Trap was not detected in plasma after ITV administration of 50 µg/eye. Plasma concentrations of free VEGF Trap were highest at ~24 hrs postdose and were approximately dose proportional in the two highest dose level groups. The applicant noted that the lack of detectable free VEGF Trap in the 50 µg/eye group may be partially a result of the sensitivity of the assay. After the third dose, free VEGF Trap was not detected in the 250 or 500 µg/eye groups at 2, 3, or 4 weeks after injection. Overall, results of free VEGF Trap plasma analyses indicate that systemic exposure to VEGF Trap at or beyond 14 days postdose was minimal. The plasma levels ranged from 403-615 ng/mL and 699-1175 ng/mL in the 250 µg/eye and 500 µg/eye cohorts, respectively. The mean levels are shown in Table 7.

Free VEGF Trap was not detected during the recovery period from Day 99 onward at 250 µg/eye and Day 99 at 500 µg/eye, except for high-dose female # AI02506. This animal continued to demonstrate detectable levels of free VEGF Trap in most samples collected after the 4th ITV injection out to 73 days, the last sample collected for this recovery animal. The level at Day 73 postdose was 1460 ng/mL (as high as those observed at T_{max} postdose), indicating that there was a collection or analysis error.

AUC values were estimated for free VEGF Trap plasma levels. Mean $AUC_{0\text{-}28\ days}$ at both 250 and 500 µg/eye decreased as the study progressed. The applicant noted this difference is most likely due to the limited number of sampling time points following the first 2 drug administrations as compared to the last two. $AUC_{0\text{-}28\ days}$ ranged from 729-2862 ng•day/mL (males) and 2221-7062 ng•day/mL (females) at 250 µg/eye, and 2465-8352 ng•day/mL (males) and 4663-16395 ng•day/mL (females) at 500 µg/eye. Exposure in females was ~2-fold higher compared to males.

Systemic exposure was also estimated for the first 72 hrs postdose. In this case, the first 3 injections showed comparable free VEGF Trap levels, with a decrease at the 4th injection. The applicant attributed this decrease to the fact that the estimates for the 4th injection were based only on data from the first 7 days following injection.

VEGF:VEGF Trap complex - Peak VEGF:VEGF Trap complex (bound VEGF Trap) levels were observed at 7 days postdose after the 3rd and 4th injections. Bound VEGF Trap levels after the first two sets of injections were still increasing 72 hrs postdose; which was the last sample collected in each of these first two cycles. An approximate dose proportional or less than dose proportional increase in bound VEGF Trap levels was observed. Bound VEGF Trap was detected at the end of the 10-week recovery period. Although in general, the animals may not have been exposed to free VEGF Trap for the entire period between doses, they were exposed to VEGF Trap complex throughout the study.

PGR2026-00039
Biocon Ex.1065
Page 445 of 595

For the two highest dosing cohorts, the majority of the total VEGF Trap (free plus bound VEGF Trap) levels observed at 24 hrs postdose were due to the presence of free VEGF Trap levels. At 72 hrs, the levels of the bound form had exceeded the free form suggesting that the test article is rapidly converted to the bound form limiting systemic exposure to free VEGF Trap. At 7 days post dose, the majority of the detected total VEGF Trap levels were observed to be mainly due to the presence of the bound VEGF Trap species.

The following table shows the mean free and bound VEGF Trap concentrations observed in the plasma and free VEGF Trap concentrations in the vitreous.

Table 7: Mean Plasma and Vitreous Free VEGF Trap and Plasma Bound VEGF Trap Concentrations in Monkeys 7 Days after the Last of 4 ITV Doses Administered Every 4 Weeks

Dose (mg/eye)	No. of animals (M/F)	Plasma		Vitreous
		Free VEGF Trap (µg/mL)	Adjusted VEGF Trap Complex[a] (µg/mL)	Free VEGF Trap (µg/mL)
0.050	4/4	0	0.126	5.32
0.250	6/6	0.0344	0.630	26.8
0.500	6/6	0.268	1.06	50.2

[a] The bound VEGF Trap concentrations are reported as total complex weight per volume (e.g. µg/mL) and must be normalized for the VEGF Trap portion of the weight alone by multiplying by 0.717 to generate adjusted-bound concentrations.

Dosing Solution Analysis – Stability was conducted in samples stored for the duration of the study (~3 months). The preliminary acceptance criteria of 90% main peak purity as determined by SE-HPLC was not met due to aggregation in the 1 mg/mL and 5 mg/mL dosing solutions (50.7-76.9% main peak area). The bioassay and binding assay results met the specifications. Therefore, the aggregation did not affect the bioactivity of the test article.

Three other 13-week ITV ocular toxicology studies were conducted in monkeys. The main findings are summarized below:

13-Week Exploratory Intravitreal Study of VEGF Trap and Mini-VEGF Trap in Cynomolgus Monkeys (Study # VGFT-TX-03053) – The purpose of this study was to evaluate the ocular toxicity of Mini-VEGF Trap (thrombin cleaved VEGF Trap) and VEGF Trap when administered every 2 weeks via ITV injection to cynomolgus monkeys for at least 3 weeks (Mini-VEGF Trap; two doses) or 13 weeks (VEGF Trap; seven doses).

Three different formulations of VEGF Trap were evaluated. The formulation compositions were the following: VEGF Trap lot # L04-064 (10 mM sodium phosphate, (b) (4) NaCl, (b) (4) PS20, (b) (4) VEGF Trap, pH (b) (4)); VEGF Trap lot # L04-065 (10 mM sodium phosphate, (b) (4) M NaCl, (b) (4)% PS20, (b) (4) (b) (4)

PGR2026-00039
Biocon Ex.1065
Page 446 of 595

(b) (4) VEGF Trap, pH (b) (4)); and VEGF Trap lot # L04-066 (10 mM sodium phosphate, (b) (4) NaCl, 0.03% PS20, (b) (4) VEGF Trap, pH (b) (4)). None of these formulations is identical to the intended clinical formulation.

Only the right eye was treated with the test article; the left eye received the vehicle. The doses used are shown in the table below:

Table 8: Intravitreal Doses Used in Study # VGFT-TX-03053

	Right Eye	Left Eye	No. of	Dose Level[a]	Dose Concentration[a]
Group	Formulation Lot No.	Placebo Lot No.	Males/Females	(µg/eye)	(mg/mL)
1 (VEGF Trap)	L04-064	L04-014	1 / 2	500	10
2 (Mini-VEGF Trap)	RSCH03006	L04-015	1 / 2	250	5
3 (VEGF Trap)	L04-065	L04-016	1 / 2	500	10
4 (VEGF Trap)	L04-066	L04-017	1 / 2	500	10

a Animals were administered the test article at a volume of 0.05 mL. The concentration for Group 2 was achieved by diluting the Mini-VEGF Trap received at a concentration of 9.79 mg/mL.

Both test articles were intended to be dosed for 13 weeks, but marked ocular inflammation attributed to Mini-VEGF Trap formulation resulted in suspension of dosing on Day 29 after two doses had been administered. Whether this degree of inflammation was attributable to the mini-VEGF Trap or to the high levels of endotoxin (19.2 EU/mg) not observed with other VEGF formulations, is uncertain.

A variable and less marked inflammatory response (anterior chamber and vitreous) was observed in VEGF Trap formulations. The inflammation increased in severity in some animals with repeated dosing and was associated with mild effects on retinal function. No discernable differences were observed between VEGF Trap formulations. Systemic exposure to VEGF trap following ITV administration was minimal (measured on Day 1 and Day 85). Only 3 animals had measurable serum levels of VEGF Trap postdose. Specifically, Group 2 animal # I09283 which had a serum level of 210.9 ng/mL 72 hrs postdose on Day 1, Group 2 animal # I09410, which had a serum level of 206.6 ng/mL 24 hrs postdose on Day 1, and Group 4 animal # I01066, which had measurable serum levels of 234.1 and 404.3 ng/mL 5 hrs and 24 hrs postdose, respectively, on Day 85.

A 13-Week Exploratory Formulation Intravitreal Toxicity and Toxicokinetic Study of a VEGF Trap in Cynomolgus Monkeys (Study # VGFT-TX-05015) – This study evaluated the ocular toxicity of 8 formulations of VEGF Trap when administered by ITV injection to cynomolgus monkeys every 4 weeks for at least 13 weeks (four doses) to aid in the selection of the proposed commercial formulation. Groups consisting of males and females for a total of 3 monkeys (2-7 yrs old; 2.7-4.6 kg males and 2.5-4.0 kg females) each received 50 µL/eye ITV doses of one of the 8 formulations, each containing 40 mg/mL VEGF Trap, to provide a VEGF Trap dose of 2 mg/eye. A control group (2 males)

PGR2026-00039
Biocon Ex.1065
Page 447 of 595

received the ITV-1 formulation vehicle [redacted] sodium chloride, 10 mM sodium phosphate, [redacted] pH [redacted]) on a comparable regimen.

Assessment of ocular toxicity was based on clinical ophthalmic signs, intraocular pressure measurements, electroretinographic and photographic evaluations (color fundus photography and fluorescein angiography), and histopathology. Animal health was assessed by clinical signs, qualitative food consumption, body weights, selected organ weights, and clinical pathology.

The formulations are described in the table below. Formulation ITV-2 is the intended commercial formulation. The purity of the formulations ranged from 98.1-99.5%.

Table 9: Placebo and VEGF Trap Formulations Evaluated in a 13-Week (4 Doses) Ocular Toxicity Study in Monkeys (Study # VGFT-TX-05015)

Group No.	Formulation Designation	Formulation	VEGF Trap Concentration mg/mL	Lot/Batch No.
1		[redacted] (10 mM Sodium phosphate, [redacted] Sodium chloride, [redacted]	0	C04004V710D02A
2	1 (ITV-1)	[redacted] (10 mM Sodium phosphate, [redacted] Sodium chloride, [redacted]	40	C04009D640G11B (synonymous with C04009M640G11)
3	2	[redacted] and PS20 (10 mM Sodium phosphate, [redacted] Sodium chloride, [redacted] 0.03% PS20, pH [redacted]	40	C1-5688-39-P20-1A
4	3	PS20 Alone (10 mM Sodium phosphate, [redacted] Sodium chloride, 0.03% PS20, [redacted]	40	C1-5688-47-SAP-1A
5	4 (ITV-2)	Sucrose and PS20 (10 mM Sodium phosphate, 40mM Sodium chloride, 0.03% PS20, 5% Sucrose, pH 6.2)	40	C2-5688-103-SPS-1A
6	5	[redacted] and PS20 (10 mM Sodium phosphate, 40mM Sodium chloride, 0.03% PS20, [redacted] pH 6.2)	40	C3-5688-114-MPS-1A
7	6	[redacted] PS20 (10 mM Sodium phosphate, [redacted] Sodium chloride, [redacted] PS20, pH [redacted]	40	C1-5688-77-PS1-1A
8	7	[redacted] PS20 (10 mM Sodium phosphate, [redacted] Sodium chloride, [redacted] PS20, [redacted]	40	C1-5688-82-PS2-1A
9	8	[redacted] PS20, [redacted] 5% Sucrose, pH 6.5)	40	L05-288-A

[redacted] PS20 = Polysorbate 20

ITV administration of the VEGF Trap and, to a somewhat lesser extent, the vehicle typically produced a mild anterior segment/vitreal cellular response. In general, the anterior chamber cellular response was greatest 2 days after dosing and usually

PGR2026-00039
Biocon Ex.1065
Page 448 of 595

achieved trace to 1+ cell scores in all nine groups with some infrequent incidences of 2+ or 3+ in groups receiving formulations 6 and 7 (1/3 animals in each group). Anterior chamber cell scores spontaneously improved in all nine groups. By 2 weeks after each dose, all eyes in all groups were free of anterior chamber cells with one exception; a male that received Formulation 4 had a trace anterior chamber cell score in one eye. Vitreal cells were typically trace to 1+ in all eyes in all groups throughout the study. Vitreal cell was rare in the control article-treated eyes (Group 1), and on only one occasion (Day 59 in one eye) was trace vitreal cell detected in this group.

No clear and consistent differences were observed between any of the VEGF Trap formulations in terms of the anterior chamber or vitreal response except for, as mentioned previously, the incidences of 2 or 3+ anterior chamber cell in one animal each receiving formulations 6 and 7. As noted by the applicant, the low severity as well as limited number of samples, may not provide a good scenario for detecting clear differences between the formulations.

No biologically significant changes from baseline on fundus photography, fluorescein angiography, or electrophysiology were noted in any animal in any group throughout the study. IOP showed values below 10 mm Hg (4-9 m Hg) in one or more animals across VEGF Trap formulations. These decreases, however, were not generally consistent with subsequent measurements, and values as low as 7 mm Hg were observed on Day 1 predose. Therefore, these lower IOP values were considered to be within normal range.

One female dose with ITV-2 formulation had AST values of 129 U/L (compared to 57 and 82 in concurrent controls and 31-43 U/L predose). ALT was also elevated (101 u/L) compared to 51 and 59 n concurrent control and 53-65 predose). No histopathology was conducted; the relevance of the findings is not clear.

Only the samples from animals in the control group and from those groups receiving the ITV-1 formulation, ITV-2 formulation, and Formulation 3 were analyzed for plasma free VEGF Trap, plasma VEGF Trap complex, and serum anti-VEGF Trap antibodies. Vitreous concentrations of free VEGF Trap were detected at 1 week following the last ITV dose of each of these formulations, indicating substantial ocular exposure to free VEGF Trap for at least one week following dosing.

Peak plasma concentrations of free VEGF Trap were reached approximately 24 hrs after an ITV injection, with mean concentrations ranging from ~4660-5526 ng/mL following the 1st injection and 3982-5563 ng/mL following the 4th injection. Free VEGF Trap was detected in the plasma of most animals at 14 days after dosing, but declined to BLQ by 29 days after dosing.

Peak plasma VEGF:VEGF Trap complex levels were achieved within 2 weeks after VEGF Trap ITV injection. The mean concentrations ranged from ~2090-3190 ng/mL 2 weeks following the 1st injection and 2095-3130 ng/mL 72 hrs following the 4th injection. Bound VEGF Trap was cleared more slowly than free VEGF Trap and was still detected

PGR2026-00039
Biocon Ex.1065
Page 449 of 595

4 weeks after injection and trough concentrations increasing after each successive dose. By 14 days following the last dose, only VEGF Trap complex was detected in the circulation. There was no apparent difference in the TK of the three VEGF Trap formulations evaluated (see Table 10). During the trough period, the majority of total VEGF Trap was in complex form while at peak concentrations free VEGF Trap protein accounted for approximately 2/3 of the total pool.

Table 10: Mean Plasma Concentrations for Free, Adjusted Bound, Total VEGF Trap Concentrations in Monkeys, 3 Days after the 4th ITV Administration of VEGF Trap 2 mg/eye Every 4 Weeks

Formulation	Plasma		
	Free VEGF Trap (µg/mL)	Adjusted VEGF Trap Complex[a] (µg/mL)	Total VEGF Trap (µg/mL)
ITV-1[b] (Formulation 1)	5.160	2.20	7.36
ITV-2[c] (Formulation 4)	3.708	1.50	5.21
Formulation 3[d]	4.212	2.24	6.45

[a] The bound VEGF Trap concentrations are reported as total complex weight per volume (e.g.µg/mL) and must be normalized for the VEGF Trap portion of the weight alone by multiplying by 0.717 to generate adjusted-bound concentrations.
[b] 10 mM sodium phosphate, (b) (4) mM sodium chloride, (b) (4), pH (b) (4)
[c] 10 mM sodium phosphate, 40 mM sodium chloride, 0.03% PS 20, 5% sucrose, pH (b) (4)
[d] 10 mM sodium phosphate, (b) (4) mM sodium chloride, 0.03% PS 20, pH (b) (4)

Anti-VEGF Trap antibodies were detected in one animal treated with formulation ITV-1. This positive finding, however, most likely reflected serum interference in the assay because, as noted by the applicant, the levels were low (less than 2-fold above the LLOQ of the assay) and were detected at similar levels prior to administration of the drug (945 mIU/mL at necropsy *vs.* 932-1401 mIU/mL at predose).

An Intravitreal Toxicity and Toxicokinetic Study with VEGF Trap in Cynomolgus Monkeys (Study # VGFT-TX-04025; GLP) – This study evaluated VEGF Trap Formulation ITV-1, which is different to the intended commercial formulation. As noted in (b) (4)

Monkeys (6/sex/dose) were administered ITV doses of 1 or 2 mg/eye once every 4 weeks for a total of 4 doses at VEGF Trap concentrations of 20 or 40 mg/mL, respectively, followed by a 10-week recovery period. A placebo control group received the vehicle on a comparable dosing regimen. Two additional groups (3/sex/dose) received a single ITV administration of vehicle or 2 mg/eye VEGF Trap, followed by a 4 week recovery period. A single group (5/sex) received an ITV dose of 4 mg/eye (80 mg/mL VEGF Trap concentration) every 6 weeks for a total of 3 doses followed by a 10-week recovery period.

PGR2026-00039
Biocon Ex.1065
Page 450 of 595

Assessment of ocular toxicity was based on slit lamp biomicroscopy, funduscopy, IOP measurements, ERG, photographic evaluations with fluorescein angiography, and histopathology. Animal health was assessed by clinical observations including clinical signs, food consumption, body weights, clinical pathology, selected organ weights, and gross necropsy. Limited systemic tissues were evaluated by histopathology. Free VEGF Trap and VEGF Trap complex in plasma, anti-VEGF Trap antibodies in serum, and free VEGF Trap in the vitreous were determined.

The results of the study for both evaluation of toxicity and plasma TK were similar to those observed in previous ITV toxicity studies with this and other VEGF Trap formulations. A mild and transient anterior segment and vitreous cellular response was observed that was not associated with other ocular abnormalities. There were no significant differences between the two different dosing concentrations or dosing regimens. The cellular response gradually reversed once dosing stopped. No systemic toxicity was observed.

A single animal administered 2 mg/eye VEGF Trap developed serum antibodies and exhibited severe ocular inflammation (3+ or 4+) after receiving 2 doses that was interpreted by the applicant to be due to an immune-mediated mechanism. Mild retinal perivenous sheathing was present in both eyes, and some venous dilatation was noted on the fluorescein angiogram. During the recovery phase, the anterior segment inflammatory response spontaneously resolved. Vitreal cell scores also gradually declined to 1+ - 2+ score at the end of the recovery period. The retinal perivascular sheathing gradually improved such that no perivascular sheathing was present on Day 50 of the recovery period. The presence of an anti-VEGF Trap antibody response in this animal appeared to correlate with decreased plasma levels of both free and bound VEGF Trap, suggesting that the presence of anti-drug antibody accelerated the clearance of both the free and bound forms of VEGF Trap.

Dose-dependent levels of free VEGF Trap were detected in vitreous humor samples collected 7 days after the last administration, with mean levels ranging between 94.3 and 284 µg/mL at 1000 and 4000 µg/eye, respectively. At the end of the 10-week recovery period, measurable levels of VEGF Trap were detected in most vitreous samples obtained from recovery animals, with mean levels ranging between 138 and 153 ng/mL at 1000-4000 µg/eye. In Study # VGFT-TX-04019 above, at the end of the 10-week recovery phase after monthly treatment for 13 weeks, VEGF Trap was not detected in the vitreous humor of any animal in the 50 or 250 µg/eye, and only two samples from two animals in the 500 µg/eye had detectable VEGF Trap levels (~86 ng/mL). In Study # VGFT-TX-04019 at monthly doses up to 4000 µg/eye for 8 months, VEGF Trap was not detected in the vitreous following a 4-month recovery period. Therefore, as would be expected, the extent of exposure to VEGF Trap in the vitreous is dose and recovery period-length dependent.

PGR2026-00039
Biocon Ex.1065
Page 451 of 595

Systemic Route Specific Studies

In repeat-dose studies, VEGF Trap was administered SC to cesarean-derived (CD)-1 (Study # VGFT-PK-01017) and severe combined immunodeficiency (SCID) mice (2x/week for up to 8 weeks) and to Sprague-Dawley (Study # PK01027; 3x/week for 4 weeks) and nude (Study # VGFT-PK-01032; 2x/week for up to 8 weeks) rats. In addition, SC toxicity studies were conducted in Sprague-Dawley rats (Study # VGFT-TX-02006) for up to 13 weeks in duration (3x/week dosing). From these studies, the applicant determined that neither rats nor mice were an appropriate species to use for repeat-dose evaluation of VEGF Trap, as these two species developed an anti-VEGF Trap antibody response associated with nephropathy that precluded long-term dosing. Therefore, the applicant selected the cynomolgus monkey as the primary relevant species for safety assessment of the systemic effects resulting from administration of VEGF Trap.

The main findings of the rat and mice studies are listed in the tables below. In addition to nephropathies, other findings in both rodent species included edema, multiorgan vascular dilatation and congestion, and vasculitis. Similar to findings in monkeys, hemorrhage in the nasoturbinates was noted in mice; bone adverse effects were noted in rats. In spite of the identification of adverse effects, the reviewer concurs that the strong antibody response in these species with the associated marked decrease in VEGF Trap levels and concurrent toxicities will preclude the use of these species for chronic systemic toxicity studies.

Table 11: Main Findings Observed in Rat Systemic Toxicity Studies following Subcutaneous Administration of VEGF Trap

Study Title: A Non-GLP, Exploratory Study to Determine the Effect of Subcutaneous Administration of VEGF Trap (25 mg/kg) on Nude (T cell deficient) Rats Twice a Week for Four or Eight Weeks (Study # PK01032; Module 4.2.3.2) **Design:** Animals were randomly assigned to receive SC injections of either 25 mg/kg of VEGF Trap (3/sex) or placebo (2/sex). Animals were treated twice a week for 4 or 8 weeks. Parameters evaluated included body weights, hematology, clinical chemistry, histopathology, and VEGT Trap and anti-VEFG Trap antibodies levels in serum. **Main Findings**: ↓ body weights and ↑ BUN at 8 weeks, ↑ cholesterol, ↑ triglycerides (4 weeks only), ↑ lipase, ↓ albumin, ↓ A/G ratio, anti-VEGF Trap antibodies not detected but VEGT Trap concentrations decreased with repeated dosing starting on Day 15 (after 4 doses), glomerulonephritis and tubular changes more pronounced at 8 weeks compared to 4 weeks
Study Title: A non-GLP, Exploratory Study to Determine the Effect of Subcutaneous Administration of VEGF Trap (10 and 15 mg/kg) on Sprague Dawley Rats Three Times per Week for Four Weeks (Study # PK01027; Module 4.2.3.2) **Design:** Rats (4/sex/group) were administered SC injections of either 10 mg/kg of VEGF Trap, 15 mg/kg of VEGF Trap, 15 mg/kg of human IgG, or placebo. Animals were treated 3x/week for 4 weeks and then observed for an additional 18 days. An additional 2 females were used as an untreated control. Same parameters as Study # PK01032 were evaluated. **Main Findings:** Mortalities [2/4 females at 15 mg/kg sacrificed due to weight loss and lethargic behavior on Day 19 (after 9 doses), 1 and 2/4 males at 10 mg/kg sacrificed due to edema on Day 21 (after 10 doses) and due to weight loss and lethargic behavior during the post-treatment period on Day 43, respectively, 1/4 males at 15 mg/kg sacrificed on Day 28 due to edema and another found dead during the post-treatment period on Day 32], ↑ body weight due to edema or body weight loss, trend towards ↑ hemoglobin and hematocrit, ↑ cholesterol, ↑ triglycerides, ↑ lipase, ↑ BUN in 4 out 6 moribund animals, glomerulonephritis, renal tubular dilatation, vascular dilatation and congestion in the spleen, liver, lung,

PGR2026-00039
Biocon Ex.1065
Page 452 of 595

kidneys, uterus, ovaries, testicles, and GI tract, vasculitis (panarteritis, periarteritis) in one male at 15 mg/kg (considered by the pathologist as possibly representing a background lesion), VEGT Trap concentrations markedly decreased starting on Day 14 (after 6 doses) associated with the development of an antibody response in both dose groups that was more evident in the female rats *Note: Regarding the renal changes, the pathologist commented that the glomerular changes may or may not be attributable to the test article due to the relatively high incidence of spontaneous progressive nephropathy in these rats.*
Study Title: A Non-GLP, Exploratory Study to Determine the Effect of Subcutaneous Administration of VEGF Trap (2 and 5 mg/kg) on Sprague Dawley Rats Three Times per week for Four Weeks (Study # PK01034; Module 4.2.3.2) **Design:** Rats (4/sex/group) were administered SC injections of either 2 mg/kg of VEGF Trap, 5 mg/kg of VEGF Trap, or placebo. Animals were treated 3x/week for 4 weeks. Same parameters as Study # PK01032 were evaluated. **Main Findings:** ↓ body weights in 3 males at 5 mg/kg starting 2 weeks after treatment initiation, ascites in 2 of these males at necropsy, ↑ cholesterol, ↑ triglycerides, ↑ lipase, ↑ BUN in 3 males at 5 mg/kg, ↑ serum creatinine in 1 male at 5 mg/kg, ↓ albumin and calcium in 2 males at 5 mg/kg, glomerulonephropathy (swelling of glomerular tufts, mesangial expansion, increased neutrophils, thickening of Bowman's membrane and capillary basement membranes) and renal tubular changes (thickened basement membranes, swollen epithelial cells, disruption, dilation with protein casts) at both doses but higher incidence at 5 mg/kg, vasculitis in a number of tissues in 2/8 rats at 5 mg/kg, inflammation in the lung and intestines, lymphoadenitis at 5 mg/kg, VEGT Trap concentrations decreased starting on Day 14 (after 6 doses) which generally correlated with the development of an antibody response at 2 mg/kg in both genders and in females at 5 mg/kg; in males at 5 mg/kg, no anti-VEGF Trap antibody was detected in spite of the decrease in VEGF Trap concentrations
Study Title: A Non-GLP, Exploratory Study to Determine the Effect of Subcutaneous Administration of VEGF Trap (0.5 and 1 mg/kg) on Sprague Dawley Rats Three Times per Week for Four Weeks (Study # PK01042; Module 4.2.3.2) **Design:** Rats (4/sex/group) were administered SC injections of either 0.5 mg/kg of VEGF Trap, 1 mg/kg of VEGF Trap, or placebo. Animals were treated 3x/week for 4 weeks and then observed for a further 4 (males) or 5 (females) days. Same parameters as Study # PK01032 above were evaluated. **Main Findings:** All parameters of toxicity were normal except for elevated serum triglycerides in 2 males at 0.5 mg/kg and 1 male at 1 mg/kg without a dose response. In addition, early glomerulopathy was noted in one animal at 0.5 mg/kg, although it was considered a background change by the pathologist. VEGT Trap concentrations decreased starting on Day 14 or 15 (after 6 or 7 doses) which generally correlated with low serum anti-VEGF Trap antibody concentrations. The NOAEL was considered 1 mg/kg.
Study Title: A 3-Month Toxicity Study of VEGF Trap by Subcutaneous Injection in Rats (Study # VGFT-TX-02006; Module 4.2.3.2). **Design:** Sprague-Dawley rats were administered the vehicle-control or VEGF Trap at 0.1, 0.5, 1.0, or 2.0 mg/kg for 1 (6 rats/sex/group) or 3 months (10 rats/sex/group) SC 3x/week. Parameters evaluated included mortality, clinical observations, body weight and weight gains, food consumption, hematology, coagulation, clinical chemistry, urinalysis, selected organ weights, gross pathology and histopathology. **Main Findings:** Mortalities at ≥ 1 mg/kg at dosing Day 43; ↑ body weight in males at ≥1 mg/kg, ↓ body weight in females at all doses but particularly at 1 mg/kg; at 1-month sacrifice, glomerulopathy at ≥ 1 mg/kg (particularly in males with only one animal affected in females at each dose); at 3-month sacrifice, glomerulopathy at all doses in males with fibrosis at ≥0.5 mg/kg and at ≥1 mg/kg in females (only 1-2 animals at each dose); polyangiitis and osteoporosis with decrease or complete absence of metaphyseal capillaries at 2 mg/kg in rats with more severe renal toxicity; ↓ total protein in males at 2 mg/kg (1-mo), ↓ albumin, ↑ globulin, and ↓albumin/globulin at ≥1 mg/kg , ↑BUN in males at 2 mg/kg (3-mo), ↑ cholesterol in males at ≥1 mg/kg, ↑ triglycerides in males at 2 mg/kg (3-mo); ↑urinary protein at all doses in males and at ≥1 mg/kg in females; ↑kidney and liver weight in males at 2 mg/kg; decreased VEGT Trap concentrations starting ~ 2-4 weeks after dosing which generally correlated with the development of an anti-VEGF antibody response as early as Day 6; NOAEL = 0.5 mg/kg for females, < 0.1 mg/kg in males

PGR2026-00039
Biocon Ex.1065
Page 453 of 595

Table 12: Main Findings Observed in Mouse Systemic Toxicity Studies following Subcutaneous Administration of VEGF Trap

Study Title: A Non-GLP, Exploratory Study to Determine the Effect of Subcutaneous Administration of VEGF Trap on SCID Mice (15 Week vs. 7 Week Old Mice) for 4 or 8 Weeks (Study # VGT3; Module 4.2.3.2) **Design:** Mice (1-5 males/group) received SC injections of 2.5 mg/kg or 25 mg/kg of VEGF Trap or placebo 2x/week except for 3x/week during Week 4. Two age groups were compared at each dose: 7 and 15 weeks old. Mice were treated for 4 weeks, 8 weeks, or 8 weeks plus 4 weeks of recovery. Same parameters as Study # PK01032 above were evaluated. **Main Findings:** ↑ weight loss in 2 males at 25 mg/kg (8 weeks), ↑ hematocrit, hemoglobin and RBC at both doses (8 weeks), hemorrhage and/or vascular congestion at 8 weeks of treatment principally in the kidney at both doses but with higher incidence at 25 mg/kg and 7 week old mice, congestion and/or edema in the GI tract including one mouse with typhlitis at 25 mg/kg in 7 week old mice and 8 weeks of treatment, periarteritis and myocarditis in one mouse at 25 mg/kg (15 weeks old, 8 wk treatment), hemorrhage in the nasoturbinates in one 7-week old and one 15-week old mouse at 2.5 mg/kg (8 wk treatment), no anti-VEGF Trap antibodies detected, VEGT Trap concentrations remained elevated; all changes showed reversibility except for mild renal tubular findings (degeneration, dilation, and protein casts) at recovery in 2 mice at 25 mg/kg
Study Title: A Non-GLP, Exploratory Study to Determine the Effect of Subcutaneous Administration of VEGF Trap (10 and 15 mg/kg) on CD-1 Mice Three Times per Week for Four Weeks (Study # PK01017; Module 4.2.3.2) **Design:** Mice (4/sex/group) received SC injections of either 10 mg/kg of VEGF Trap, 15 mg/kg of VEGF Trap, 15 mg/kg human IgG, or placebo (2/sex/group). Mice were treated 3x/week for 4 weeks and then observed for an additional 2 weeks. In addition, 3 untreated females were included for comparative purposes. Same parameters as Study # PK01032 above were evaluated (clinical pathology data was not interpretable). **Main Findings:** Mortalities (2 females at 10 mg/kg found dead on Day 18, another female at 10 mg/kg sacrificed moribund on Day 20, 1 female at 15 mg/kg found dead on Day 20, and 2 other females at 15 mg/kg sacrificed moribund on Day 20 and Day 31); edema in all unscheduled sacrifice animals; ↑ body weights in all unscheduled sacrifice animals; glomerulopathy (enlargement of the mesangial tufts, deposition of eosinophilic material, increased numbers of mesangial cells, thickening and some displacement of capillary loops) and dilated tubules at both doses; vascular dilation with fluid exudation into the subcutaneous space and GI tract at both doses; VEGF Trap concentrations declined starting on Day 14 which correlated with the development of an antibody response

As noted above, the monkey was selected as the relevant species. Therefore, the monkey studies were reviewed in greater detail.

Study title: A 6-Month Intravenous Toxicity Study of VEGF Trap in Cynomolgus Monkeys with a 5-Month Recovery Period

Study no.:	VGFT-TX-05009
Study report location:	Module 4.2.3.2
Conducting laboratory and location:	(b) (4) (b) (4)
Date of study initiation:	March 17, 2006
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	VEGF Trap, lot # C06001J600X1, ≥97% pure

Key Study Findings

PGR2026-00039
Biocon Ex.1065
Page 454 of 595

- One 3 mg/kg/dose male was euthanized prior to the end of the study primarily due to anemia and nasal bleeding secondary to extensive nasal lesions.
- The remaining animals exhibited hunching, nose bleeding, sneezing, reduced activity, appetite, and body weights.
- Absent or irregular menses associated with alterations in female reproductive hormone levels, and changes in sperm morphology and motility were considered test article-related.
- Test article-related changes in hematology, serum chemistry, urinalysis parameters and bone resorption markers were observed.
- Radiological diagnoses included kyphosis, degenerative joint disease (DJD), and periosteal reactions at all VEGF Trap dose levels.
- Macro- and microscopic test article-related changes were present in bones, nasal cavities, adrenals, brain (choroid plexus), liver, kidneys, ovaries, and digestive system. Vasculitis was noted in several tissues.
- At the end of a 5-month recovery period, principal findings included kyphosis with osteocartilaginous exostoses, nasal cavities deformation, DJD, and changes in the digestive system and the brain (choroid plexus).
- Based upon the above observations, the NOAEL was <3 mg/kg, the lowest dose evaluated.
- Based on C_{max} and $AUC_{0\text{-}168hrs}$, the systemic exposure was 4900-fold and 1550-fold higher, respectively, than the exposure observed in humans after an ITV dose of 2 mg/eye once every 4 weeks (C_{max} and $AUC_{0\text{-}last}$ of 0.0193 µg/mL and 2.856 µg•hr/mL, respectively).

Methods

Doses:	0, 3, 10, or 30 mg/kg
Frequency of dosing:	Once weekly for 15 weeks For the final 12 weeks, the dosing frequency was reduced to every other week due to toxicity (decreased body weights).
Route of administration:	IV (30-min infusion); peripheral vein (brachial and/or saphenous)
Dose volume:	3.75 mL/kg
Formulation/Vehicle:	(b) (4) sodium phosphate, (b) (4) sodium citrate, 33 mM sodium chloride, 0.033% (w/v) PS20 and (b) (4) sucrose, pH (b) (4)
Species/Strain:	Cynomolgus monkeys (*Macaca fascicularis*)
Number/Sex/Group:	4
Age:	5-12 yrs old males; 3-5 yrs old females
Weight:	4.1-12.3 kg for males; 2.3-4.1 kg for females
Satellite groups:	An additional 2 monkeys/sex/dose were used for a 5-month recovery period.
Unique study design:	Based on target organs identified in earlier studies, a series of special evaluations were performed.
Deviation from study protocol:	None that could adversely affect interpretation of

PGR2026-00039
Biocon Ex.1065
Page 455 of 595

the study results

Observations and Results

Mortality (Twice daily) – A male at 3 mg/kg (# 202), was euthanized on Day 182 (Week 26) primarily due to a rapid clinical deterioration secondary to a marked anemia due to nasal bleeding. Extensive macroscopic lesions were observed in the nasal cavities, including blood clots (or hemorrhages) in the right caudal nasal cavity and maxillary sinus, a bent nasal septum and an absence of the right middle concha. These observations, as well as corresponding microscopic lesions (atrophy/loss of the nasal septum and/or turbinates associated with necrotizing inflammation), were similar to those noted in several other VEGF Trap-treated animals. Therefore, they were regarded as compound-related. Macroscopic findings also included pale discoloration of the kidneys, liver, and stomach and a darkly discolored digestive content. Histopathologically, erythroid hyperplasia in the bone marrow and extramedullary hematopoiesis in several tissues was consistent with the hematological evidences of a marked regenerative anemia detected prior to euthanasia.

Clinical Signs (Daily; detailed examination once prior to the start of treatment and weekly throughout the treatment and recovery periods) – Main treatment-related clinical signs included sneezing with or without discharge, red fur staining, dry skin, swelling, scabbing and/or redness of the muzzle/lower jaw, hunched or abnormal posture, reduced appetite, thin aspect and/or decreased activity at all dose levels.

During recovery, one male at 30 mg/kg (# 406) was noted with discharge from the muzzle during the first week of the recovery period (Week 28); skin scab or redness of the muzzle/lower jaw was seen in one male in each VEGF Trap treated group (# 210, 308, and 406); and one male at 30 mg/kg (# 406) started to show a hunched posture during the recovery period (Week 32), which persisted until the end of the recovery period. Similarly, signs of hunched posture noted during the treatment period in animals assigned to the recovery phase persisted until the end of the recovery period.

Body Weights (Weekly) - Decreases in mean body weight were noted compared to control values at all VEGF Trap dose levels starting around Week 13 in males (5-14%) and Week 9 in females (8-13%). As a result of this weight loss, the treatment interval was changed to every other week after Week 15 for the remaining 12 weeks. Body weights were still lower than controls for the remainder of the study. The decrease was dose-dependent only in females.

By the end of treatment (Week 27), mean body weight gain in females was dose-dependently decreased (0.4, 7.8, and 20.4 % respectively at 3, 10, and 30 mg/kg). Males did not show a dose response. The percent decreases for males were 7.6, 15.1, and 8.4% respectively at 3, 10, and 30 mg/kg.

The decrease in body weight was reversed during the recovery period.

PGR2026-00039
Biocon Ex.1065
Page 456 of 595

Feed Consumption (Once daily; qualitatively) – Reduced appetite (associated with thin aspect) was noted in all males treated with VEGF Trap as well as with the vehicle control. In females, there was an increased incidence of reduced appetite, particularly at the 2 highest doses (3, 4, 6, and 6 at 0, 3, 10, and 30 mg/kg, respectively). Reduced appetite was noted in all control and test article-treated animals during the recovery period. Animals were provided with food supplementation as required.

Ophthalmoscopy [Once prior to the start of treatment (all animals) and during Weeks 13 and 26 of treatment and at the end of the recovery period (Week 47) using funduscopic (direct and indirect ophthalmoscopy) and biomicroscopic (slit lamp) examinations] - One male at 3 mg/kg (# 210) showed focal areas of retinal edema and subretinal depigmentation in the peripapillary and macular regions at both Weeks 13 and 26 in both eyes. One male at 30 mg/kg (# 408) showed fine granular opacities scattered in the macular area of each eye at Week 26. Another male at 30 mg/kg (# 406) had focal area of edema-like retinal opacity in the inferior papillary area at Week 26 on the left eye only. No histopahtological correlates were noted.

The lesions in animal # 210 were still present during recovery and had become larger and degenerative with retinal edema no longer present. One recovery male at 10 mg/kg (#308) appeared to be functionally blind and had a vertical nystagmus. Histopathological findings included bilateral severe chronic perineural inflammation and moderate nerve fiber degeneration with gliosis of cranial nerves II, III, IV and VI.

Because these lesions were of low incidence and not observed in the 13-week or 8-month ITV toxicity studies, the relationship to treatment is uncertain.

ECG and Blood Pressure [Twice prior to commencement of treatment (three weeks apart) and again during Weeks 4, 12, and 26 of the treatment period and during Weeks 37 and 48 of the recovery period; QTc calculated using Fredericia.s equation] – No test article-related effects

Hematology and coagulation (Once prior to the start of treatment and during Weeks 4, 12, and 25 of the treatment period and during Weeks 37 and 48 of the recovery period) – A series of parameters showed differences when compared with the vehicle control and predose values. The following % change is based on vehicle control values.

In females at all doses, mean hematocrit was increased (12-14%; $p \leq 0.05$) at Week 4. In males at Week 4, mean hemoglobin was increased (11%; $p \leq 0.01$) at the mid and high dose, although the mean values were within physiological range.

At Week 12, mean # reticulocytes and fibrinogen were increased at the high dose (15%) and at all doses in males [72% ($p \leq 0.01$), 69% ($p \leq 0.01$), and 33%, at 3, 10, and 30 mg/kg, respectively]. At Week 12 in females, the high dose showed increased mean % neutrophils (58%; $p \leq 0.05$) and decreased % lymphocytes (22%; $p \leq 0.05$); mean hematocrit was increased (10%; $p \leq 0.05$) and mean APTT was decreased (10-30%; $p \leq 0.05$ at the high dose only) at all doses.

PGR2026-00039
Biocon Ex.1065
Page 457 of 595

At Week 25, increased mean # reticulocytes (83%, 29%, and 112% at 3, 10, and 30 mg/kg, respectively) and fibrinogen (39%, 26%, and 18% at 3, 10, and 30 mg/kg, respectively) were observed at all doses in males. At the high dose in males, increases were observed in mean red cell distribution width (19%) and platelet volume (24%). At Week 25 in females, mean hemoglobin (13%) and # reticulocytes (70%) were increased and APTT was decreased (22%; $p \leq 0.01$) at the high dose. Except where indicated, the difference was not statistically significant.

Most of these changes were reversible.

Clinical Chemistry (Once prior to the start of treatment and during Weeks 4, 12, and 25 of the treatment period and during Weeks 37 and 48 of the recovery period) -The applicant noted that cholesterol was increased in animals of both sexes treated at all dose levels during Weeks 4, 12, and 25. However, values were within normal biological range, except for one male at 10 mg/kg (# 310) with values of 223 mg/dL (Week 4) and 251 mg/dL (Week 12) but normal at Week 25 (186 mg/dL). Treatment-related and marked increases in GGT, AST, ALP and/or ALT were noted at all doses in individual males and females. The elevation in mean values compared to controls was 2-3x, although individual values showed increases up to 5x, 8x, 10x, and 10x, respectively. These elevations were observed primarily at Week 25 with some animals showing changes at Week 12. Females were more affected than males. At the end of the recovery, some parameters were still elevated.

These changes are described in more detail below:

Treatment-related marked increase in AST was noted at Week 25 in two females at 10 mg/kg (# 355 and 357) and two females at 30 mg/kg (# 454 and 455) relative to controls or acclimation values. At the end of the recovery period, these values largely returned to their acclimation values for animal # 355 and 454.

Females # 355, 357, 454, and 455 with increases in AST, also had increases in GGT relative to controls or acclimation values at Week 25. By the end of the recovery period, female # 355 continued to have elevated GGT. Treatment-related marked increase in GGT was also noted at Weeks 12 and/or 25 in one male at 3 mg/kg (# 207), one male at 10 mg/kg (# 307) and one male at 30 mg/kg (# 405). Except as noted above, elevated GGT values were not noted by the end of the recovery.

Females # 355, 357, 454 and 455 also showed increases in ALP relative to controls or acclimation values at Week 25. An additional female at 10 mg/kg (#361) also had elevated ALP. A slight increase in ALP was noted at Weeks 12 and/or 25 in two males at 3 mg/kg (# 202 and 207) and one male at 30 mg/kg (#408). Elevated ALP values were not noted by the end of the recovery.

Females # 355, 357, 454 and 455 also had increases in ALT relative to controls or acclimation values at Week 25. By the end of the recovery period, female # 355 continued to have elevated ALT levels.

PGR2026-00039
Biocon Ex.1065
Page 458 of 595

Urinalysis (Once prior to the start of treatment and during Weeks 4, 12, and 25 of the treatment period and during Weeks 37 and 48 of the recovery period) - Mean microalbumin (5-100x) and protein (2-8x) levels were increased in males. Relative to controls and baseline values at Weeks 4, 12 and/or 25, microalbumin and protein were increased in 3 males (# 201, 208 and/or 210) at 3 mg/kg, in 4 males (# 306, 307, 309 and/or 310) at 10 mg/kg, and in 4 males (# 406, 407, 409 and 410) at 30 mg/kg. Increased levels of microalbumin were noted in 2 females (# 453 and 455) at 30 mg/kg at Week 25, but these levels were within the range of values seen in control animals. In general, microscopic kidney changes identified in VEGF Trap treated animals explain the proteinuria and albuminuria. These changes reverse during recovery.

Gross Pathology (All animals euthanized at the end of the treatment and recovery periods) - Macroscopic findings were noted for several tissues, affecting primarily the nasal cavities and skeletal system as well as the adrenal glands, duodenum, and gallbladder. The findings in the bones and nasal cavities are summarized in the table below:

Table 13: Incidence of VEGF Trap-related Macroscopic Findings in Bones and Nasal Cavities in the 6-Month Intravenous Toxicity Study in Cynomolgus Monkeys

Tissue/Finding	Sex	Male				Female			
	Dose (mg/kg/dose)	0	3	10	30	0	3	10	30
	Number of animals examined	4	4	4	4	4	4	4	4
Bone-Vertebra[#]									
	Area raised	0	1	0	0	0	0	0	1
	Bent: kyphosis	0	2	2	3	0	1	4	3
	Fusion	0	1	1	0	0	0	0	1
	Thickening	0	0	0	1	0	0	1	0
Bone-Other sites									
	Femur-Mass	0	1	0	1	0	0	1	1
	Ilium-Mass	0	0	0	1	0	0	0	1
	Radius[&]-Mass	0	0	0	0	0	0	0	1
	Sternum-Mass	0	0	0	0	0	1	0	0
Cavity nasal/Sinuses									
	Area dark	0	1	2	0	0	0	0	0
	Area raised	0	2	0	0	0	0	0	0
	Bent: septum	0	1	1	0	0	0	0	0
	Clot	0	1	0	0	0	0	0	0
	Discoloration dark	0	1	0	1	0	0	0	0
	Material pale	0	0	1	0	0	0	0	1
	Not present*: septum	0	0	1	1	0	0	0	1
	Not present*: turbinate/concha	0	1	0	0	0	0	0	1
	Perforation: septum	0	1	2	0	0	0	0	0
	Small: turbinate/concha	0	0	0	0	0	0	0	1
	Thickening: septum	0	1	0	0	0	0	0	0

The number of animals that presented the finding in at least one segment of the cervical, thoracic and/or lumbar vertebral column.

& Recorded under Bone miscellaneous.

* Finding subdivided according to anatomical modifier.

PGR2026-00039
Biocon Ex.1065
Page 459 of 595

In the skeletal system, the most common macroscopic finding was noted in the thoracic and/or lumbar vertebrae being described as bent: kyphosis. This change found in males and females at ≥3 mg/kg was centered on the caudal thoracic vertebrae and cranial lumbar vertebrae and extended maximally from T5 to L6.

In other skeletal sites of animals given ≥3 mg/kg, pale and firm mass(es) were occasionally noted with a polyostotic and/or bilaterally symmetric distribution, such as in the left proximal femur and both ilia of one high-dose animal (# 408) and in the right proximal femur, right ilium and both radii in a second high-dose animal (# 455). The most frequently affected long bone was the proximal femur and, in one low dose animal (# 208), the mass was associated with ankylosis of the coxofemoral joint. In addition to these above listed sites, a single occurrence of sternal mass was found in one female treated with 3 mg/kg.

Thickening of the gallbladder wall was seen in 2 females at 30 mg/kg. Dark areas on the duodenal mucosa were present in 1 male at 10 mg/kg and in 1 male and 2 females at 30 mg/kg. Dark discoloration of the adrenal glands was noted in 2 and 1 males at 3 and 30 mg/kg, respectively, and in 1 and 2 females at 10 and 30 mg/kg, respectively. These gross changes were regarded as VEGF Trap-related in light of their histological correlates.

These macroscopic findings persisted in several tissues after the 5-month recovery period, affecting primarily the nasal cavities, skeletal system, and the gallbladder. No findings were noted in the adrenal glands or duodenal mucosa. A dark depressed area on the stomach mucosa was noted in one female at 10 mg/kg.

Organ Weights (adrenals, brain, epididymides, heart, kidneys, liver, lungs, ovaries/testes, pituitary, prostate, seminal vesicles, spleen, thymus, thyroid/parathyroids, and uterus) – A dose-related decrease in mean absolute uterine weights was observed in females; 26%, 37% ($p \leq 0.05$), and 42% ($p \leq 0.05$) at 3, 10, and 30 mg/kg, respectively. Relative to body weight, a 5, 12, and 10% decrease was observed, respectively. This variation correlated with endometrial and myometrial atrophy noted histologically in most females of these groups.

Marked but non-significant decreases in mean absolute ovary weights (77, 83, and 83% at 3, 10, and 30 mg/kg, respectively) were noted in all VEGF Trap treated groups when compared to the controls, which correlated with the scant luteal activity noted during histological examination. Relative to body weight, decreases of ~70% (no statistical significance) were observed at all VEGF Trap doses.

At recovery, only the high-dose females still showed decreased weight of the ovaries (23% absolute weight and 9% relative to body weight) compared to controls. The reduced magnitude of the change suggests partial recovery.

PGR2026-00039
Biocon Ex.1065
Page 460 of 595

In males, decreases in absolute seminal vesicle weight were observed without a dose response (16, 52, and 6% at 3, 10, and 30 mg/kg, respectively; no statistical significance). Relative to body weight, decreases of 7, 39, and 14% were observed, respectively. These decreases were still observed at recovery (10, 50, and 25% absolute weight; 38, 51, and 26%, relative to body weight, respectively), although the data is not reliable as the control group consisted of one animal. There was no histopathological correlate for this change but sperm motility and morphology was affected at ≥3 mg/kg (see below).

Thymus weight was decreased at the high dose compared to controls; 41% in males and 74% in females (absolute values); 34% in males and 62% in females relative to body weights. No statistical significance was observed. Recovery was observed in females. In males, thymus weight was still decreased at the end of recovery, but the data was no reliable as only 1 control animal was left. This decrease correlated with a higher incidence of thymic lymphoid atrophy.

Histopathology

Adequate Battery - Yes

Note: Bone marrow smears were collected but not evaluated. Testicular histopathological evaluation included assessment of the spermatogenic cycle.

Peer Review - Yes

Histological Findings - Microscopic findings were observed in the nasal cavities, various bones, kidneys, female reproductive system, digestive system (liver, gallbladder, duodenum and stomach), adrenal glands, brain, thymus, and trachea. Microvascular effects were noted in most of these tissues and, sporadically, in the heart and a few other tissues.

Nasal cavities: Histopathological findings that correlated with macroscopic observations noted during trimming were seen in the nasal cavities of some males and females dosed at ≥3 mg/kg. These alterations included an atrophy/loss of the septum and/or turbinates associated with necrotizing inflammation and various other epithelial, microvascular, cartilaginous, and osseous findings (Table 14). In animals allowed a drug-free 5-month recovery period after treatment completion, there was reversibility of most compound-related changes, either inflammatory, vascular and targeting the epithelia, but no reversibility of some of the changes affecting the osseous and cartilaginous support in the nasal cavities.

PGR2026-00039
Biocon Ex.1065
Page 461 of 595

Table 14: Incidence and Severity of VEGF Trap-related Histopathological Findings in Nasal Cavities in the 6-Month Intravenous Toxicity Study in Monkeys

Tissue/Finding	Sex	Male				Female			
Dose (mg/kg/dose)		0	3	10	30	0	3	10	30
Nasal cavity/sinus	Number examined	4	4	4	4	4	4	4	4
Atrophy/loss: septum									
	Total number affected	0	2	3	1	0	2	1	3
	Minimal	-	-	-	-	-	1	1	2
	Slight	-	-	1	-	-	1	-	1
	Moderate	-	2	1	-	-	-	-	-
	Marked	-	-	1	1	-	-	-	-
Atrophy/loss: turbinate									
	Total number affected	0	1	3	1	0	1	0	1
	Slight	-	1	1	-	-	1	-	-
	Moderate	-	-	-	-	-	-	-	1
	Marked	-	-	2	1	-	-	-	-
Cartilaginous metaplasia: ethmoturbinate									
	Total number affected	0	1	1	1	0	0	1	2
	Minimal	-	1	1	-	-	-	1	2
	Slight	-	-	-	1	-	-	-	-
Degeneration/regeneration: respiratory epithelium	Total number affected	0	4	4	3	0	4	4	4
	Minimal	-	1	-	-	-	1	2	-
	Slight	-	1	1	-	-	2	-	3
	Moderate	-	2	1	2	-	1	2	1
	Marked	-	-	2	1	-	-	-	-
Degeneration/regeneration: olfactory epithelium	Total number affected	0	0	1	1	0	1	0	1
	Minimal	-	-	-	-	-	1	-	-
	Slight	-	-	1	-	-	-	-	1
	Moderate	-	-	-	1	-	-	-	-
Eosinophilic cartilage/activated chondrocytes: septum	Total number affected	0	4	4	3	0	4	3	4
	Minimal	-	2	1	1	-	2	1	1
	Slight	-	1	3	-	-	1	-	2
	Moderate	-	1	-	1	-	1	2	1
	Marked	-	-	-	1	-	-	-	-
Exudate									
	Total number affected	1	4	4	3	2	3	3	4
	Minimal	1	1	-	-	2	1	2	1
	Slight	-	1	2	2	-	2	1	2
	Moderate	-	2	2	-	-	-	-	1
	Marked	-	-	-	1	-	-	-	-

PGR2026-00039
Biocon Ex.1065
Page 462 of 595

Cont'd Table 14

Tissue/Finding	Sex	Male				Female			
Dose (mg/kg/dose)		0	3	10	30	0	3	10	30
Nasal cavity/sinus	Number examined	4	4	4	4	4	4	4	4
Hemorrhage									
	Total number affected	0	4	4	3	0	1	3	2
	Minimal	-	2	1	1	-	1	3	2
	Slight	-	1	3	1	-	-	-	-
	Moderate	-	1	-	1	-	-	-	-
Inflammation: necrotizing									
	Total number affected	0	2	3	1	0	1	1	1
	Slight	-	-	-	-	-	1	1	-
	Moderate	-	1	3	-	-	-	-	1
	Marked	-	1	-	1	-	-	-	-
Proliferation/degeneration: vascular									
	Total number affected	0	2	3	3	0	1	2	3
	Minimal	-	-	3	1	-	1	2	2
	Slight	-	2	-	2	-	-	-	1
Thrombosis									
	Total number affected	0	1	0	1	0	0	0	1
	Minimal	-	1	-	1	-	-	-	1
Ulceration: respiratory epithelium									
	Total number affected	0	2	2	3	0	2	2	3
	Minimal	-	-	-	1	-	2	1	1
	Slight	-	-	2	1	-	-	1	2
	Moderate	-	2	-	1	-	-	-	-

Bones/Muscles: The most important finding was the development of osteocartilaginous exostoses in males and females dosed with ≥3 mg/kg. In the spine, the exostoses were most frequently observed on the arches of the thoracic and lumbar vertebrae and often correlated macroscopically with a bent in kyphosis deformation of the vertebral column. Exostoses, correlating with mass(es) at necropsy, were less common in other bones and predominantly involved the proximal femur. Muscular myofiber atrophy and less commonly vascular proliferation/degeneration were often seen as concurrent findings with the exostoses. There was no reversal of these osseous and muscular findings after recovery.

Whenever the physis was not closed in various bone sites, a thickened hypertrophic chondrocyte layer was a common and minor VEGF Trap-induced effect in animals treated with ≥3 mg/kg. In these groups, another minor histological finding was a cartilaginous metaplasia localized in the ventral cortex of vertebral bodies. There was almost complete reversibility of these changes following recovery.

Kidneys: An increased eosinophilic matrix (minimal to moderate) in the glomerular tuft that stained positively with the periodic acid Schiff reaction was noted in males

PGR2026-00039
Biocon Ex.1065
Page 463 of 595

and females at ≥3 mg/kg. In addition, glomerulopathy (minimal-slight), often with tubulointerstitial inflammation (minimal-slight) and/or cast formation (minimal-moderate), were commonly seen in males at ≥3 mg/kg and in a single female at 30 mg/kg. These changes showed decreased incidence and severity at the end of the recovery phase.

Female Reproductive System: Ovarian luteal development was markedly compromised in females at ≥3 mg/kg (Table 15). This change correlated with a decreased weight of the ovaries at treatment completion. In some of these sexually mature females, follicular maturation was also decreased in number and quality. Uterine endometrial and myometrial atrophy and vaginal epithelial atrophy were noted in most females at ≥3 mg/kg and in a few females at ≥10 mg/kg, respectively. The uterine atrophy correlated with a decreased weight of this organ at completion of treatment. Proliferation/degeneration of the uterus and vagina was noted in 1 female at 30 mg/kg. Reversibility of the effects in the female reproductive tract was observed after the 5-month recovery period, with the exception of the ovarian weights that were still slightly decreased at 30 mg/kg.

PGR2026-00039
Biocon Ex.1065
Page 464 of 595

Table 15: Incidence and Severity of VEGF Trap-related Histolopathological Findings in the Female Reproductive System in the 6-Month Intravenous Toxicity Study in Monkeys

Tissue/Finding	Sex	Female			
Dose (mg/kg/dose)		0	3	10	30
Ovary	Number examined	4	4	4	4
Decreased granulosa cells					
	Total number affected	0	2	0	3
	Minimal	-	-	-	1
	Slight	-	2	-	1
	Moderate	-	-	-	1#
Decreased maturing follicles					
	Total number affected	1	0	1	3
	Minimal	-	-	1	-
	Slight	1	-	-	1
	Moderate	-	-	-	1
	Marked	-	-	-	1
Presence of corpus luteum					
	Total number affected	4	3	2	3
	Very small	-	1	1	1
	Small	-	1	-	2
	Large	2	1	1	-
	Extensive size	2	-	-	-
Uterus	Number examined	4	4	4	4
Atrophy: endometrial and myometrial					
	Total number affected	0	3	3	4
	Minimal	-	2	1	-
	Slight	-	1	2	3&
	Moderate	-	-	-	1
Vagina	Number examined	4	4	4	4
Atrophy: epithelium					
	Total number affected	0	0	1	2
	Slight	-	-	1	1
	Moderate	-	-	-	1&

Associated with slight decreased theca cells.

& Associated with moderate vascular proliferation/degeneration in one female.

Digestive System: Vascular degeneration/proliferation was noted in the duodenum, stomach, rectum, gallbladder, and pancreas at ≥10 mg/kg. The duodenum and gallbladder were the main target organs, which often presented slight-moderate secondary mucosal damage (atrophy/ulceration) and inflammation, respectively. Following recovery, findings were still observed in the gallbladder, duodenum, and stomach

Liver: Hepatic portal inflammation (minimal to moderate) and periportal necrosis (minimal to slight), usually with diffuse pigment deposits in Kupffer cells, were seen in 1 male and 2 females at 30 mg/kg. Following recovery, one female each at 10 and 30 mg/kg showed slight multifocal chronic active portal inflammation and bile duct hyperplasia. Minimal multifocal chronic portal inflammation was seen in one at 10 mg/kg.

PGR2026-00039
Biocon Ex.1065
Page 465 of 595

Adrenal Glands: In the cortex, decreased cytoplasmic vacuolation (minimal to moderate) with increased cytoplasmic eosinophilia, which correlated with macroscopic dark discoloration, was observed in 2 and 1 males at 3 mg/kg and 30 mg/kg, respectively, and in 2 and 1 females at 10 mg/kg and 30 mg/kg, respectively. This finding was not observed in recovery animals.

Brain: Minimal infiltration of macrophages was observed in the choroid plexus in 1 and 2 females at 3 and 30 mg/kg, respectively. In addition, minimal vascular degeneration/fibrosis, which affected mainly the small arterioles of the choroid plexus, was noted in 1 male and 3 females at 30 mg/kg. These findings were present in one male at 10 mg/kg and/or 30 mg/kg at the end of the recovery period.

Vasculopathies: In addition to the organs mentioned above, minimal vascular proliferation/degeneration was noted in the heart in 2 males and 1 female at 10 mg/kg. The cardiac vascular findings were not limited to the arterioles; they involved the major coronary artery next to the right atrium in 2 monkeys. Other tissues in which vascular proliferation/degeneration was found included the epididymis in 1 male at 30 mg/kg (slight) and in the femorotibial joint, jejunum, sciatic nerve, and skin in 1 female at 30 mg/kg (minimal).

At recovery, vascular degeneration/fibrosis was noted in the renal papilla of 1 male at 10 mg/kg and vascular proliferation/degeneration was seen in the femorotibial joint of 1 male at 30 mg/kg. The heart was spared in animals of the recovery phase. Overall, there was some evidence of persistence of the compound-related vasculopathy after completion of the treatment-free period (mainly in the digestive system). The applicant noted these changes were generally undergoing repair by fibrosis, as diagnosed by vascular proliferation/fibrosis.

Thymus: Increased incidence of thymic lymphoid atrophy was observed in both males and females compared to controls (0, 2, 4, and 3 in males and 1, 2, 1, and 4 in females at 0, 3, 10, and 30 mg/kg, respectively). The severity ranged from slight-severe in males, slight in the female control, and slight-marked in VEGF Trap-treated females. At recovery, the incidence (1-2 animals/group) and severity was similar to that seen in control groups (marked in the male control and slight-marked in VEGF Trap-treated males and minimal-slight in control and VEGF Trap-treated females).

In 3 males out of 4 in the control and 2 males out of 4 in the low dose groups, there was no thymus or remnant found in the sections of mediastinal fat provided for evaluation, which complicated the interpretation of this finding. The applicant considered that no thymic remnant was indicative of severe thymic atrophy in most control males and consequently, that no compound related effect was present in this organ in males.

In females, the incidence and severity of thymic lymphoid atrophy was more severe at 30 mg/kg (4 animals affected among which 2 were graded moderate or

PGR2026-00039
Biocon Ex.1065
Page 466 of 595

marked in severity) when compared to controls (1 animal affected and graded slight in severity). However, the applicant regarded the effect upon the thymus as indirect, secondary to the multi-systemic effects induced by the test article and/or stress-related. The reviewer concurs that the existent data do not allow for a clear assessment of a test article-related effect.

Trachea: Atrophy (minimal-moderate) of the epithelium was observed with slightly higher incidence compared to controls in both males and females (0, 1, 1, and 2 at 0, 3, 10, and 30 mg/kg, respectively). At recovery, the finding was noted in 1 male each in control and high-dose groups. As noted by the applicant, the significance of this observation is uncertain because it is possible that it may be a consequence of the endotracheal intubation required when the animals were anesthetized for bone densitometry measurements. However, it may also be an indirect consequence of the observed compound-related effects in the nasal cavities and/or the adjacent cervical spine.

Special Evaluations:

Body Temperature (Twice prior to commencement of treatment (three weeks apart) and during Weeks 2, 4, 12, and 26 of the treatment period and during Weeks 37 and 48 of the recovery period] – No test article-related effects

Vaginal Bleeding (Daily by performing vaginal swabbing using a cotton swab commencing during the acclimation period and extending throughout the treatment and recovery periods) – Arrest of regular menstrual bleeding was observed in 1, 4, 5, and 5 females at 0, 3, 10, and 30 mg/kg which lasted for prolonged durations (7-22 weeks). One or more episodes of abnormally protracted or frequent bleeding that ranged from 10-17 days (and for 23 days extending into the recovery period for one female at 3 mg/kg) was observed in 3 and 1 females at 3 mg/kg and 30 mg/kg, respectively. During the recovery period, the animals started to show more frequent/regular signs of menses or menses duration.

Male Reproductive System (Twice during the acclimation period, Weeks 5, 8, 12, and 25 of the treatment period and at the mid (Week 38) and end of the recovery period; volume, sperm concentration, motility and morphology] – A pronounced reduction in sperm motility and increased morphological abnormalities in spermatozoa were observed at ≥3 mg/kg. These effects, noted at Week 5, persisted throughout the treatment period. Complete reversal of these findings was noted as early as 12 weeks after cessation of compound administration in recovery animals. The administration of VEGF Trap did not induce changes in mean testicular volume and sperm counts.

Hormone Analysis [Males - twice during the acclimation period (two weeks apart), and once every two weeks throughout the treatment and recovery periods and prior to terminal necropsies (blood FSH, LH, and testosterone); Females – once every week or every two weeks during the acclimation period, once a week during the first month of dosing and once every two weeks thereafter, except once a week for females

PGR2026-00039
Biocon Ex.1065
Page 467 of 595

during the last month of the recovery period) and prior to terminal and recovery necropsies (blood estradiol, progesterone, FSH, and inhibin B] –

Females: Mean progesterone levels were decreased within 1 week of dosing throughout the treatment period, although statistical significance was only reached at the mid- and/or high dose on Weeks 19, 23, and 27. At Week 27, mean levels were decreased by 78, 82, and 86% at 3, 10, or 30 mg/kg, respectively, compared to controls. The individual animal listings showed a wide range of values in the control group (1.76-26.2 ng/mL) which included the range of values observed in VEGF Trap-treated groups (2.12-3.89, 1.26-3.22, and 1.26-3.22 ng/mL at 3, 10, and 30 mg/kg, respectively). The reviewer, therefore, finds it difficult to conclude there was a clear treatment related effect. The applicant counted the number of ovulatory cycles by counting the number of discrete progesterone peaks that were ≥5 ng/mL. A definitive negative effect on progesterone was noted in this parameter. The mean number of progesterone peaks observed per month during the treatment period was 0.69, 0.05, 0.05, and 0.02 in groups receiving 0, 3, 10, or 30 mg/kg, respectively. During recovery, the mean number of progesterone peaks observed per month was 0.91, 0.45, 0.64, and 0.36, respectively, indicating recovery of normal menses was occurring.

Group mean estradiol levels were generally non-significantly decreased in females treated with VEGF Trap, particularly at doses of 10 and 30 mg/kg when compared to controls beginning at Week 15. At Week 27, mean estradiol levels were decreased by 14% (10 mg/kg) and 40% (30 mg/kg). However, individual animal listings showed values within the range observed in control animals at diverse time points throughout the study. The applicant noted that the failure to detect significant decreases in estradiol levels during VEGF Trap treatment was likely attributable to the relatively brief duration of the preovulatory estradiol surge (usually 4-5 days), relatively infrequent blood sampling (usually once every two weeks), and because cycle phases were not temporally aligned. However, that normal follicular development was compromised was clearly evident from the effects of VEGF Trap treatment on inhibin B and FSH levels (see below).

Group mean inhibin B values were statistically significantly reduced compared to controls for all VEGF Trap female groups (≥3 mg/kg/dose) starting from the first week of treatment and throughout the treatment period. At Week 27, mean levels were decreased by 74, 73, and 81% at 3, 10, and 30 mg/kg, respectively. During the recovery period, inhibin B levels were increased within 4-10 weeks of cessation of treatment.

Mean FSH levels exhibited a marked increase (≤5.5x) in all females receiving ≥ 3 mg/kg. The increase in FSH level, was evident within the first 1-2 weeks of the treatment period, and in most cases was sustained for the duration of treatment. Recovery was evident beginning 4-8 weeks following cessation of treatment.

PGR2026-00039
Biocon Ex.1065
Page 468 of 595

Males: In contrast to the effects noted in sperm motility and morphology, no biologically meaningful effects were detected in FSH and LH levels. During pretreatment Week -2 and the treatment period, group mean testosterone levels were generally lower in groups that received VEGF Trap compared to controls. At Week 27, testosterone levels were decreased by 41, 71 ($p \leq 0.01$), and 62% ($p \leq 0.05$) at 3, 10, and 30 mg/kg, respectively. However, a clear relationship to treatment is not clear because of the following observations: there was wide within group variability, a dose response was not apparent, and for all groups, mean testosterone levels remained at or above pretreatment values throughout the treatment period. As noted previously, there were no histopathological findings in male sex organs, although the weight of the seminal vesicles was decreased.

Blood C-Reactive Protein (Once during the acclimation period, Weeks 4, 13 and 26 of the treatment period, and during Weeks 37 and 48 of the recovery period) – In males, mean levels were higher at 3 mg/kg (6x) and 10 mg/kg (10x) at Week 4 and at all doses (6x, 3x, and 3.5x at 3, 10, and 30 mg/kg, respectively) at Week 26. In females, mean levels were increased at 10 mg/kg (5x; $p \leq 0.05$) and 30 mg/kg (6x) on Week 13 and at all doses (2x, 5x, and 4x at 3, 10, and 30 mg/kg, respectively) on Week 26. The lack of statistical significance reflects the fact that only 1-2 out of 6 animals were affected at the low and mid dose and 3 out of 6 animals were affected at the high dose and showing a wide range of values. These changes were not present at recovery.

Biochemical Markers of Bone Resorption [Once prior to the start of treatment and during Weeks 4, 12, and 25 of the treatment period and during Weeks 37 and 48 of the recovery period; urine C-Telopeptide (CTx) N-Telopeptide (NTx), and Deoxypyridinoline (DPD); normalized by urine creatinine levels] – The data were difficult to interpret due to the wide range of values observed in each group. The range of values observed on each group during acclimation period and in controls, overlapped with the range of values observed in VEGF Trap treated groups. In addition, the changes for most part did not show a dose response or persisted throughout the dosing period. Therefore, in spite of the changes in mean values noted below, it is difficult to definitely attribute these changes to the test article.

CTx: Compared to controls (and acclimation), lower mean CTx levels were noted at Week 4 in both males (30-50%; non-dose dependent) and females (40-45%; dose dependent) at all doses (statistical significance only in high dose females). Females also had statistically significant lower levels at Week 12 (30-45%; non-dose dependent) with movement toward recovery at Week 25. Males showed movement toward recovery at Weeks 12 and 25.

NTx: Lower (statistically non-significant) NTx mean concentrations were observed in males treated with VEGF Trap at all dose levels on Week 4 (8-45%; non-dose dependent) and Week 12 (24-45%; non-dose dependent) and in females treated at all dose levels throughout the study when compared to controls (22-49%; non-dose dependent). At Weeks 48 of the recovery period, the levels of N-Telopeptide

PGR2026-00039
Biocon Ex.1065
Page 469 of 595

were increased (2-10x) in 2 females relative to their values at Week 25 (end of the treatment period).

DPD: No test article-related effects were noted during the treatment period. At recovery, the levels of DPD were increased in 1 female each at all doses at Week 37 (14.99-18.41 *vs.* 4.94-12.39 nM/mM creatinine in pooled controls and acclimation periods).

Bone Densitometry Measurements [Once during the acclimation period, during Weeks 4, 13, and 26 of the treatment period, and during Weeks 37 and 48 of the recovery period by Dual energy X-ray absorptiometry (DXA) to measure bone mineral density (BMD), bone mineral content (BMC), and total body area] – The applicant noted that the positioning of some animals during the treatment period was not consistent with the initial scan due to the skeletal abnormalities induced by VEGF Trap. As a result, the results obtained for BMD were not considered accurate and BMC values were used to interpret the effects on bone densitometry data. Significant changes in BMC were not observed. The applicant attributed the slight decreases in BMC (whole body and femur) observed at all doses during treatment to body weight losses. Again, given the wide variability within groups with overlapping range of values between controls (and acclimation) and VEGF Trap treated groups, it was difficult to clearly identify a treatment related effect.

Digital Radiographs (Once during the acclimation period and once during Weeks 4, 13, and 26 of the treatment period and during Weeks 37 and 48 of the recovery period) – An increased incidence of kyphosis (generally at the thoraco-lumbar junction), degenerative joint disease (DJD) of articular facets (generally from T10 to L7), periosteal reaction of the femur (at the proximal diaphysis, distally to the lesser trochanter) and periosteal reaction at the lateral aspect of the ilium body (cranial acetabulum) were noted in animals treated with VEGF Trap independent of dose. DJD was more severe in males. The bone changes were still observed at recovery. These findings are summarized in the table below.

PGR2026-00039
Biocon Ex.1065
Page 470 of 595

Table 16: Bone Abnormalities Detected by Digital Radiographs in the 6-Month Intravenous Toxicity Study in Monkeys

	Males				Females			
Group	1	2	3	4	1	2	3	4
Kyphosis								
Total number affected	-	5	4	5	-	1	5	4
Minimal	-	1	-	1	-	1	1	2
Slight	-	1	3	-	-	0	2	1
Moderate	-	0	1	1	-	-	-	1
Marked	-	3	-	1	-	-	1	-
Severe	-	-	-	2	-	-	1	-
DJD of Articular Facets for Thoracic and Lumbar Spine								
Total number affected	-	6	4	5	-	1	5	4
Minimal	-	-	-	-	-	-	-	1
Slight	-	-	-	1	-	-	1	-
Moderate	-	4	2	-	-	-	2	1
Marked	-	2	-	2	-	1	2	1
Severe	-	-	2	2	-	-	-	1
Periosteal Reaction Ilium								
Total number affected	-	-	2	1	-	-	-	-
Minimal	-	-	-	-	-	-	-	-
Slight	-	-	1	-	-	-	-	-
Moderate	-	-	1	-	-	-	-	-
Marked	-	-	-	1	-	-	-	-
Severe	-	-	-	-	-	-	-	-
Periosteal Reaction Femur								
Total number affected	-	3	2	1	-	-	1	2
Minimal	-	-	-	-	-	-	-	-
Slight	-	2	2	1	-	-	-	1
Moderate	-	1	-	-	-	-	-	1
Marked	-	-	-	-	-	-	-	-
Severe	-	-	-	-	-	-	1	-

Group 1 = Control; Group 2 = 3 mg/kg; Group 3 = 10 mg/kg; Group 4 = 30 mg/kg

Anti-VEGF Trap Antibodies (Prior to the first dose and once a month thereafter (prior to dosing); prior to the terminal necropsy of the dosing period, and during Weeks 37 (mid-recovery) and 48 (prior to recovery necropsy)] – Fourteen animals distributed among all VEGF Trap dose groups exhibited anti-VEGF Trap antibodies during the dosing phase of the study (levels ranging from 908-245000 mIU/mL). Of these animals, one monkey each at 3 and 30 mg/kg (# 255 and # 410, respectively) had a marked reduction in circulating free, bound, and adjusted bound VEGF Trap levels, which correlated to the presence of anti-drug antibodies. It is possible that the accelerated clearance of VEGF Trap and Trap complex was due to anti-VEGF Trap antibodies.

PGR2026-00039
Biocon Ex.1065
Page 471 of 595

During recovery, one male at 10 mg/kg (# 308) exhibited anti-VEGF Trap antibodies (2140 mIU/mL) at Week 37 but not at Week 48. Unfortunately, except for animal # 308, most animals with a high positive anti-drug antibody response during the dosing period, were not part of the recovery group (i.e., they were sacrificed at the end of dosing). Therefore, limited data was collected to determine the reversibility of the anti-drug antibody response.

Toxicokinetics [Predose, ~5 min, 24 hrs and 168 hrs after the end of the infusions on dosing Days 1, 29 (1st month), 57 (2nd month), 85 (3rd month), 113 (4th month), 141 (5th month) and 183 (7th month - prior to necropsy); Weeks 37 (mid-recovery) and 48 (prior to recovery necropsy); bound and free VEGF Trap) -

Free VEGF Trap - The mean peak and trough plasma concentrations of free and total VEGF Trap increased in a dose-dependent manner. The change in dosing schedule slightly decreased peak free drug levels but did substantially reduce trough levels of free VEGF Trap. The greater decrease in trough levels with increased time between doses was observed at the lower dose, which was considered due to the conversion of free drug to bound drug in plasma over time. At the lower concentrations of drug, proportionally more of the free VEGF Trap is converted to the bound form. During recovery, free VEGF Trap was not detected in all but one male at 10 mg/kg (# 308) during Week 37. No main gender differences were noted.

The average mean free VEGF Trap concentrations at peak (5 min postdose) on Days 29, 57 and 85, when drug was administered weekly, were about 105, 307, and 847 µg/mL in the 3, 10 and 30 mg/kg dose cohorts, respectively. During this same period, average mean trough levels (predose) were about 12, 52, and 130 µg/mL in the 3, 10 and 30 mg/kg cohorts, respectively.

The average mean free VEGF Trap concentration at peak (5 min postdose) on Days 141 and 183, when drug was administered bi-weekly, were about 76.9, 287 and 731 µg/mL in the 3, 10 and 30 mg/kg dose groups, respectively. During this same period, average mean trough levels (predose) were about 0.898, 8.29 and 28.8 µg/mL in the 3, 10 and 30 mg/kg cohorts, respectively.

$VEGF_{165}$:VEGF Trap Complex – The plasma levels increased throughout the first few IV infusions of VEGF Trap reaching steady state levels by approximately Day 29 for the three VEGF Trap-treated cohorts. Unlike free VEGF Trap, the $VEGF_{165}$:VEGF Trap complex was still detected at the end of the recovery period in several of the recovery animals. Generally, females showed a slightly higher (≤1.5x) level than males particularly at ≥10 mg/kg.

The average mean adjusted bound VEGF Trap concentration in the predose samples on Days 29, 57 and 85, when drug was administered weekly, were about 3.8, 5.8, and 4.8 µg/mL in the 3, 10 and 30 mg/kg dose cohorts, respectively. The mean average adjusted bound VEGF Trap concentrations in the predose samples on

PGR2026-00039
Biocon Ex.1065
Page 472 of 595

Days 141 and 183, when drug was administered bi-weekly, were about 3.24, 4.80 and 4.43 µg/mL in the 3, 10 and 30 mg/kg dose cohorts, respectively.

The majority of the total amount of VEGF Trap (Free + Adjusted Bound) measured in the circulation up to 24 hrs post IV administration at doses of 3, 10 and 30 mg/kg was present in the form of free, active drug. At all of the time points analyzed for these three dosing cohorts, the mean free concentration of VEGF Trap exceeded the amount of adjusted bound form. However just prior to each administration of VEGF-Trap, free VEGF-Trap levels from only the 10 and 30 mg/kg cohorts remained in excess relative to bound VEGF-Trap levels suggesting that complete VEGF ligand binding was maintained in these cohort for the entire dosing period. These data also suggest that doses of VEGF Trap above 3 mg/kg are likely to be saturating for sequestration of endogenous VEGF165.

Dosing Solution Analysis: Dosing solutions were collected over the 6-month dosing period. Overall, the concentrations ranged from 101-113% of the target concentration.

Four- and 13-Week Systemic Toxicity Studies in Monkeys: Other repeated-dose GLP compliant toxicity studies of 4- or 13-week duration were conducted in monkeys via the subcutaneous and IV routes. Overall, the doses ranged from 1.5-30 mg/kg 1-3x/week. These studies identified similar findings to those observed in the 6-month studies. Noteworthy is the fact that the effects in RBC parameters, bone, kidney, ovary, and adrenals were observed as early as 4 weeks after treatment at VEGF Trap doses of 2-30 mg/kg 1x/week IV or 1.5-15 mg/kg 3x/week SC. With longer duration of dosing, hunched posture and kyphosis, vasculitis, and nasal bleeding were observed. A NOAEL was not identified in any of these studies. The main findings from each study are summarized below.

A 4-Week Subcutaneous Toxicity Study of VEGF Trap in Cynomolgus Monkeys Followed by a 4-Week Recovery Period (Module 4.2.3.2, VGFT-TX-03004) - Doses of 0, 1.5, 5, or 15 mg/kg SC were administered 3x/ week for 4 weeks. A 4-week recovery period was evaluated in control and high-dose groups. The main findings include increased hemoglobin, RBC, and hematocrit at all doses and still present at 15 mg/kg during recovery; effects on the growth plate of the femur (degeneration and disorganization) and effects on the ovary (decreased numbers of maturing follicles, granulosa cells, and/or thecal cells) at doses ≥5 mg/kg; effects on the kidney (increased glomerular mesangial matrix, associated with decreased serum total protein and albumin and increased serum BUN and urine protein levels) at all doses; and decreased vacuolation of adrenal zona fasciculata cells with cytoplasmic eosinophilia at all dose levels. The femoral changes were not observed at the end of the recovery period. Kidney, ovary, and adrenal changes were still observed at 15 mg/kg after the 4-week recovery period.

All animals had high plasma levels of free VEGF Trap (from 69-499 µg/ml on Day 26) throughout the treatment period. Free VEGF Trap was detected systemically in plasma during the recovery period at the only dose evaluated (15 mg/kg). Only one monkey (5 mg/kg) developed low levels of antibodies to VEGF Trap, which did not

PGR2026-00039
Biocon Ex.1065
Page 473 of 595

adversely impact the exposure of this animal to free VEGF Trap. A NOAEL was not determined in this study.

A 13-Week Subcutaneous Toxicity Study of VEGF Trap in Cynomolgus Monkeys Followed by a 6-Week Recovery Period (Module 4.2.3.2, VGFT-TX-02037) - Doses of 0, 1.5, 5, 15, or 30 mg/kg IV were administered 2x/week for 13 weeks. A 6-week recovery period was evaluated in control, 15, and 30 mg/kg groups. The main findings include increase in blood pressure on Week 13 in 2 females each at 15 and 30 mg/kg; slight increases in mean hemoglobin, hematocrit and RBC at all doses which were generally not reversible; increased urine protein and/or serum BUN levels; histopathologic findings in the femoral growth plates, kidneys and ovaries at all dose levels at all doses similar to those observed in the 4-week SC study. The histopathologic findings were still present after the 6-week recovery period at 30 mg/kg, with the exception of the ovaries (decreased numbers of maturing follicles, granulosa cells, and/or thecal cells) which were also present at recovery necropsy at 15 mg/kg.

Plasma levels of free VEGF Trap increased in proportion with dose, with a mean concentration ≥ 510 µg/ml measured from the high-dose animals 24 hrs after dosing during the course of the dosing period. At the end of the 6-week recovery period, the plasma levels of free VEGF Trap were 2.62 µg/mL and 17.7 µg/mL at 15 and 30 mg/kg, respectively. The plasma levels of free VEGF Trap were not determined in the other dose groups. Only one monkey developed an antibody response against VEGF Trap, resulting in a marked drop in free VEGF Trap levels in that animal. A NOAEL was not determined.

A 4-Week Intravenous Toxicity Study of VEGF Trap with a 6-Week Recovery Period in Cynomolgus Monkeys (Module 4.2.3.2, VGFT-TX-02029) - Doses of 0, 2, 10, or 30 mg/kg were administered once weekly for 4 weeks. A 6-week recovery period was evaluated in control and high-dose groups. Similar targets to those observed after SC administration were identified including the bone growth plates and renal glomeruli (associated with increased urine protein and BUN levels and decreased serum albumin and/or serum total protein) at all doses, the ovaries at ≥10 mg/kg, and adrenal cortex at all doses.

Growth plate changes were characterized by a decrease in metaphyseal capillary invasion, a decrease in primary bony trabeculae, degeneration of the cartilage matrix, disorganization of the chondrocyte columns, increased thickening of the physeal cartilage, and transverse subchondral bony plate.

Kidney and bone growth plate changes were partially, but not completely reversible at the end of the 6-week recovery period at 30 mg/kg.

Mean plasma peak free VEGF Trap levels increased proportionally with dose, with peak levels reaching 7868 µg/ml at the high dose on Day 15. Concentrations of VEGF Trap were detected throughout the dosing interval at all dose levels. At the end of the recovery period, low concentrations (≤2 µg/mL) of VEGF Trap were detected at 30 mg/kg, the only dose group evaluated. A NOAEL was not determined.

PGR2026-00039
Biocon Ex.1065
Page 474 of 595

A 13-Week Repeat-Dose Intravenous Toxicity Study of VEGF Trap in Cynomolgus Monkeys and a 13-Week Recovery Period (Module 4.2.3.2, VGFT-TX-03048) - Doses of 0, 3, 10, or 30 mg/kg IV were administered once weekly for 13 weeks. A 13-week recovery period was evaluated at doses of 0, 10, and 30 mg/kg. Clinical observations included hunched posture and kyphosis (associated with atrophy/degeneration of the muscle fibers of the paravertebral skeletal muscle sections from the thoracic or lumbar regions) at all dose levels, which increased at Weeks 11, 12 and 13 of dosing. Red nasal discharge was very occasionally observed in a few animals at all doses. Slight increases in mean RBC, hemoglobin, and hematocrit were noted at all doses in females on Weeks 4 and/or 13 (statistically significant at ≥10 mg/kg) and in RBC and hemoglobin males at 10 and/or 30 mg/kg at Week 13. One high-dose male (# 54) among all animals with nose bleeding showed decreases in all these parameters. Clinical pathology findings noted during the dosing period consisted of high urinary total protein in 3 monkeys at 10 mg/kg and 1 female at 30 mg/kg and high urinary microalbumin levels in 6 monkeys at 10 mg/kg and 3 monkeys at 30 mg/kg that was associated in some monkeys with a mildly decreased serum albumin and A/G ratio. Increases in blood pressure were not observed in this study.

Ovaries weight was decreased at all doses; uterine weight was decreased at 30 mg/kg. These changes were not observed at the end of the 13-week recovery period.

Histopathologic changes were similar to those described under the 4-week, 13-week, and 6-month IV and/or SC toxicology studies previously reviewed. These findings included effects in the kidneys (increased glomerular mesangial matrix, tubular nephropathy), bones (disorganization of the chondrocyte columns and increased thickening of the growth plate cartilage and transverse subchondral bony plate), adrenals (decreased vacuolation with eosinophilia in the zona fasciculata), gallbladder (inflammation), and ovaries (decrease in the number of maturing follicles, granulosa and/or theca cells, absence of corpora lutea) at all doses. Focal vasculitis was observed in the submucosa of the duodenum (2 males each at 10 and 30 mg/kg), urinary bladder (1 high-dose male), and/or heart (1 male at 10 mg/kg) of individual monkeys.

In recovery animals, kyphosis was observed at ≥10 mg/kg (only doses evaluated) accompanied with atrophy/degeneration/necrosis of muscle fibers. Microscopic findings were noted in the kidneys (increased glomerular mesangial cells in males), ovaries (absence of corpora lutea and decreased maturing follicles) and femur/sternum bones (disorganization of the chondrocyte columns and increased thickening of transverse subchondral bony plate) at ≥10 mg/kg but incidences/severity was lower, suggesting reversibility. Moderate inflammation of the gallbladder was present in 1 high-dose male.

Immunohistochemical staining for IgG, IgM, and C3 was observed in the glomeruli at all VEGF Trap doses, compatible with immune-complex deposition. However, since no antibodies were detected in most of these animals (see below), IgG, IgM, and C3 staining may have been related to increase filtration of these molecules subsequent to damage to the filtration barrier resulting from VEGF antagonism, along with increase

PGR2026-00039
Biocon Ex.1065
Page 475 of 595

recruitment of IgG, IgM, and C3 to damaged glomerular components. In fact, transmission electron microscopy revealed ultrastructural changes mainly characterized by reduction or loss of filtration slit diaphragms between the terminal foot processes of podocytes (epithelial cells) and hypertrophy, swelling of endothelial cells with irregularity of their cytoplasmic fenestrations in the glomerulus at ≥10 mg/kg (the low dose was not examined). When the severity of changes in podocytes was higher (fused foot processes), variably sized lysosomes and lipid vacuoles were present in endothelial cells, podocytes from glomeruli and cells from the S1 segment of proximal tubules.

At each dose level, both free VEGF Trap and VEGF Trap complex concentrations were detectable over all dose intervals. Mean plasma maximal concentrations (C_{max}) and trough concentrations of free VEGF Trap increased proportionally with dose (1300 and 200 µg/mL, respectively). Free drug levels were undetectable at the end of the recovery period but were likely present for a substantial portion of that phase, based on an estimated free VEGF Trap elimination $t_{1/2}$ of 4 to 5 days in the monkey. Bound VEGF Trap was detected throughout the duration of the recovery period. Plasma exposure of free VEGF Trap increased by a factor of approximately 2 between Week 1 and Week 13, at all doses, also consistent with the elimination $t_{1/2}$.

One monkey each at 10 and 30 mg/kg exhibited detectable anti-VEGF Trap antibodies. Both animals had notable reductions in plasma drug concentrations, indicating that the immune response was contributing to increased clearance of the drug. Three additional animals (one predose) showed antibody titers less than 2-fold above the limit of quantitation only at one time point, which were regarded as nonspecific serum interference. One mid-dose animal had reactive antibodies just prior to the last infusion yet none at the end of the recovery period. A NOAEL was not determined.

7 Genetic Toxicology

In accordance with ICH Guidance for Industry S6, genotoxicity studies were not conducted because these are not applicable to biotechnology-derived pharmaceuticals.

8 Carcinogenicity

No studies were conducted. The Division agreed that these studies were not required in this case (See Memo to File IND 12462 and (b) (4) dated June 17, 2009).

9 Reproductive and Developmental Toxicology

9.1 Fertility and Early Embryonic Development

The potential effects of VGF Trap in male and female fertility were evaluated as part of the 6-month IV toxicity study in monkeys (Study # VGFT-TX-05009).

PGR2026-00039
Biocon Ex.1065
Page 476 of 595

Absent or irregular menses associated with reductions in ovarian hormones (progesterone, inhibin B, and likely, estradiol) and increases in FSH levels were observed at ≥ 3 mg/kg during the dosing phase. Ovary weight changes at doses ≥ 3 mg/kg were accompanied by compromised luteal development and reduction of maturing follicles. Following recovery, all VEGF Trap-treated females presented normal ovarian folliculogenesis and presence of medium to large size corpora lutea. In addition, uterine and vaginal atrophy were not seen, indicating complete reversibility. The high-dose females still showed decreased weight of the ovaries (23% absolute weight and 9% relative to body weight) compared to controls. However, the reduced magnitude of the change suggests recovery was ongoing.

There were no clear test article-related effects on male reproductive hormone levels (FSH, LH, and testosterone). Decreased sperm motility and increased sperm abnormalities were evident at all doses in the treatment phase but were fully reversible after the treatment-free phase. Decreases were also observed in the weight of the seminal vesicles but without a histopathological correlate.

Therefore, a NOAEL for fertility was not determined. Based on C_{max} and $AUC_{0\text{-}168hrs}$ for free VEGF Trap observed at the 3 mg/kg IV dose, the lowest dose at which the findings were observed, the exposure was 4902-fold and 1546-fold higher, respectively, than the exposure observed in humans (C_{max} and $AUC_{0\text{-}last}$ of 0.0193 µg/mL and 0.119 µg•day/mL, respectively) after an ITV dose of 2 mg/eye every 4 weeks.

9.2 Embryonic Fetal Development

Study title: AVE005: Intravenous (30-Minute Infusion) Embryo-Fetal Toxicity Study in Rabbits

Study no.:	VGFT-TX-06002
Study report location:	Module 4.2.3.5.2
Conducting laboratory and location:	(b) (4) [redacted]
Date of study initiation:	Sept 4, 2006
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	AVE0005 (VEGF Trap); lot # C04008D630B12A

Key Study Findings

- At all doses, there were slight effects in the dams body weight gain and food consumption primarily during dosing with a movement towards recovery once dosing was stopped.
- When corrected for uterine weight, terminal mean body weight was similar to controls.
- Decreased uterine weight was observed at 60 mg/kg.

PGR2026-00039
Biocon Ex.1065
Page 477 of 595

- Abortions and increased mean number of postimplantation loss and early resorptions were noted in females at 60 mg/kg. Consequently, the mean number of viable fetuses was slightly lower at 60 mg/kg, corresponding to the decrease in uterine weight. Mean fetal weight was slightly decreased at the high dose.
- A series of external, visceral, and skeletal malformations were observed primarily at 60 mg/kg. A few findings were noted at 3 and/or 15 mg/kg.
- The maternal NOAEL was considered to be 3 mg/kg and the developmental NOAEL was considered to be <3 mg/kg.
- Based on C_{max} and $AUC_{0\text{-}168hrs}$ for free VEGF Trap observed at the 3 mg/kg IV dose, the exposure was 2900-fold and 600-fold higher, respectively, than the exposure observed in humans after an ITV dose of 2 mg/eye every 4 weeks (C_{max} and $AUC_{0\text{-}last}$ of 0.0193 µg/mL and 2.856 µg•hr/mL, respectively)

Methods

Doses:	0, 3, 15 or 60 mg/kg
Frequency of dosing:	Gestation Days (GD) 6, 9, 12, 15, and 18
Dose volume:	4 mL/kg
Route of administration:	30-min IV infusion
Formulation/Vehicle:	(b) (4) sodium phosphate, (b) (4) sodium chloride. (b) (4)% (w/v) sucrose and ((b) (4) (w/v) PS20, pH (b) (4)
Species/Strain:	New Zealand White rabbits
Number/Sex/Group:	22-26 mated females (20 pregnant rabbits in the control and 3 and 15 mg/kg groups, 22 pregnant rabbits in the high-dose group)
Satellite groups:	3 mated females in controls (2 pregnant); 6 mated females (5-6 pregnant) in VEGF Trap dose groups
Study design:	Standard ICH recommendations; terminal necropsy on GD 29; doses selected based on dose-ranging study # VGFT-TX-06001 (See below)
Deviation from study protocol:	None that could adversely affect interpretation of the study results

Observations and Results

Mortality (Daily) - Three out of 22 pregnant females at 60 mg/kg were euthanized between GD 21 and 26 following compound-related abortion. Clinical signs noted prior to euthanasia consisted of fetal/placental remnant under the cage and/or red material under the cage, and body weight loss associated with reduced food consumption.

Clinical Signs (Daily; main animals only) – No test article-related clinical signs were noted in the females surviving to scheduled euthanasia.

Body Weight (GD 1, 6, 9, 12, 15, 18, 21, 25 and 29 for the main animals and on GD 1, 6, 9,12, 15, 18 and 21 for toxicokinetic animals) – There were no significant effects in mean

PGR2026-00039
Biocon Ex.1065
Page 478 of 595

body weights compared to controls. On GD 18 (last day of dosing), mean body weights were ~6% lower than controls at all doses. On GD 29, mean body weights were 4.6%, 2.8%, and 2.3% lower at 3, 15, and 60 mg/kg, respectively.

Lower mean body weight gain (non-statistically significant) was observed at all intervals during the dosing period with a trend towards recovery once dosing was stopped. At the interval GD 6-18 (dosing period), this decreases were 30%, 60%, and 64% at 3, 15, and 60 mg/kg, respectively. At the interval GD 6-29, these decreases were 3.6%, 4%, and 10% at 3, 15, and 60 mg/kg, respectively.

When corrected for uterus weight, there was no difference in mean body weight compared to control.

Feed Consumption (Daily; main animals only) – Starting on the GD 7-8 interval, a minimal decrease in mean food consumption was noted at all doses throughout the study. For example, a 9%, 18%, and 12% decrease was observed at the GD 17-18 interval at 3, 15, and 60 mg/kg, respectively. After dosing was stopped on GD 18, food consumption moved toward control values with comparable or higher values after the GD 28-29 interval.

Toxicokinetics (At 0.5, 6, 24, 48 and 72 hrs after the last dosing on Day 18) - Mean plasma concentrations of free and total VEGF Trap on GD18 (after the 5th dose) increased with dose in proportion or less than dose proportional to the dose between 15 and 30 mg/kg but greater than dose proportional between 3 and 15 mg/kg (Table 17). Estimates of $AUC_{0.5\text{-}72hrs}$ were greater than dose proportional between 3 and 15 mg/kg and lower than dose proportional between15 and 30 mg/kg. The amount of VEGF:VEGF Trap complex was similar at all doses. As noted by the applicant, this suggests that sufficient levels of drug were present even at 3 mg/kg to bind essentially all the circulating VEGF present in these animals. The concentration of free VEGF Trap exceeded the concentration of bound VEGF Trap at all time points.

PGR2026-00039
Biocon Ex.1065
Page 479 of 595

Table 17: Mean Plasma Concentrations of Free and Bound VEGF Trap in Pregnant Rabbits in the IV Embryofetal Toxicity Study

	Time post dose	Free AVE0005			Bound AVE0005			Total AVE0005		
Dose	(mg/kg/administration)	3	15	60	3	15	60	3	15	60
Gestation Day 18	0.5h	56.1	707	2460	3.07	4.79	5.05	59.2	711	2460
	6h	53.8	624	1640	6.85	6.83	5.53	60.6	630	1650
Gestation Day 19	24h	19.5	332	839	4.14	5.10	4.57	23.6	337	843
Gestation Day 20	48h	23.8	275	807	8.13	6.78	5.15	31.9	282	812
Gestation Day 21	72h	14.0	121	333	2.84	4.10	5.05	16.8	125	338
$AUC_{0.5\text{-}72}$	-	1935	24300	67018	NC	NC	NC	NC	NC	NC

$AUC_{0.5\text{-}72}$: Area under the curve from 0.5 h to 72 h; AUC are expressed in µg*h/mL
NC: Not calculated
Plasma exposures are expressed in µg/mL.

Anti-Product Antibodies (Before dosing on GD 6 and before euthanasia on GD 29; main animals only) – Detectable anti-product antibodies were noted on GD 29 in 2 out of 22 animals at 3 mg/kg (1750 and 2070 ng/mL), 5 out of 22 rabbits at 15 mg/kg (2370-28800 ng/mL), and 14 out of 26 rabbits at 60 mg/kg (776-25400 ng/mL). Given that the toxicokinetic and antibody determinations were conducted on different animal subgroups, it is not known whether the presence of anti-product antibodies affected the clearance of VEGF Trap from the circulation of pregnant rabbits.

Dosing Solution Analysis – All solutions were 92.5-98.7% of theoretical content.

Necropsy (GD 29; main animals only) – The mean uterus weight was lower at 60 mg/kg (25%; $p \leq 0.05$), compared to control. This effect was considered secondary to the lower mean number of fetuses/litter. No test article-related macroscopic findings were observed.

Cesarean Section Data (Implantation Sites, Pre- and Post-Implantation Loss, etc.) - Increased mean number of postimplantation loss (3.7x; $p \leq 0.05$) and early resorptions (4x) was noted in females at 60 mg/kg, compared to controls. Consequently, the mean number of viable fetuses was slightly lower (26%; $p \leq 0.05$) at 60 mg/kg. A slight, non-statistically significant decrease (5%) in mean fetal weight was observed at the high dose.

Offspring (Malformations, Variations, etc.) – A series of external, visceral, and skeletal malformations were observed at all doses.

External malformations: Findings included anasarca in 2 fetuses (2 litters) at 3 mg/kg, ectrodactyly and umbilical hernia in 1 fetus at 15 mg/kg, and anasarca, gastroschisis, umbilical hernia, anal atresia and/or short tail in 1-10 fetuses (1-7 litters) at 60 mg/kg. Most of these findings were noted in fetuses with multiple external malformations

PGR2026-00039
Biocon Ex.1065
Page 480 of 595

associated with visceral and/or skeletal anomalies. One polymalformed fetus at 3 mg/kg presented anasarca, paw hyperflexion, umbilical and diaphragmatic hernia associated with skeletal (fused sternebrae) and visceral (dilation of pulmonary trunk and aortic arch and malpositioned kidney) anomalies. At 60 mg/kg, 6 fetuses presented multiple external malformations including anasarca, cleft palate, hyperflexion of hindlimb or paw, umbilical hernia, gastroschisis, anal atresia and/or tail malformation in association with visceral and/or skeletal anomalies. None of these findings were observed in controls.

Visceral malformations: At 3 mg/kg, visceral malformations were limited to dilation of the great vessels of the pulmonary trunk and aortic arch in one fetus with multiple malformations (See External malformations above).

At 60 mg/kg, malformations were mainly noted in the heart, great vessels, and arteries. Malformations in the heart consisted of ventricular septum defect (10 fetuses/7 litters), small (10 fetuses/7 litters) or enlarged (9 fetuses/7 litters) ventricular chamber, and absence of the atrioventricular valve (2 fetuses/2 litters). Malformations in the great vessels and arteries included: narrowed pulmonary trunk (4 fetuses/4 litters), dilated aorta (5 fetuses/2 litters), reduced pulmonary artery branch (1 fetus), absent (2 fetuses/2 litters) or narrowed (9 fetuses/5 litters) ductus arteriosus, retroesophageal (2 fetuses/2 litters) or dilated aortic arch (16 fetuses/9 litters), dilated aorta (5 fetuses/2 litters). None of these findings were observed in controls. Compared to controls, an increase incidence was noted for retroesophageal subclavian artery (10 fetuses/7 litters vs 1 fetus in control) at 60 mg/kg and malpositioned branch subclavian artery at ≥15 mg/kg (5 fetuses/3 litters at 15 mg/kg, 7 fetuses/4 liters at 30 mg/kg vs 2 fetuses/2 litters in controls)

Intestinal atresia (2 fetuses/2 litters), convolution and dilation of the ureter (4 fetuses/3 litters), dilated renal pelvis (4 fetuses/3 litters), and distension of the urinary bladder (2 fetuses/2 litters) were noted at 60 mg/kg. None of these findings were observed in controls.

Skeletal malformations: At 60 mg/kg, there was an increased incidence of skeletal malformations or variations consisting of fused caudal vertebrae (2 fetuses/2 litters vs none in control), fused (4 fetuses/2 litters vs 1 fetus in control) or supernumerary ribs (4 fetuses/2 litters vs none in control), fused sternebrae (17 fetuses/9 litters vs 4 fetuses/4 litters in control), supernumerary arch (2 fetuses/1 litter vs none in control) and/or centrum (5 fetuses/4 litters vs 1 fetus in control) of lumbar vertebrae and absence of arch and/or centrum of sacral vertebrae (3 fetuses/2 litters vs none in control). A compound-related increase in the incidence of absent or small interparietal skull bone (30 fetuses/13 litters vs 15 fetuses/9 litters in control) was also noted at 60 mg/kg.

In addition, incomplete ossification was noted in the hyoid (5 fetuses/3 litters), thoracic (9 fetuses/9 litters), lumbar (4 fetuses/3 litters) and sacral vertebrae (2 fetuses/1 litter), and sternebrae (9 fetuses/5 litters) at 60 mg/kg as compared to none in controls. Compared to controls, a higher incidence was noted at 60 mg/kg for incomplete ossification in the hindpaw phalanx (6 fetuses/4 litters vs 1 fetus in control) and forepaw phalanx (42 fetuses/14 litters vs 17 fetuses/9 litters in control).

PGR2026-00039
Biocon Ex.1065
Page 481 of 595

Compared to controls, a higher incidence of incomplete ossification was also noted in the ribs (2 fetuses/2 litters vs 1 fetus in control) and talus (2 fetuses/2 litters vs none in control) at 3 mg/kg. Incomplete ossification of the hyoid and thoracic vertebra were observed in 1 fetus and malformation in the thoracic vertebra in 2 fetuses/2 litters (vs none in controls) at 15 mg/kg.

AVE0005: Intravenous (30-min Infusion) Range-Finding Toxicity Study in Pregnant Rabbits (Study # VGFT-TX-06001; Module 4.2.3.5.2.1) – VEGF Trap doses of 0 (controls), 3, 15 and 45 mg/kg were given as a 30-min IV infusion to pregnant rabbits (5-6/group) on GD 6, 9, 12, 15 and 18. Main results include abortion in 1 female at 45 mg/kg on GD 21, premature delivery in 1 female at 15 mg/kg on GD 29, decreased mean body weight gain (e.g., 61-210% during GD6-18; non-dose dependent; non statistically significant) associated with decreased food consumption mainly from GD 12-22 (10-30%; non-dose dependent; non-statistically significant), and increased incidence of reduced feces at all dose levels. After dosing was stopped, animals showed a tendency towards recovery of the effects on body weight gain and food consumption. At 45 mg/kg, a slightly higher mean number of postimplantation loss (2.7x) associated with a slightly lower mean number of viable fetuses (15%) was noted as compared to controls. A decrease in mean fetal weight was noted at all dose levels (13, 14, and 9% at 3, 15, and 45 mg/kg, respectively; non-statistically significant). No external abnormalities were noted at any dose level. The maternal NOAEL was considered to be 3 mg/kg (Day 21 Free VEGF Trap C_{max} = 14 µg/mL).

Additional TK information was obtained from this study compared to final study # VGFT-TX-06002. One animal at 15 mg/kg and 3 animals at 45 mg/kg on GD 29 had antibody levels in excess of 14 µg/mL. The presence of anti-VEGF Trap antibodies was associated with lower levels of free and bound (and total) VEGF Trap concentrations on GD 21 and levels below the lower limit of quantitation on Day 29, indicating the antibodies accelerated the clearance of VEGF Trap. Free VEGF Trap was measured in amniotic fluid samples collected on gestation Day 29 (11 days after the last infusion). Mean concentrations of free VEGF Trap in amniotic fluid increased with dose (6.73 ± 6.48, 33.8 ± 31.5, and 731 ± 1435 ng/mL at 3, 15, and 45 mg/kg, respectively). There was substantial variation among the levels of VEGF Trap within each dose cohort.

9.3 Prenatal and Postnatal Development

No pre-and post-natal toxicity studies were conducted because they were not considered by the applicant necessary for this indication (treatment of AMD), which affects an older population (≥50 yrs old). At a sponsor meeting held on June 1, 2009 (See Memo to File: IND 12467 (b) (4) dated June 17, 2009), the Division agreed that these studies were not required for the proposed indication. It was stated on this meeting that based on documented adverse reproductive and developmental effects of VEGF Trap and other pharmacological blockers of VEGF signaling, any eventual label will include qualifying statements regarding compound effects on fertility and pregnancy and/or categorization restrictions.

PGR2026-00039
Biocon Ex.1065
Page 482 of 595

10 Special Toxicology Studies

Cross-Reactivity of VEGF Trap with Human Tissue Ex Vivo (Study # SPS 01-141; Module 4.2.3.7.7; GLP) – Biotin-VEGF Trap binding was evaluated in a panel of 33 human tissues obtained from 3 separate individuals. No specific staining was observed in any tissues at Biotin-VEGF Trap concentrations of 5 or 25 µg/mL. Five µg/mL was determined to be the lowest concentration of test article that produced the maximum (plateau) binding of the target antigen.

Evaluation of VEGF Trap to Induce Hemolysis in Monkey Blood and to Induce Flocculation in Monkey Plasma and Serum (Study # Hem#1; non-GLP; Module 4.2.3.7.7) - VEGF Trap formulated in 5 mM sodium phosphate, 5 mM sodium citrate, 100 mM sodium chloride, 0.1% (w/v) PS20, and 20% (w/v) sucrose at a concentration of 25 mg/mL and pH 6.0 was evaluated at concentrations of 0.69, 2.09, and 4.17 mg/mL. VEGF Trap did not induce hemolysis when incubated with monkey blood and did not cause the formation of flocculants or precipitates when incubated with either monkey serum or plasma.

Evaluation of VEGF Trap to Induce Hemolysis in Whole Blood from Humans and to Induce Flocculation in Human Plasma and Serum (Study # Hem#3; non-GLP; Module 4.2.3.7.7) – VEGF Trap formulated in (b) (4) l sodium phosphate, (b) (4) sodium chloride, (b) (4)) PS20 and (b) (4) (w/v) sucrose sucrose at a concentration of (b) (4) and pH (b) (4) was evaluated at concentrations of 0.5, 2, and 4 mg/mL. VEGF Trap did not induce hemolysis when incubated with human blood and did not cause the formation of flocculants or precipitates when incubated with either human serum or plasma.

Evaluation of VEGF Trap to Induce Hemolysis in Whole Blood from Humans and to Induce Flocculation in Human Plasma and Serum (Study # Hem#4; non-GLP; Module 4.2.3.7.7) – VEGF Trap formulated in 0.45% or 0.9% NaCl was evaluated at a concentration of 4 mg/mL. VEGF Trap did not induce hemolysis when incubated with human blood and did not cause the formation of flocculants or precipitates when incubated with either human serum or plasma.

Evaluation of VEGF Trap to Induce Hemolysis in Whole Blood from Humans and to Induce Flocculation in Human Plasma and Serum (Study # Hem#5; non-GLP; Module 4.2.3.7.7) - VEGF Trap formulated in 0.9% NaCl was evaluated at a concentration of 8 mg/mL. VEGF Trap did not induce hemolysis when incubated with human blood and did not cause the formation of flocculants or precipitates when incubated with either human serum or plasma.

11 Integrated Summary and Safety Evaluation

VEGF Trap is intended for the treatment of wet age-related macular degeneration. The proposed dosing regimen is 2 mg monthly for the first 3 months and every 2 months

PGR2026-00039
Biocon Ex.1065
Page 483 of 595

afterwards administered by ITV injection. The expected patient population for this indication is male and females ≥50 yrs of age.

The monkey was selected as the relevant species because of identical VEGF-A protein sequence on the amino acid level to its human counterpart. The binding affinity of VEGF Trap to VEGF-A from cynomolgus monkey was not tested but the applicant assumed the binding interaction of human and monkey VEGF-A with VEGF Trap should likely be indistinguishable due to the identical amino acid sequence. The binding of VEGF Trap to monkey VEGF-A was supported by the following observations: (1) the systemic toxicity studies (see below) showed targets of toxicity known for VEGF inhibitors, and (2) efficacy was observed in a monkey model of choroidal neovascularization (CNV).

Binding affinity was demonstrated for mouse, rat, and rabbit VEGF-A. However, mice and rats developed a strong anti-VEGF Trap antibody response after systemic administration of VEGF Trap at doses of 0.1-15 mg/kg (rats) and 10 and 25 mg/kg (rats and mice), 3x/week for 1 month (3 months in one rat study). The anti-drug antibody response was associated with enhanced clearance of VEGF Trap, which precluded the use of these species for long-term toxicity studies. In addition to nephropathies, findings identified in these short term studies in both mice and rats included mortalities, edema, multiorgan vascular dilatation and congestion, and vasculitis. Similar to findings in monkeys (see below), hemorrhage in the nasoturbinates was noted in mice; bone adverse effects were noted in rats. An antibody response associated with enhanced clearance was also detected in pregnant rabbits, which suggested these species may also have limited use for chronic studies.

ITV ocular toxicity studies were conducted in monkeys with duration of 4 and 8 months. The doses ranged from 0.05-0.5 mg/eye or 1 or 2 mg/eye in the 4-month studies and 0.5-4 mg/eye in the 8-month study with a dosing frequency of once every 4 weeks in all studies. An additional 4-month study used a dose of 0.5 µg/mL administered every 2 weeks.

Ocular findings in the ocular toxicity studies were consistent in all studies and included mild and transient increases in anterior segment and vitreous cellularity (interpreted as a mild inflammation) that was not associated with other ocular abnormalities. The anterior segment cell scores declined during the interval between doses and generally, the finding was not present one week postdose. In contrast, vitreal cells were observed throughout the dosing phase and gradually disappeared during the recovery period. These findings were observed at all doses. The lowest dose of 0.5 mg/eye once every 4 weeks evaluated in the longer-term ocular toxicity study (8 months) is 0.5 times the intended clinical dose when correcting for vitreous volume (i.e., assuming a vitreous volume of 2 mL in monkeys and 4 mL in humans). However, the mild and transient nature of the finding does not represent a major clinical concern.

Other VEGF inhibitors (e.g., Lucentis™, Macugen®) have been shown to increase intraocular pressure (IOP) in humans when administered by ITV injection. In all monkey

PGR2026-00039
Biocon Ex.1065
Page 484 of 595

ocular toxicity studies of VEGF Trap, there was an increase in IOP immediately postdose across all groups including the controls. This increase was considered related to the sudden increase in intraocular volume after a bolus injection into the vitreous. IOP returned to normal range by the next time point measured. In the clinical trials conducted for VEGF Trap, an increase in IOP was observed and warnings are included in the proposed label.

In the monkey 8-month ITV ocular toxicity study, epithelial erosion/ulceration of the nasal turbinates accompanied with chronic-active inflammation was noted at doses of 2 and 4 mg/eye once every 4 weeks. After a 4-month recovery period, the chronic-active inflammation was still present but the other findings were not observed, suggesting partial recovery. Similar, albeit more severe lesions in the nasal cavity were noted in systemic toxicity studies in monkeys following repeated, IV administration of VEGF Trap. Hemorrhage in the nasoturbinates was also noted in mice after SC administration, suggesting the potential for the adverse nasal effects to occur across species. The reviewer is not aware of the observation of similar nasal findings with any other approved VEGF inhibitor following ITV injection. The applicant monitored for nasal adverse effects in a subset of patients in the clinical trials with VEGF Trap and found no evidence for an increase incidence with VEGF Trap (see medical officer review for further details). At the NOAEL of 0.5 mg/eye, the systemic exposure was 42 and 56 times higher based on C_{max} and AUC, respectively, than the exposure observed in humans after an ITV dose of 2 mg every 4 weeks (Table 17). The proposed label includes these nonclinical findings under Section 13.2 Animal Toxicology and/or Pharmacology. The reviewer recommended some changes to the proposed label regarding the safety margins (See Section 1.3.3).

Dose-dependent levels of free VEGF Trap were detected in vitreous humor samples collected 7 days after the last monthly ITV dose in monkeys. The extent that free VEGF Trap was detected in the vitreous was dependent on the dose and length of the recovery period. No VEGF Trap was detected at the end of 10-week recovery period at monthly doses of 0.05-0.250 mg/eye or at monthly doses up to 4 mg/eye following a 4-month recovery period. However, at the end of the 10-week recovery period, measurable levels of VEGF Trap were detected in most vitreous samples obtained from recovery animals after monthly doses of 1 and 4 mg/eye.

Compared with the free VEGF Trap concentration in the vitreous after ITV injection in monkeys, the systemic concentration was low (e.g., <3% of the ITV concentration during administration of 4 mg/eye once every four weeks for 8 months). However, there was substantial systemic exposure of VEGF Trap (free and/or bound) in monkeys after ITV injection as concentrations were in the µg/mL range at doses ≥0.5 mg/eye. However, besides the findings in the nasal turbinates, no other local or systemic toxicity was evident after administration of VEGF Trap by ITV injection at doses up to 4 mg/eye once every 4 weeks for up to 8 months.

Depending on the dose, free VEGF Trap generally cleared from the circulation before the next monthly ITV injection. The systemic T_{max} was observed 24 hrs after ITV injection. Unlike free VEGF Trap, the bound complex has a much slower clearance and

PGR2026-00039
Biocon Ex.1065
Page 485 of 595

elimination rate, as it was still detected well into the recovery period. As noted by the applicant, the results indicate that the majority of the total drug concentration in the circulation (Free VEGF Trap + Adjusted Bound VEGF Trap) after each ITV administration of VEGF Trap was the free form (active species) directly following administration, and the bound form (inactive species) at later time points. Therefore, although most of the monkeys may not have been systemically exposed to free VEGF Trap for the entire time period between doses, the monkeys were exposed to VEGF:VEGF Trap complex throughout the study.

Anti-VEGF Trap antibodies were detected in the serum of monkeys after ITV administration of VEGT Trap, generally at monthly doses ≥0.5 mg/eye. However, there was no obvious correlation between the appearance of these putative antibodies and any change in either free and/or bound VEGF Trap levels except for one animal administered 2 mg/eye once every 4 weeks in a formulation different to the commercial formulation. This animal showed enhanced VEGF Trap clearance.

The potential systemic toxicity was addressed in monkeys after the SC and IV routes. In these studies, free VEGF Trap produced systemic toxicities mostly related to the its pharmacology. The main target organs identified in these studies include bone (interference with growth plate maturation of long bones, osteocartilaginous exostoses of vertebrae which correlated marcroscopically with kyphosis, degenerative joint disease, degeneration of the cartilage matrix, etc.), kidney (frequently increased glomerular mesangial matrix, occasionally hyperplasia of parietal epithelium, and periglomerular fibrosis), adrenals (decreased vacuolation with eosinophilia in the zona fasciculata), ovary (decreased number of maturing follicles, granulosa cells, and/or theca cells), and nasal cavity (atrophy/loss of the septum, erosion/ulceration of the respiratory and olfactory epithelium of nasal turbinates). Other microscopic findings observed in the longer-term chronic study (6 months) included vascular alterations in the choroid plexus and digestive tract (duodenum, stomach, gallbladder, pancreas), vascular degeneration and fibrosis in several tissues including the heart, and hepatic portal inflammation and periportal necrosis. Alterations on red blood cell parameters and changes in blood markers indicating damage to the kidney and liver/biliary tract were noted. At the end of a 5-month recovery period in the 6-month systemic toxicity study, findings observed included kyphosis with osteocartilaginous exostoses, nasal cavities deformation, degenerative joint disease, and changes in the digestive system, liver, and brain (choroid plexus).

A NOAEL was not established following systemic (IV and SC) administration to monkeys. However, exposure multiples, calculated by comparing free VEGF Trap concentrations (C_{max}) and systemic exposure (AUC) at the lowest doses associated with findings in animals to exposures observed in humans administered a VEGF Trap dose of 2 mg ITV in clinical studies, provide adequate support for the proposed dose regimen of VEGF Trap in humans (Table 17).

Effects on male and female fertility were assessed as part of the 6-month systemic toxicity study in monkeys at doses of 3.0-30 mg/kg. Absent or irregular menses associated with alterations in female reproductive hormone levels, ovarian and uterine

PGR2026-00039
Biocon Ex.1065
Page 486 of 595

changes, reduction in sperm motility, and sperm morphological abnormalities were observed at all dose levels. Ovarian and uterine changes included decreased ovary and uterine weights accompanied with reduction of maturing follicles, granulosa cells, and absence of corpora lutea. These changes correlated with uterine and vaginal atrophy. All changes were reversible after a 5-month recovery period although ovarian weights were still slightly decreased at the high dose. As noted by the applicant, the potential of VEGF inhibition to impair fertility is a known class effect and related to the relevance of VEGF for development and function of male and female reproductive organs. Based on C_{max} and AUC for free VEGF Trap observed at the 3 mg/kg IV dose, the systemic exposures were approximately 4900-fold and 1500-fold higher, respectively, than the exposure observed in humans after an ITV dose of 2 mg (Table 17). The reviewer recommended some changes to the proposed label to more adequately represent these findings (See Section 1.3.3).

In an embryo-fetal toxicity study in the rabbit, IV doses of VEGF Trap ≥ 3 mg/kg produced dose-related increases in fetal resorptions, abortions, and numerous fetal (external, visceral and skeletal) malformations. A compound-related increase in mean number of postimplantation loss (early resorptions) was noted at 60 mg/kg as compared to controls. Consequently, the mean number of viable fetuses was slightly lower at 60 mg/kg as compared to controls. The mean fetal weight was also slightly decreased at 60 mg/kg. Free VEGF Trap was detected in amniotic fluid samples in the dose range-finding study. The maternal NOAEL was considered to be 3 mg/kg, whereas the developmental NOAEL was not identified. At the dose of 3 mg/kg, the systemic exposures based on C_{max} and AUC for free VEGF Trap were approximately 2900 and 600-fold, respectively, the corresponding values observed in humans after an ITV dose of 2 mg (Table 17). The safety margins suggest there is low probability that embryo-fetal toxicity will be observed in humans receiving VEGF Trap at the intended dosing regimen. The reviewer recommended some changes to the proposed label to more adequately represent these findings (See Section 1.3.3).

In humans, VEGF/VEGFR signaling plays a role in modulating blood pressure homeostasis and VEGF inhibitors, as a class, are known to increase blood pressure after systemic administration of pharmacologically active doses. In the SC and IV toxicity studies conducted in monkeys, VEGF Trap generally had no significant effect on arterial blood pressure or EKG parameters. The exception was one study in which an increase in blood pressure was observed in 2 monkeys each administered VEGF Trap at 15 and 30 mg/kg SC 2x/week for 13 weeks. In contrast, single SC injections to Wistar-Kyoto (WKY) rats (>0.15 mg/kg) or C57BL/6 mice (≥2.5 mg/kg) produced relatively rapid increases in blood pressure. In both rats and mice, heart rate tended to transiently decrease below baseline levels at all VEGF Trap doses tested. This drop in heart rate appears to be a reflex reaction to the elevation in blood pressure. The duration of blood pressure elevation was correlated with the presence of free VEGF Trap in the circulation, such that systolic and diastolic blood pressure remained elevated above pre-treatment baseline values until circulating VEGF Trap levels fell below ~ 1 µg/mL in both species. The mean C_{max} (0.0193 µg/mL) observed after ITV injection of 2 mg/eye in humans is ~50x lower the identified threshold in rodents. Thus, these data support that there is a low probability that ITV administration of VEGF Trap-Eye at a monthly dose of 2 mg/eye will result in

PGR2026-00039
Biocon Ex.1065
Page 487 of 595

systemic exposure to free VEGF Trap in amounts sufficient to affect cardiovascular parameters in patients. Blood pressure changes were monitored in the clinical trials.

Genotoxicity studies were not conducted because these are not applicable to biotechnology-derived pharmaceuticals. Carcinogenicity studies were not considered required in this case per a meeting conducted on June 17, 2009.

The table below (as presented by the applicant), shows the estimates of safety margins for systemic toxicities based on comparisons between the systemic exposure to free VEGF Trap observed at the NOAEL or LOAEL in the nonclinical toxicity studies with that observed in human clinical trials (mean C_{max} of 0.019 µg/mL; range of 0-0.054 µg/mL; mean $AUC_{0\text{-last}}$ of 2.856 µg•hr/mL). Systemic adverse effects identified in the nonclinical studies occurred at systemic exposures well in excess of the exposure observed in humans. In conclusion, the nonclinical studies conducted support the safety of ITV administration of VEGF Trap at the intended dose regimen for the treatment of wet AMD, and the reviewer recommends approval of the BLA.

PGR2026-00039
Biocon Ex.1065
Page 488 of 595

Table 18: Safety Margins for Systemic Toxicities Based on the Animal and Human Free VEGF Exposures

Study Type / Study No.	Free VEGF Trap in Plasma			Exposure Ratios[a]	
	Dose	C_{max}[b] (µg/mL)	AUC_{0-t} (µg•h/mL)	Based on C_{max}	Based on AUC
Phase I VEGF Trap-Eye Pharmacokinetic Sub-study in Humans Module 5.3.3.2, VGFT-OD-0702.PK	2 mg/eye	0.0193	2.856	NA	NA
Cynomolgus Monkeys					
13-Week IVT Toxicity Module 4.2.3.2, VFGT-TX-04025	NOAEL: ND				
	LOAEL: 1 mg/eye[c]	2.45	384	127	135
8-Month IVT Toxicity Module 4.2.3.2, VFGT-TX-05011	NOAEL: 0.5 mg/eye[d]	0.802	160	42	56
	LOAEL: 2 mg/eye[e]	4.46	2023	231	708
6-month IV Toxicity Module 4.2.3.2, VFGT-TX-05009	NOAEL: ND				
	LOAEL 3 mg/kg[f]	94.6	4416	4902	1546
3-month IV Toxicity in Juveniles Module 4.2.3.2, VFGT-TX-05010	NOAEL: ND				
	LOAEL: 0.5 mg/kg[g]	9.71	384	503	134
Rabbits					
Reproductive IV Toxicity Module 4.2.3.5.2, VFGT-TX-06002					
Maternal toxicity	NOAEL: 3 mg/kg[h]	56.1	1935	2907	678
Embryo-Fetal toxicity	NOAEL: ND				
	LOAEL: 3 mg/kg	56.1	1935	2907	678

AUC = Area under the concentration time curve; C_{max} = Maximal concentration; GD = Gestation day; IV = Intravenous; IVT = Intravitreal; NA = Not applicable; ND = Not determined; NOAEL = No observed adverse effect level; LOAEL = Lowest observable adverse effect level; T_{max} = Time of maximal concentration, VEGF = Vascular endothelial growth factor.

[a] Exposure ratio = = C_{max} or AUC values in the toxicity studies divided by the C_{max} (from 0.0193 mg/L reported value) or AUC (from 0.0119 mg•day/L reported value) estimated in humans after a 2 mg intravitreal dose every 4 weeks (Module 5.3.3.2, VGFT-OD-0702.PK, Table PK2.1; 21 Sep 2010).

[b] For IVT toxicity studies, C_{max} was generally observed at T_{max} of 1 day. For IV toxicity studies, C_{max} was observed at at T_{max} of 5 minutes after completion of IV infusion. For reproductive IV toxicity studies, C_{max} was observed at at T_{max} of 0.5 hours after dosing.

[c] The C_{max} value after the third 0.5 mg/eye dose was calculated by averaging the observed C_{max} values for individual animals (Module 4.2.3.2, VGFT-TX-04025, Appendix 19 Toxicokinetics (plasma) and antibody determination, Appendix A, Table 3). C_{max} occurred at a calculated average T_{max} of 1.67 days. The mean AUC_{0-28d} (from 16.0 µg•day/mL reported value) after the third 0.5 mg/eye dose in Module 4.2.3..2, VGFT-TX-04025, Appendix 19, Appendix A, Table 43.

[d] The mean C_{max} and $AUC_{0-28days}$ (AUC from 6.66 µg•day/mL reported value) at the NOAEL (0.5 mg/eye) in Module 4.2.3.2, VFGT-TX-05011, Appendix 6 Toxicokinetics (plasma) and antibody determination, Appendix A, Tables 4 and 43; after the 7th dose.

[e] The mean C_{max} and $AUC_{0-28days}$ (AUC from 84.3 µg•day/mL reported value) at 2 mg/eye in Module 4.2.3..2, VFGT-TX-05011, Appendix 6 Toxicokinetics (plasma) and antibody determination, Appendix A, Tables 12 and 46; after the 7th dose.

[f] The mean C_{max} after the first dose and AUC_{0-168h} (AUC from 184 µg•day/mL reported value) at week 21 at 3 mg/kg in Module 4.2.3.2 VFGT-TX-05009, Appendix 12 Analysis of free and bound VEGF Trap and anti-VEGF Trap antibody, Appendix A, Tables 4 and 30.

[g] The mean C_{max} and AUC_{0-168h} (AUC from 19 µg•day/mL reported value) at 0.5 mg/kg in Module 4.2.3.2, VFGT-TX-05010, Appendix 13 Amended toxicokinetics and antibody report, Appendix A Tables 4 and 30; after the fifth dose.

[h] The mean C_{max} and $AUC_{0.5-72h}$ at 3mg/kg in Module 4.2.3.5.2, VFGT-TX-06002, Appendix V Toxicokinetic evaluation phase report, Appendix A Table 18; GD18 data.

PGR2026-00039
Biocon Ex.1065
Page 489 of 595

Note: *The correct AUC value reported for humans under superscript "a" is 0.119 mg•day/L. The 3-month toxicity study in juvenile monkeys was not reviewed as the intended patient population is at least of 50 years of age.*

Signatures:

Reviewer Signature María I. Rivera 6-30-2011
María I Rivera, Ph.D.

Supervisor Signature William H Taylor Concurrence Yes ✓ No ___
William Taylor, PhD 6/30/2011

PGR2026-00039
Biocon Ex.1065
Page 490 of 595

Comments on BLA 125387 Aflibercept ophthalmic solution
From: Abigail Jacobs, Assoc. Dir
Date: June 30, 2011

There are no outstanding pharm/tox issues for this BLA and the pregnancy category C is appropriate.

I have discussed some comments with the Team Leader and they have been addressed as appropriate.

PHARMACOLOGY/TOXICOLOGY NDA FILEABILITY CHECKLIST

BLA Number: 125387 **Applicant: Regeneron Pharmaceuticals** **Stamp Date: 2-18-2011**
Drug Name: Aflibercept Ophthalmic Solution

IS THE PHARM/TOX SECTION OF THE APPLICATION FILEABLE? Yes [x] No [ ]

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Parameters	Yes	No	Comment
1	On its face, is the Pharmacology/Toxicology section of the NDA organized in a manner to allow substantive review to begin?	X		
2	Is the Pharmacology/Toxicology section of the NDA indexed and paginated in a manner to allow substantive review to begin?	X		
3	On its face, is the Pharmacology/Toxicology section of the NDA legible so that substantive review can begin?	X		
4	Are ALL required* and requested IND studies completed and submitted in this NDA (carcinogenicity, mutagenicity*, teratogenicity*, effects on fertility*, juvenile studies, ocular toxicity studies*, acute adult studies*, chronic adult studies*, maximum tolerated dosage determination, dermal irritancy, ocular irritancy, photocarcinogenicity, animal pharmacokinetic studies, etc)?	X		In accordance with ICH guideline S61 and CPMP/ICH/302/95 (1998), genotoxicity studies were not conducted. Since VEGF Trap is a large molecule, it is not expected to interact directly with DNA or other chromosomal material. Carcinogenicity studies were not conducted. The Division agreed in a sponsor meeting held on 6-1-09 that these studies were not required.
5	If the formulation to be marketed is different from that used in the toxicology studies, has the sponsor made a appropriate effort to either repeat the studies with the to be marketed product or to explain why such repetition should not be required?	X		The formulation was optimized as development progressed. A 13-week formulation study and an 8-month study in monkeys were conducted to support long-term intravitreal dosing with the intended clinical formulation.
6	Are the proposed labeling sections relative to pharmacology appropriate (including human dose multiples expressed in mg/m^2 or comparative serum/plasma levels) and in accordance with 201.57?	X		
7	Has the sponsor submitted all special studies/data requested by the Division during pre-submission discussions?	X		
8	On its face, does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the sponsor submitted a rationale to justify the alternative route?	X		Intravitreal (intended human rotute) as well as systemic route (SC and IV) studies were conducted.
9	Has the sponsor submitted a statement(s) that all of the pivotal pharm/tox studies been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	X		
10	Has the Sponsor submitted the data from the nonclinical carcinogenicity studies, in the STUDIES electronic format, for the review by Biometrics?		X	Not applicable
11	Has the sponsor submitted a statement(s) that the pharm/tox		X	The Sponsor did not submit a statement but

	studies have been performed using acceptable, state-of-the-art protocols which also reflect agency animal welfare concerns?			the protocols reflect that animals were treated humanely.
12	From a pharmacology perspective, is this NDA fileable?	X		
13	If the NDA is fileable, are there any issues that need to be conveyed to the Sponsor?		X	

Reviewing Pharmacologist: María I. Rivera 3-23-11

María I. Rivera, Ph.D. Date:

Team Leader: Wendelyn Schmidt 3/23/11

Wendelyn Schmidt, Ph.D. Date:

cc:

S. Wadhwa/MO
M. Puglisi/PM

APPENDIX EMA02

https://web.archive.org/web/20160701000000*/https://www.gene.com/download/pdf/lucentis_prescribing.pdf September 17, 2025

INTERNET ARCHIVE WEB TEXTS VIDEO AUDIO SOFTWARE IMAGES SIGN UP | LOG IN UPLOAD Search

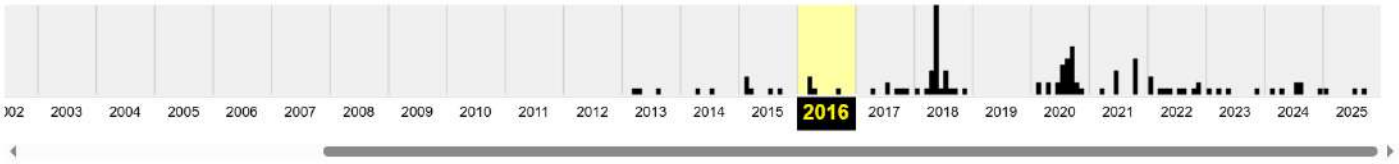
ABOUT BLOG PROJECTS HELP DONATE CONTACT JOBS VOLUNTEER PEOPLE

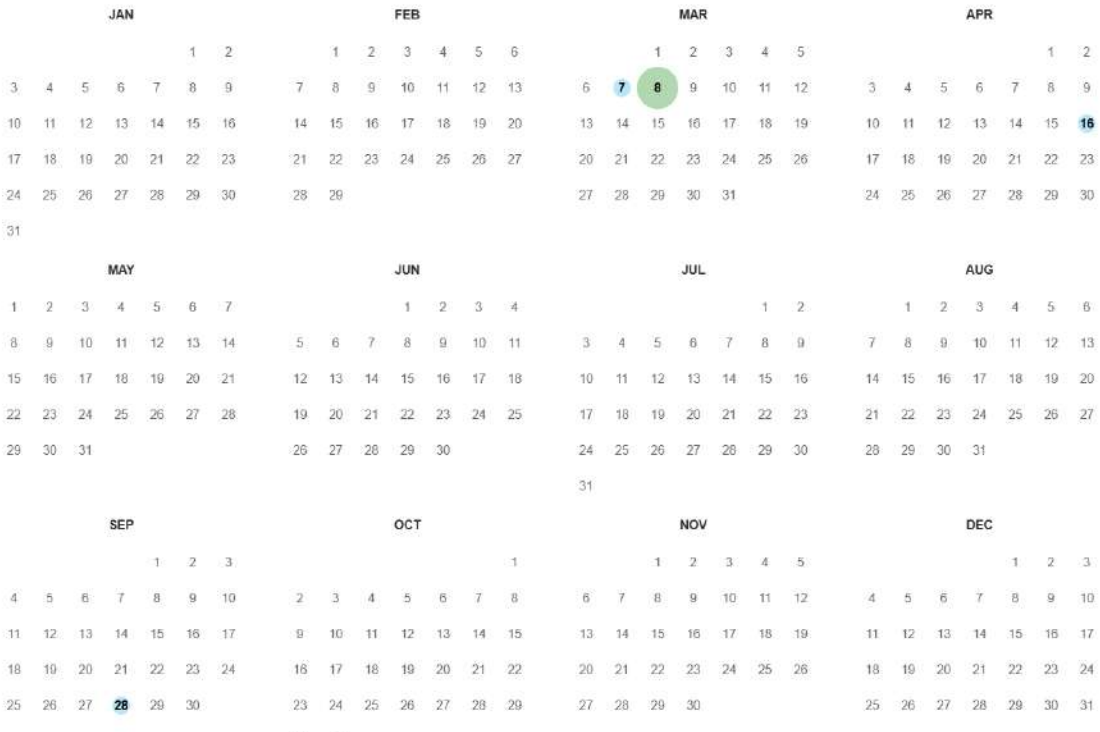
DONATE INTERNET ARCHIVE WayBackMachine Explore more than 946 billion web pages saved over time

https://www.gene.com/download/pdf/lucentis_prescribing.pdf

Calendar · Collections · Changes · Summary · Site Map · URLs

Saved **115 times** between March 3, 2013 and September 8, 2025.





Note

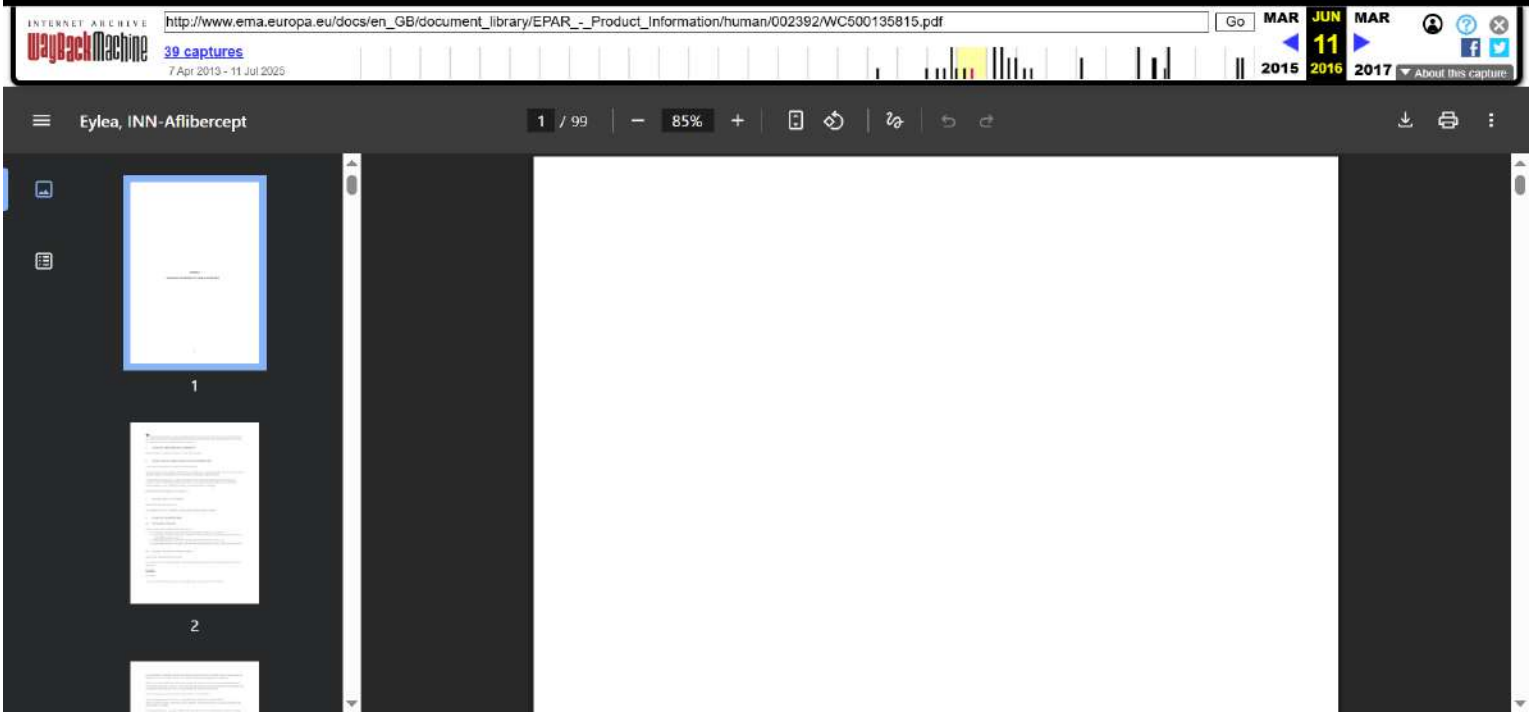
This calendar view maps the number of times **https://www.gene.com/download/pdf/lucentis_prescribing.pdf** was crawled by the Wayback Machine, *not* how many times the site was actually updated. More info in the FAQ. Green indicates redirects (3xx).

FAQ | Contact Us | Terms of Service (Dec 31, 2014)

The Wayback Machine is an initiative of the Internet Archive, a 501(c)(3) non-profit, building a digital library of Internet sites and other cultural artifacts in digital form. Other projects include Open Library & archive-it.org.

Your use of the Wayback Machine is subject to the Internet Archive's Terms of Use.

https://web.archive.org/web/20160611010852/http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002392/WC500135815.pdf September 17, 2025



ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

PGR2026-00039
Biocon Ex.1065
Page 497 of 595

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Eylea 40 mg/ml solution for injection in pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml solution for injection contains 40 mg aflibercept*.

One pre-filled syringe contains 90 microlitres, equivalent to 3.6 mg aflibercept. This provides a usable amount to deliver a single dose of 50 microlitres containing 2 mg aflibercept.

*Fusion protein consisting of portions of human VEGF (Vascular Endothelial Growth Factor) receptors 1 and 2 extracellular domains fused to the Fc portion of human IgG1 and produced in Chinese hamster ovary (CHO) K1 cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection)

The solution is a clear, colourless to pale yellow and iso-osmotic solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Eylea is indicated for adults for the treatment of

- neovascular (wet) age-related macular degeneration (AMD) (see section 5.1),
- visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO) (see section 5.1),
- visual impairment due to diabetic macular oedema (DME) (see section 5.1),
- visual impairment due to myopic choroidal neovascularisation (myopic CNV) (see section 5.1).

4.2 Posology and method of administration

Eylea is for intravitreal injection only.

Eylea must only be administered by a qualified physician experienced in administering intravitreal injections.

Posology

wet AMD

The recommended dose for Eylea is 2 mg aflibercept, equivalent to 50 microlitres.

PGR2026-00039
Biocon Ex.1065
Page 498 of 595

Eylea treatment is initiated with one injection per month for three consecutive doses, followed by one injection every two months. There is no requirement for monitoring between injections.

After the first 12 months of treatment with Eylea, the treatment interval may be extended based on visual and/or anatomic outcomes. In this case the schedule for monitoring should be determined by the treating physician and may be more frequent than the schedule of injections.

Macular oedema secondary to RVO (branch RVO or central RVO)

The recommended dose for Eylea is 2 mg aflibercept equivalent to 50 microlitres.
After the initial injection, treatment is given monthly. The interval between two doses should not be shorter than one month.

If visual and anatomic outcomes indicate that the patient is not benefiting from continued treatment, Eylea should be discontinued.

Monthly treatment continues until maximum visual acuity is achieved and/or there are no signs of disease activity. Three or more consecutive, monthly injections may be needed.

Treatment may then be continued with a treat and extend regimen with gradually increased treatment intervals to maintain stable visual and/or anatomic outcomes, however there are insufficient data to conclude on the length of these intervals. If visual and/or anatomic outcomes deteriorate, the treatment interval should be shortened accordingly.

The monitoring and treatment schedule should be determined by the treating physician based on the individual patient's response.

Monitoring for disease activity may include clinical examination, functional testing or imaging techniques (e.g. optical coherence tomography or fluorescein angiography).

Diabetic macular oedema

The recommended dose for Eylea is 2 mg aflibercept equivalent to 50 microlitres.

Eylea treatment is initiated with one injection per month for five consecutive doses, followed by one injection every two months. There is no requirement for monitoring between injections.

After the first 12 months of treatment with Eylea, the treatment interval may be extended based on visual and/or anatomic outcomes. The schedule for monitoring should be determined by the treating physician.

If visual and anatomic outcomes indicate that the patient is not benefiting from continued treatment, Eylea should be discontinued.

Myopic choroidal neovascularisation

The recommended dose for Eylea is a single intravitreal injection of 2 mg aflibercept equivalent to 50 microlitres.

Additional doses may be administered if visual and/or anatomic outcomes indicate that the disease persists. Recurrences should be treated as a new manifestation of the disease.

The schedule for monitoring should be determined by the treating physician.

The interval between two doses should not be shorter than one month.

PGR2026-00039
Biocon Ex.1065
Page 499 of 595

Special populations

Hepatic and/or renal impairment
No specific studies in patients with hepatic and/or renal impairment have been conducted with Eylea.

Available data do not suggest a need for a dose adjustment with Eylea in these patients (see section 5.2).

Elderly population
No special considerations are needed. There is limited experience in patients older than 75 years with DME.

Paediatric population
Safety and efficacy have not been established in children and adolescents. There is no relevant use of Eylea in the paediatric population in the indications wet AMD, CRVO, BRVO, DME and myopic CNV.

Method of administration

Intravitreal injections must be carried out according to medical standards and applicable guidelines by a qualified physician experienced in administering intravitreal injections. In general, adequate anaesthesia and asepsis, including topical broad spectrum microbicide (e.g. povidone iodine applied to the periocular skin, eyelid and ocular surface), have to be ensured. Surgical hand disinfection, sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent) are recommended.

The injection needle should be inserted 3.5-4.0 mm posterior to the limbus into the vitreous cavity, avoiding the horizontal meridian and aiming towards the centre of the globe. The injection volume of 0.05 ml is then delivered; a different scleral site should be used for subsequent injections.

Immediately following the intravitreal injection, patients should be monitored for elevation in intraocular pressure. Appropriate monitoring may consist of a check for perfusion of the optic nerve head or tonometry. If required, sterile equipment for paracentesis should be available.

Following intravitreal injection patients should be instructed to report any symptoms suggestive of endophthalmitis (e.g. eye pain, redness of the eye, photophobia, blurring of vision) without delay.

Each pre-filled syringe should only be used for the treatment of a single eye.

The pre-filled syringe contains more than the recommended dose of 2 mg aflibercept. The extractable volume of the syringe (90 microlitres) is not to be used in total. The excess volume should be expelled before injecting.
Injecting the entire volume of the prefilled syringe could result in overdose. To expel the air bubble along with excess medicinal product, slowly depress the plunger to align the cylindrical base of the dome plunger with the black dosing line on the syringe (equivalent to 50 microlitres i.e. 2 mg aflibercept).

After injection any unused product must be discarded.

For handling of the medicinal product, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance aflibercept or to any of the excipients listed in section 6.1.
Active or suspected ocular or periocular infection.

PGR2026-00039
Biocon Ex.1065
Page 500 of 595

Active severe intraocular inflammation.

4.4 Special warnings and precautions for use

Intravitreal injection-related reactions

Intravitreal injections, including those with Eylea, have been associated with endophthalmitis, intraocular inflammation, rhegmatogenous retinal detachment, retinal tear and iatrogenic traumatic cataract (see section 4.8). Proper aseptic injection techniques must always be used when administering Eylea. In addition, patients should be monitored during the week following the injection to permit early treatment if an infection occurs. Patients should be instructed to report any symptoms suggestive of endophthalmitis or any of the above mentioned events without delay.

Increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including those with Eylea (see section 4.8). Special precaution is needed in patients with poorly controlled glaucoma (do not inject Eylea while the intraocular pressure is ≥ 30 mmHg). In all cases, both the intraocular pressure and the perfusion of the optic nerve head must therefore be monitored and managed appropriately.

Immunogenicity
As this is a therapeutic protein, there is a potential for immunogenicity with Eylea (see section 4.8). Patients should be instructed to report any signs or symptoms of intraocular inflammation, e.g. pain, photophobia, or redness, which may be a clinical sign attributable to hypersensitivity.

Systemic effects
Systemic adverse events including non-ocular haemorrhages and arterial thromboembolic events have been reported following intravitreal injection of VEGF inhibitors and there is a theoretical risk that these may relate to VEGF inhibition. There are limited data on safety in the treatment of patients with CRVO, BRVO, DME or myopic CNV with a history of stroke or transient ischaemic attacks or myocardial infarction within the last 6 months. Caution should be exercised when treating such patients.

Other
As with other intravitreal anti-VEGF treatments for AMD, CRVO, BRVO, DME and myopic CNV the following also applies:

- The safety and efficacy of Eylea therapy administered to both eyes concurrently have not been systematically studied (see section 5.1). If bilateral treatment is performed at the same time this could lead to an increased systemic exposure, which could increase the risk of systemic adverse events.
- Concomitant use of other anti-VEGF (vascular endothelial growth factor)
  There is no data available on the concomitant use of Eylea with other anti-VEGF medicinal products (systemic or ocular).
- Risk factors associated with the development of a retinal pigment epithelial tear after anti-VEGF therapy for wet AMD, include a large and/or high pigment epithelial retinal detachment. When initiating Eylea therapy, caution should be used in patients with these risk factors for retinal pigment epithelial tears.
- Treatment should be withheld in patients with rhegmatogenous retinal detachment or stage 3 or 4 macular holes.
- In the event of a retinal break the dose should be withheld and treatment should not be resumed until the break is adequately repaired.
- The dose should be withheld and treatment should not be resumed earlier than the next scheduled treatment in the event of:
    - a decrease in best-corrected visual acuity (BCVA) of ≥30 letters compared with the last assessment of visual acuity;

PGR2026-00039
Biocon Ex.1065
Page 501 of 595

- a subretinal haemorrhage involving the centre of the fovea, or, if the size of the haemorrhage is ≥50%, of the total lesion area.

- The dose should be withheld within the previous or next 28 days in the event of a performed or planned intraocular surgery.
- Eylea should not be used in pregnancy unless the potential benefit outweighs the potential risk to the foetus (see section 4.6).
- Women of childbearing potential have to use effective contraception during treatment and for at least 3 months after the last intravitreal injection of aflibercept (see section 4.6).
- There is limited experience with treatment of patients with ischaemic CRVO and BRVO. In patients presenting with clinical signs of irreversible ischaemic visual function loss, the treatment is not recommended.

Populations with limited data
There is only limited experience in the treatment of subjects with DME due to type I diabetes or in diabetic patients with an HbA1c over 12% or with proliferative diabetic retinopathy.
Eylea has not been studied in patients with active systemic infections or in patients with concurrent eye conditions such as retinal detachment or macular hole. There is also no experience of treatment with Eylea in diabetic patients with uncontrolled hypertension. This lack of information should be considered by the physician when treating such patients.

In myopic CNV there is no experience with Eylea in the treatment of non-Asian patients, patients who have previously undergone treatment for myopic CNV, and patients with extrafoveal lesions.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Adjunctive use of verteporfin photodynamic therapy (PDT) and Eylea has not been studied, therefore, a safety profile is not established.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
Women of childbearing potential have to use effective contraception during treatment and for at least 3 months after the last intravitreal injection of aflibercept (see section 4.4).

Pregnancy
There are no data on the use of aflibercept in pregnant women.
Studies in animals have shown embryo-foetal toxicity (see section 5.3).

Although the systemic exposure after ocular administration is very low, Eylea should not be used during pregnancy unless the potential benefit outweighs the potential risk to the foetus.

Breastfeeding
It is unknown whether aflibercept is excreted in human milk. A risk to the breast-fed child cannot be excluded.

Eylea is not recommended during breastfeeding. A decision must be made whether to discontinue breastfeeding or to abstain from Eylea therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Fertility
Results from animal studies with high systemic exposure indicate that aflibercept can impair male and female fertility (see section 5.3). Such effects are not expected after ocular administration with very low systemic exposure.

PGR2026-00039
Biocon Ex.1065
Page 502 of 595

4.7 Effects on ability to drive and use machines

Injection with Eylea has a minor influence on the ability to drive and use machines due to possible temporary visual disturbances associated either with the injection or the eye examination. Patients should not drive or use machines until their visual function has recovered sufficiently.

4.8 Undesirable effects

Summary of the safety profile

A total of 3,102 patients constituted the safety population in the eight phase III studies. Among those, 2,501 patients were treated with the recommended dose of 2 mg.

Serious ocular adverse reactions in the study eye related to the injection procedure have occurred in less than 1 in 1,900 intravitreal injections with Eylea and included blindness, endophthalmitis, retinal detachment, cataract traumatic, cataract, vitreous haemorrhage, vitreous detachment, and intraocular pressure increased (see section 4.4).

The most frequently observed adverse reactions (in at least 5% of patients treated with Eylea) were conjunctival haemorrhage (25%), visual acuity reduced (11%), eye pain (10%), cataract (8%), intraocular pressure increased (8%), vitreous detachment (7%) and vitreous floaters (7%).

Tabulated list of adverse reactions
The safety data described below include all adverse reactions from the eight phase III studies in the indications wet AMD, CRVO, BRVO, DME and myopic CNV with a reasonable possibility of causality to the injection procedure or medicinal product.

The adverse reactions are listed by system organ class and frequency using the following convention:

Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥ 1/10,000 to < 1/1,000)

Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness.

PGR2026-00039
Biocon Ex.1065
Page 503 of 595

Table 1: All treatment-emergent adverse drug reactions reported in patients in phase III studies (pooled data of the phase III studies for the indications wet AMD, CRVO, BRVO, DME and myopic CNV)

System Organ Class	Very common	Common	Uncommon	Rare
Immune system disorders			Hypersensitivity***	
Eye disorders	Visual acuity reduced, Conjunctival haemorrhage, Eye pain	Retinal pigment epithelial tear*, Detachment of the retinal pigment epithelium, Retinal degeneration, Vitreous haemorrhage, Cataract, Cataract cortical, Cataract nuclear, Cataract subcapsular, Corneal erosion, Corneal abrasion, Intraocular pressure increased, Vision blurred, Vitreous floaters, Vitreous detachment, Injection site pain, Foreign body sensation in eyes, Lacrimation increased, Eyelid oedema, Injection site haemorrhage, Punctate keratitis, Conjunctival hyperaemia, Ocular hyperaemia	Endophthalmitis**, Retinal detachment, Retinal tear, Iritis, Uveitis, Iridocyclitis, Lenticular opacities, , Corneal epithelium defect, Injection site irritation, Abnormal sensation in eye, Eyelid irritation, Anterior chamber flare, Corneal oedema,	Blindness, Cataract traumatic, Vitritis, Hypopyon

* Conditions known to be associated with wet AMD. Observed in the wet AMD studies only.

** Culture positive and culture negative endophthalmitis

*** including allergic reactions

Description of selected adverse reactions

In the wet AMD phase III studies, there was an increased incidence of conjunctival haemorrhage in patients receiving anti-thrombotic agents. This increased incidence was comparable between patients treated with ranibizumab and Eylea.

Arterial thromboembolic events (ATEs) are adverse events potentially related to systemic VEGF inhibition. There is a theoretical risk of arterial thromboembolic events following intravitreal use of VEGF inhibitors.

ATEs, as defined by Antiplatelet Trialists' Collaboration (APTC) criteria, include nonfatal myocardial infarction, nonfatal stroke, or vascular death (including deaths of unknown cause).

The incidence of ATEs in the phase III wet AMD studies during the 96 weeks study duration was 3.3% (60 out of 1,824) in the combined group of patients treated with Eylea compared to 3.2% (19 out

PGR2026-00039
Biocon Ex.1065
Page 504 of 595

of 595) in patients treated with ranibizumab (see section 5.1). The corresponding numbers in the DME studies during the first 100 weeks were 6.4% (37 out of 578) (Eylea) and 4.2% (12 out of 287) (control group) (see section 5.1).

The incidence of ATEs in the phase III CRVO studies during the 76/100 weeks study duration was 0.6% (2 out of 317) in patients treated with at least one dose of Eylea compared to 1.4% (2 out of 142) in the group of patients receiving only sham treatment (see section 5.1) whilst for the Phase III BRVO study during the 52 weeks study duration it was 0% (0 out of 91) in patients treated with Eylea compared with 2.2% (2 out of 92) in the control group (see section 5.1). One of these patients in the control group had received Eylea rescue treatment.

The incidence of ATEs in the myopic CNV study during the 48 weeks study duration was 1.1% (1 out of 91) (Eylea) compared to 0% (0 out of 31) (control group).

As with all therapeutic proteins, there is a potential for immunogenicity with Eylea.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

In clinical trials, doses of up to 4 mg in monthly intervals have been used and isolated cases of overdoses with 8 mg occurred.

Overdosing with increased injection volume may increase intraocular pressure. Therefore, in case of overdose, intraocular pressure should be monitored and if deemed necessary by the treating physician, adequate treatment should be initiated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmologicals / Antineovascularisation agents
ATC code: S01LA05

Aflibercept is a recombinant fusion protein consisting of portions of human VEGF receptor 1 and 2 extracellular domains fused to the Fc portion of human IgG1.

Aflibercept is produced in Chinese hamster ovary (CHO) K1 cells by recombinant DNA technology.

Aflibercept acts as a soluble decoy receptor that binds VEGF-A and PlGF with higher affinity than their natural receptors, and thereby can inhibit the binding and activation of these cognate VEGF receptors.

Mechanism of action
Vascular endothelial growth factor-A (VEGF-A) and placental growth factor (PlGF) are members of the VEGF family of angiogenic factors that can act as potent mitogenic, chemotactic, and vascular permeability factors for endothelial cells. VEGF acts via two receptor tyrosine kinases; VEGFR-1 and VEGFR-2, present on the surface of endothelial cells. PlGF binds only to VEGFR-1, which is also present on the surface of leucocytes. Excessive activation of these receptors by VEGF-A can result in

PGR2026-00039
Biocon Ex.1065
Page 505 of 595

pathological neovascularisation and excessive vascular permeability. PlGF can synergize with VEGF-A in these processes, and is also known to promote leucocyte infiltration and vascular inflammation.

Pharmacodynamic effects

wet AMD

Wet AMD is characterised by pathological choroidal neovascularisation (CNV). Leakage of blood and fluid from CNV may cause retinal thickening or oedema and/or sub-/intra-retinal haemorrhage, resulting in loss of visual acuity.

In patients treated with Eylea (one injection per month for three consecutive months, followed by one injection every 2 months), retinal thickness decreased soon after treatment initiation, and the mean CNV lesion size was reduced, consistent with the results seen with ranibizumab 0.5 mg every month.

In the VIEW1 study there were mean decreases in retinal thickness on optical coherence tomography (OCT) (-130 and -129 microns at week 52 for the Eylea 2 mg every two months and ranibizumab 0.5 mg every month study groups, respectively). Also at the 52 week time point, in the VIEW2 study there were mean decreases in retinal thickness on OCT (-149 and -139 microns for the Eylea 2 mg every two months and ranibizumab 0.5 mg every month study groups, respectively). The reduction of CNV size and reduction in retinal thickness were generally maintained in the second year of the studies.

Macular oedema secondary to CRVO and BRVO

In CRVO and BRVO, retinal ischaemia occurs and signals the release of VEGF which in turn destabilises the tight junctions and promotes endothelial cell proliferation. Up-regulation of VEGF is associated with the breakdown of the blood retina barrier and this increased vascular permeability results in retinal oedema, stimulation of endothelial cell growth and neovascularisation.

In patients treated with Eylea (one injection every month for six months), there was consistent, rapid and robust response in morphology (central retinal thickness [CRT] as assessed by OCT). Improvements in mean CRT were maintained through week 24.

In the COPERNICUS and GALILEO studies (CRVO) the mean decrease from baseline in CRT at week 24 was significantly greater in patients treated with Eylea 2 mg every month than in the control group (-457 microns vs. -145 microns in COPERNICUS, and -449 microns vs. -169 microns in GALILEO).

In the VIBRANT study (BRVO) the mean decrease from baseline in CRT at week 24 was significantly greater in patients treated with Eylea 2 mg every month than in the control group (-280 microns vs. -128 microns). This decrease from baseline was maintained to end of study, week 100 in COPERNICUS, week 76 in GALILEO and week 52 in VIBRANT.

Diabetic macular oedema

Diabetic macular oedema is characterised by increased vasopermeability and damage to the retinal capillaries which may result in loss of visual acuity.

In patients treated with Eylea, the majority of whom were classified as having Type II diabetes, rapid and robust response in morphology (central retinal thickness [CRT]) as assessed by OCT was seen soon after treatment initiation. The mean change in CRT from baseline to week 52 was statistically significant favouring Eylea.

In the VIVID-^{DME} and the VISTA-^{DME} studies the mean decreases in CRT at week 52 were -192.4 and -183.1 microns for the 2Q8 Eylea groups and -66.2 and -73.3 micronsfor the control groups,

PGR2026-00039
Biocon Ex.1065
Page 506 of 595

respectively. At week 100 the decrease was maintained with -195.8 and -191.1 microns for the 2Q8 Eylea groups and -85.7 and -83.9 microns for the control groups, in the VIVID-^{DME} and VISTA-^{DME} studies, respectively.

A ≥ 2 step improvement in DRSS was assessed in a pre-specified manner in VIVID-^{DME} and VISTA-^{DME}. The DRSS score was gradable in73.7% of the patients in VIVID-^{DME} and 98.3% of the patients in VISTA-^{DME}. At week 52, 27.7% and 29.1% of the Eylea 2Q8 groups, and 7.5% and 14.3% of the control groups experienced a ≥2 step improvement in the DRSS. At week 100, the respective percentages were 32.6% and 37.1% of the Eylea 2Q8 groups and 8.2% and 15.6% of the control groups.

Myopic choroidal neovascularisation

Myopic choroidal neovascularisation (myopic CNV) is a frequent cause of vision loss in adults with pathologic myopia. It develops as a wound healing mechanism consequent to Bruch's membrane ruptures and represents the most vision-threatening event in pathologic myopia.

In patients treated with Eylea in the MYRROR study (one injection given at start of therapy, with additional injections given in case of disease persistence or recurrence), retinal thickness assessed by OCT decreased soon after treatment initiation and the mean CNV lesion size was reduced. The mean change in CRT from baseline to week 24 was statistically significant favouring Eylea (-79 microns and -4 microns for the Eylea 2 mg treatment group and the control group, respectively). The decrease from baseline in retinal thickness in the Eylea 2 mg group was maintained through week 48.

Clinical efficacy and safety

wet AMD

The safety and efficacy of Eylea were assessed in two randomised, multi-centre, double-masked, active-controlled studies in patients with wet AMD. A total of 2,412 patients were treated and evaluable for efficacy (1,817 with Eylea) in the two studies (VIEW1 and VIEW2). In each study, patients were randomly assigned in a 1:1:1:1 ratio to 1 of 4 dosing regimens:

1) Eylea administered at 2 mg every 8 weeks following 3 initial monthly doses (Eylea 2Q8);
2) Eylea administered at 2 mg every 4 weeks (Eylea 2Q4);
3) Eylea administered at 0.5 mg every 4 weeks (Eylea 0.5Q4); and
4) ranibizumab administered at 0.5 mg every 4 weeks (ranibizumab 0.5Q4).

Patient ages ranged from 49 to 99 years with a mean of 76 years.

In the second year of the studies, patients continued to receive the dosage strength to which they were initially randomised but on a modified dosing schedule guided by assessment of visual and anatomic outcomes with a protocol-defined maximum dosing interval of 12 weeks.

In both studies, the primary efficacy endpoint was the proportion of patients in the Per Protocol Set who maintained vision, defined as losing fewer than 15 letters of visual acuity at week 52 compared to baseline.

In the VIEW1 study, at week 52, 95.1% of patients in the Eylea 2Q8 treatment group maintained vision compared to 94.4% patients in the ranibizumab 0.5Q4 group. Eylea treatment was shown to be non-inferior and clinically equivalent to the ranibizumab 0.5Q4 group.

PGR2026-00039
Biocon Ex.1065
Page 507 of 595

In the VIEW2 study, at week 52, 95.6% of patients in the Eylea 2Q8 treatment group maintained vision compared to 94.4% patients in the ranibizumab 0.5Q4 group. Eylea treatment was shown to be non-inferior and clinically equivalent to the ranibizumab 0.5Q4 group.

Detailed results from the combined analysis of both studies are shown in the Table 2 and Figure 1 below.

Table 2: Efficacy outcomes at week 52 (primary analysis) and week 96; combined data from the VIEW1 and VIEW2 studies[B)]

Efficacy Outcome	**Eylea 2Q8** [E)] (Eylea 2 mg every 8 weeks following 3 initial monthly doses) **(N = 607)**		**Ranibizumab 0.5Q4** (ranibizumab 0.5 mg every 4 weeks) **(N = 595)**	
	Week 52	Week 96[G)]	Week 52	Week 96[G)]
Mean number of injections from baseline	7.6	11.2	12.3	16.5
Mean number of injections during second year (Week 52 to 96)		4.2		4.7
Proportion of patients with maintained visual acuity (< 15 letters of BCVA[A)] loss) (Per Protocol Set)	95.33%[B)]	92.42%	94.42% [B)]	91.60%
Difference[C)] (95% CI)[D)]	0.9% (-1.7, 3.5)[F)]	0.8% (-2.3, 3.8)[F)]		
Mean change in BCVA as measured by ETDRS[A)] letter score from baseline	8.40	7.62	8.74	7.89
Difference in LS [A)] mean change (ETDRS letters)[C)] (95% CI)[D)]	-0.32 (-1.87, 1.23)	-0.25 (-1.98, 1.49)		
Proportion of patients who gained at least 15 letters of vision from baseline	30.97%	33.44%	32.44%	31.60%
Difference[C)] (95% CI)[D)]	-1.5% (-6.8, 3.8)	1.8% (-3.5, 7.1)		

[A)] BCVA: Best Corrected Visual Acuity
ETDRS: Early Treatment Diabetic Retinopathy Study
LS: Least square means derived from ANCOVA

[B)] Full Analysis Set (FAS), Last Observation Carried Forward (LOCF) for all analyses except proportion of patients with maintained visual acuity at week 52 which is Per Protocol Set (PPS)

[C)] The difference is the value of the Eylea group minus the value of the ranibizumab group. A positive value favours Eylea.

[D)] Confidence interval (CI) calculated by normal approximation

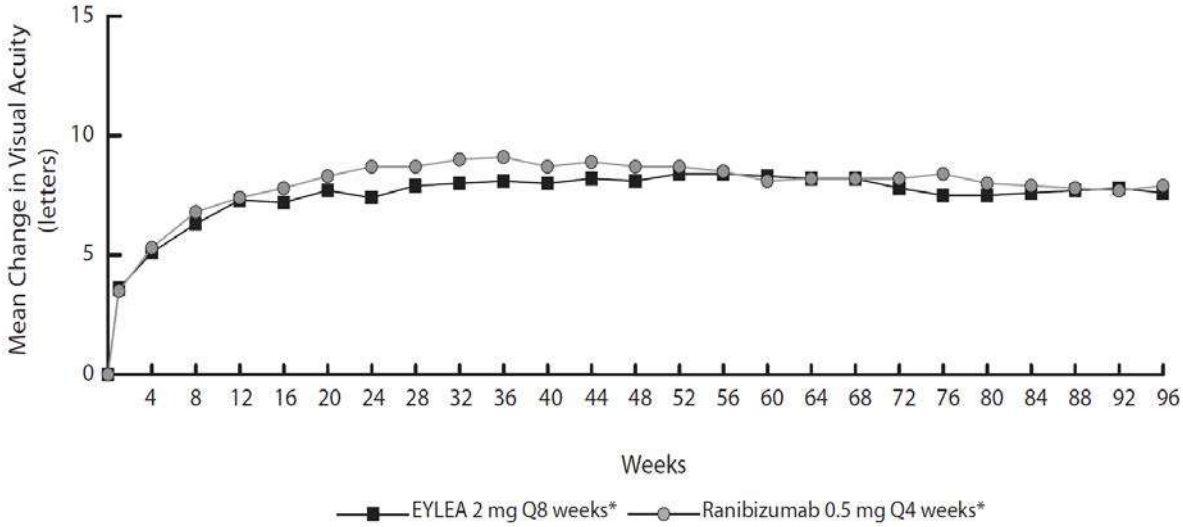
[E)] After treatment initiation with three monthly doses

[F)] A confidence interval lying entirely above -10% indicates a non-inferiority of Eylea to ranibizumab

[G)] Beginning at week 52, all groups were treated using a modified quarterly treatment paradigm where patients could be dosed as frequently as every 4 weeks but not less frequently than every 12 weeks based upon pre-specified retreatment criteria

PGR2026-00039
Biocon Ex.1065
Page 508 of 595

Figure 1. Mean Change in Visual Acuity
from Baseline to Week 96 for the Combined
Data from the View1 and View2 Studies



*) From Baseline to Week 52, Eylea was dosed every 8 weeks following 3 initial monthly doses. From Baseline to Week 52, ranibizumab 0.5 mg was dosed every 4 weeks. Beginning at Week 52, all groups were treated using a modified quarterly treatment paradigm where patients could be dosed as frequently as every 4 weeks but not less frequently than every 12 weeks based upon pre-specified retreatment criteria.

The proportion of patients at week 96 gaining at least 15 letters from baseline was 33.44% in the Eylea 2Q8 group, and 31.60% in the ranibizumab 0.5Q4 group.

In combined data analysis of the VIEW1 and VIEW2 studies, Eylea demonstrated clinically meaningful changes from baseline in pre-specified secondary efficacy endpoint National Eye Institute Visual Function Questionnaire (NEI VFQ-25). The magnitude of these changes was similar to that seen in published studies, which corresponded to a 15-letter gain in Best Corrected Visual Acuity (BCVA).

No clinically meaningful differences were found between Eylea and the reference product ranibizumab in changes of NEI VFQ-25 total score and subscales (near activities, distance activities, and vision-specific dependency) at week 52 from baseline.

Decreases in mean CNV area were evident in all dose groups in both studies.

Efficacy results in all evaluable subgroups (e.g. age, gender, race, baseline visual acuity, lesion type, lesion size) in each study and in the combined analysis were consistent with the results in the overall populations.

In the second year of the studies, efficacy was generally maintained through the last assessment at week 96.

In the second year of the studies, 2-4% of patients required all injections on a monthly basis, and a third of patients required at least one injection with a treatment interval of only one month.

Elderly Population

In the clinical studies, approximately 89% (1,616/1,817) of the patients randomised to treatment with Eylea were 65 years of age or older and approximately 63% (1,139/1,817) were 75 years of age or older.

PGR2026-00039
Biocon Ex.1065
Page 509 of 595

Macular oedema secondary to CRVO

The safety and efficacy of Eylea were assessed in two randomised, multi-centre, double-masked, sham-controlled studies in patients with macular oedema secondary to CRVO. A total of 358 patients were treated and evaluable for efficacy (217 with Eylea) in the two studies COPERNICUS and GALILEO. In both studies, patients were randomly assigned in a 3:2 ratio to either 2 mg Eylea administered every 4 weeks (2Q4) or the control group receiving sham injections every 4 weeks for a total of 6 injections.

After 6 monthly injections, patients received treatment only if they met pre-specified retreatment criteria, except for patients in the control group in the GALILEO study who continued to receive sham (control to control) until week 52. Starting from this timepoint all patients were offered treatment if they met pre-specified criteria.

Patient ages ranged from 22 to 89 years with a mean of 64 years.

In both studies, the primary efficacy endpoint was the proportion of patients who gained at least 15 letters in BCVA at week 24 compared to baseline.

Change in visual acuity at week 24 compared to baseline was a secondary efficacy variable in both COPERNICUS and GALILEO studies.

The difference between treatment groups was statistically significant in favour of Eylea in both studies. In both pivotal studies the maximal improvement in visual acuity has been achieved at month 3 with subsequent stabilisation of the effect on visual acuity and central retinal thickness until month 6. The statistically significant difference was maintained through week 52.

Detailed results from the analysis of both studies are shown in the Table 3 and Figure 2 below.

PGR2026-00039
Biocon Ex.1065
Page 510 of 595

Table 3: Efficacy outcomes at week 24, week 52 and week 76/100 (Full Analysis Set with LOCF[C)]) in COPERNICUS and GALILEO studies

Efficacy Outcomes	**COPERNICUS**						**GALILEO**					
	24 Weeks		**52 Weeks**		**100 Weeks**		**24 Weeks**		**52 Weeks**		**76 Weeks**	
	Eylea 2 mg Q4 (N = 114)	**Control (N= 73)**	**Eylea 2 mg (N = 114)**	**Control[E)] (N =73)**	**Eylea[F)] 2 mg (N= 114)**	**Control[E,F)] (N=73)**	**Eylea 2 mg Q4 (N = 103)**	**Control (N = 68)**	**Eylea 2 mg (N = 103)**	**Control (N = 68)**	**Eylea[G)] 2 mg (N = 103)**	**Control[G)] (N = 68)**
Proportion of patients who gained at least 15 letters in BCVA[C)] from baseline	56%	12%	55%	30%	49.1%	23.3%	60%	22%	60%	32%	57.3%	29.4%
Weighted difference[A,B,E)] (95% CI)	44.8% (33.0, 56.6)		25.9% (11.8, 40.1)		26.7% (13.1, 40.3)		38.3% (24.4, 52.1)		27.9% (13.0, 42.7)		28.0% (13.3, 42.6)	
p-value	p < 0.0001		p = 0.0006		p=0.0003		p < 0.0001		p = 0.0004		p=0.0004	
Mean change in BCVA as measured by ETDRS[C)] letter score from baseline (SD)	17.3 (12.8)	-4.0 (18.0)	16.2 (17.4)	3.8 (17.1)	13.0 (17.7)	1.5 (17.7)	18.0 (12.2)	3.3 (14.1)	16.9 (14.8)	3.8 (18.1)	13.7 (17.8)	6.2 (17.7)
Difference in LS mean[A,C,D,E)] (95% CI)	21.7 (17.4, 26.0)		12.7 (7.7, 17.7)		11.8 (6.7, 17.0)		14.7 (10.8, 18.7)		13.2 (8.2, 18.2)		7.6 (2.1, 13.1)	
p-value	p < 0.0001		p < 0.0001		p < 0.0001		p < 0.0001		p < 0.0001		p=0.0070	

A) Difference is Eylea 2 mg Q4 weeks minus control

B) Difference and confidence interval (CI) are calculated using Cochran-Mantel-Haenszel (CMH) test adjusted for region (America vs. rest of the world for COPERNICUS and Europe vs. Asia/Pacific for GALILEO) and baseline BCVA category (> 20/200 and ≤ 20/200)

C) BCVA: Best Corrected Visual Acuity
ETDRS: Early Treatment Diabetic Retinopathy Study
LOCF: Last Observation Carried Forward
SD: Standard deviation
LS: Least square means derived from ANCOVA

D) LS mean difference and confidence interval based on an ANCOVA model with factors treatment group, region (America vs. rest of the world for COPERNICUS and Europe vs. Asia/Pacific for GALILEO) and baseline BCVA category (> 20/200 and ≤ 20/200)

E) In COPERNICUS study, control group patients could receive Eylea on an as-needed basis as frequently as every 4 weeks during week 24 to week 52; patients had visits every 4 weeks.

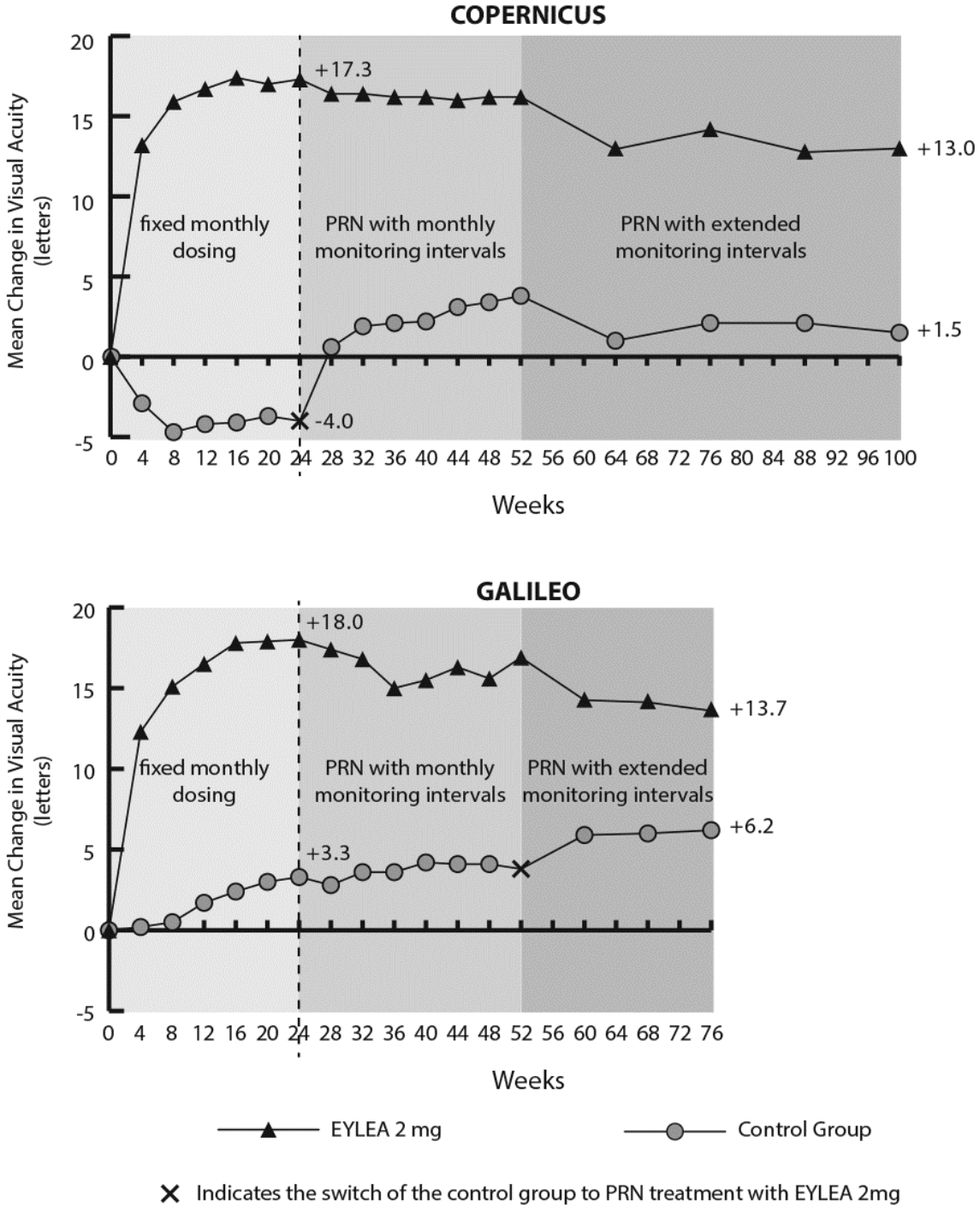
F) In COPERNICUS study, both control group and Eylea 2mg patients received Eylea 2 mg on an as-needed basis as frequently as every 4 weeks starting from Week 52 to Week 96; patients had mandatory quarterly visits but may have been seen as frequently as every 4 weeks if necessary.

PGR2026-00039
Biocon Ex.1065
Page 511 of 595

[G)] In GALILEO study, both control group and Eylea 2mg patients received Eylea 2 mg on an as-needed basis every 8 weeks starting from Week 52 to Week 68; patients had mandatory visits every 8 weeks.

PGR2026-00039
Biocon Ex.1065
Page 512 of 595

Figure 2: Mean Change from Baseline to Week 76/100 in Visual Acuity by Treatment Group for the COPERNICUS and GALILEO Studies (Full Analysis Set)



The proportion of perfused patients in the Eylea group was high in the GALILEO study at baseline 86.4%; (n = 89). Perfusion at week 24 primary endpoint was 91.8% (n = 89). The patients were largely able to maintain their perfusion status until week 76, 84.3% (n = 75). The number of perfused patients that started on sham was 79.4% (n = 54) at baseline. Perfusion at week 24 primary endpoint was 85.5% (n = 47). Patients in the sham group were switched to Eylea according to pre-specified criteria at week 52, 83.7% (n = 41) were perfused at this time. The patients were able to maintain their perfusion status until week 76, 84.0% (n = 42).

PGR2026-00039
Biocon Ex.1065
Page 513 of 595

The proportion of perfused patients in the Eylea group in the COPERNICUS study at baseline was 67.5% (n = 77). Perfusion at week 24 primary endpoint was 87.4% (n = 90). After week 24, patients in the Eylea group were treated according to pre-specified criteria. At week 100, 76.8 % (n = 76) of patients were perfused. The percentage of perfused patients that started on sham was 68.5% (n = 50) at baseline. Perfusion at week 24 primary endpoint was 58.6% (n = 34). Patients in the sham arm were eligible to receive Eylea from week 24. The proportion of perfused patients increased to 83.9% (n = 47) at week 52 and was largely maintained until week 100, 78% (n = 39).

The beneficial effect of Eylea treatment on visual function was similar in the baseline subgroups of perfused and non-perfused patients.

In combined data analysis of the GALILEO and COPERNICUS studies, Eylea demonstrated clinically meaningful changes from baseline in pre-specified secondary efficacy endpoint National Eye Institute Visual Function Questionnaire (NEI VFQ-25). The magnitude of these changes was similar to that seen in published studies, which corresponded to a 15-letter gain in Best Corrected Visual Acuity (BCVA).

Treatment effects in all evaluable subgroups (e.g. age, gender, race, baseline visual acuity, retinal perfusion status, CRVO duration) in each study were in general consistent with the results in the overall populations.

Elderly population

In the CRVO studies, approximately 52% (112/217) of the patients randomised to treatment with Eylea were 65 years of age or older, and approximately 18% (38/217) were 75 years of age or older.

Macular oedema secondary to BRVO

The safety and efficacy of Eylea were assessed in a randomised, multi-centre, double-masked, active-controlled study in patients with macular oedema secondary to BRVO which included Hemi-Retinal Vein Occlusion. A total of 181 patients were treated and evaluable for efficacy (91 with Eylea) in the VIBRANT study. In the study, patients were randomly assigned in a 1:1 ratio to either 2 mg Eylea administered every 8 weeks following 6 initial monthly injections' or laser photocoagulation administered at baseline (laser control group). Patients in the laser control group could receive additional laser photocoagulation (called 'rescue laser treatment') beginning at week 12, if needed. The minimum interval between laser photocoagulation treatments was 12 weeks. Beginning at week 24, patients in the laser treatment group could receive rescue treatment with Eylea 2mg, if needed, administered every 4 weeks for 3 months followed by intravitreal injections every 8 weeks, based on pre-specified criteria.

Patient ages ranged from 42 to 94 years with a mean of 65 years.

In the VIBRANT study, the primary efficacy endpoint was the proportion of patients who gained at least 15 letters in BCVA at week 24 compared to baseline. At week 24, the Eylea group was superior to laser control for the primary endpoint.

Change in visual acuity at week 24 compared to baseline was a secondary efficacy variable in the VIBRANT study. The difference between treatment groups was statistically significant in favour of Eylea. The course of visual improvement was rapid and maximal improvement was achieved at month 3 with subsequent stabilisation of the effect on visual acuity and central retinal thickness until month 6 and subsequent maintenance of the effect until month 12.

In the laser group 67 patients received rescue treatment with Eylea beginning at week 24 (Active Control/ Eylea 2mg group). In this treatment group visual acuity improved by about 5 letters from week 24 to 52.

PGR2026-00039
Biocon Ex.1065
Page 514 of 595

Detailed results from the analysis of the VIBRANT study are shown in the Table 4 and Figure 3 below.

Table 4: Efficacy outcomes at week 24 and week 52 (Full Analysis Set with LOCF) in VIBRANT study

Efficacy Outcomes	**VIBRANT**			
	24 weeks		**52 weeks**	
	Eylea 2mg Q4 (N = 91)	**Active Control (laser) (N = 90)**	**Eylea 2mg Q8 (N = 91) [D]**	**Active Control (laser)/Eylea 2mg[E] (N = 90)**
Proportion of patients who gained at least 15 letters in BCVA from Baseline (%)	52.7%	26.7%	57.1%	41.1%
Weighted Difference [A,B] (%) (95% CI) p-value	26.6% (13.0, 40.1) p=0.0003		16.2% (2.0, 30.5) p=0.0296	
Mean change in BCVA as measured by ETDRS letter score from Baseline (SD)	17.0 (11.9)	6.9 (12.9)	17.1 (13.1)	12.2 (11.9)
Difference in LS mean [A,C] (95% CI) p-value	10.5 (7.1, 14.0) p<0.0001		5.2 (1.7, 8.7) p=0.0035[F]	

A) Difference is Eylea 2 mg Q4 weeks minus Laser Control

B) Difference and 95% CI are calculated using Mantel-Haenszel weighting scheme adjusted for region (North America vs. Japan) and baseline BCVA category (> 20/200 and ≤ 20/200)

C) LS mean difference and 95% CI based on an ANCOVA model with treatment group, baseline BCVA category (> 20/200 and ≤ 20/200) and region (North America vs. Japan) as fixed effects, and baseline BCVA as covariate.

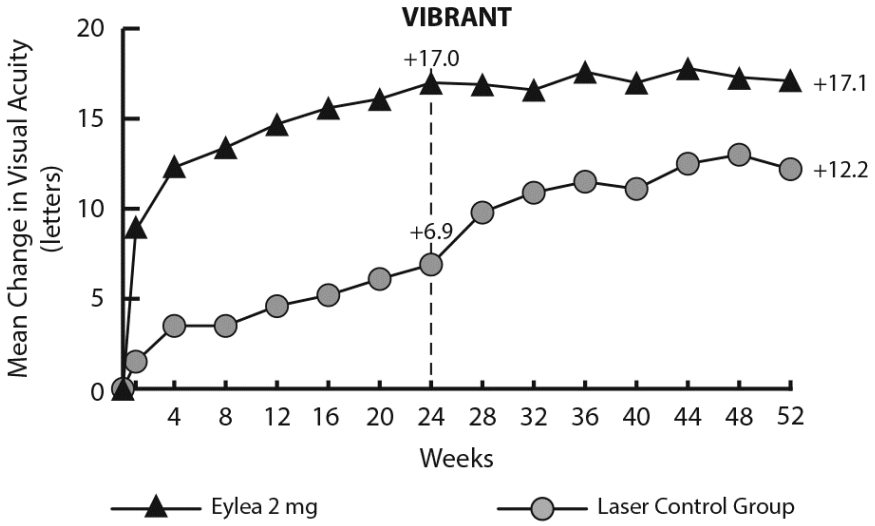
D) From Week 24 on the treatment interval in the Eylea treatment group was extended for all subjects from 4 weeks to 8 weeks through week 48.

E) Beginning at Week 24 subjects in the Laser Group could receive rescue treatment with Eylea, if they met at least one pre-specified eligibility criterion. At total of 67 subjects in this group received Eylea rescue treatment. The fixed regimen for Eylea rescue was three times Eylea 2mg every 4 weeks followed by injections every 8 weeks.

F) Nominal p-value

PGR2026-00039
Biocon Ex.1065
Page 515 of 595

Figure 3: Mean Change in BCVA as Measured by ETDRS Letter Score from Baseline to Week 52 in VIBRANT Study.



At baseline, the proportion of perfused patients in the Eylea and laser groups was 60% and 68%, respectively. At week 24 these proportions were 80% and 67%, respectively. In the Eylea group the proportion of perfused patients was maintained through week 52. In the laser group, where patients were eligible for rescue treatment with Eylea from week 24, the proportion of perfused patients increased to 78% by week 52.

Elderly population

In the BRVO study, approximately 58% (53/91) of the patients randomised to treatment with Eylea were 65 years of age or older, and approximately 23% (21/91) were 75 years of age or older.

Diabetic macular oedema

The safety and efficacy of Eylea were assessed in two randomised, multi-centre, double-masked, active-controlled studies in patients with DME. A total of 862 randomised and treated patients were evaluable for efficacy. Of those, 576 were randomised to the Eylea groups in two studies (VIVID^{DME} and VISTA^{DME}). In each study, patients were randomly assigned in a 1:1:1 ratio to 1 of 3 dosing regimens:
1) Eylea administered 2 mg every 8 weeks following 5 initial monthly injections (Eylea 2Q8);
2) Eylea administered 2 mg every 4 weeks (Eylea 2Q4); and
3) macular laser photocoagulation (active control).
Beginning at week 24, patients meeting a pre-specified threshold of vision loss were eligible to receive additional treatment: patients in the Eylea groups could receive laser and patients in the control group could receive Eylea.
Patient ages ranged from 23 to 87 years with a mean of 63 years.

The majority of patients in both studies had Type II diabetes.

PGR2026-00039
Biocon Ex.1065
Page 516 of 595

In both studies, the primary efficacy endpoint was the mean change from baseline in BCVA at Week 52 as measured by ETDRS letter score. Both Eylea 2Q8 and Eylea 2Q4 groups were shown to have efficacy that was statistically significantly superior to the control group. This benefit was maintained through week 100.

Detailed results from the analysis of the VIVID^{DME} and VISTA^{DME} studies are shown in Table 5 and Figure 4 below.

PGR2026-00039
Biocon Ex.1065
Page 517 of 595

Table 5: Efficacy outcomes at week 52 and week 100 (Full Analysis Set with LOCF) in VIVID[DME] and VISTA[DME] studies

Efficacy Outcomes	**VIVID[DME]**						**VISTA[DME]**					
	52 Weeks			**100 Weeks**			**52 Weeks**			**100 Weeks**		
	Eylea 2 mg Q8 [A] (N = 135)	**Eylea 2 mg Q4 (N = 136)**	**Active Control (laser) (N = 132)**	**Eylea 2 mg Q8 [A] (N = 135)**	**Eylea 2 mg Q4 (N = 136)**	**Active Control (laser) (N = 132)**	**Eylea 2 mg Q8 [A] (N = 151)**	**Eylea 2 mg Q4 (N = 154)**	**Active Control (laser) (N = 154)**	**Eylea 2 mg Q8 [A] (N = 151)**	**Eylea 2 mg Q4 (N = 154)**	**Active Control (laser) (N = 154)**
Mean change in BCVA as measured by ETDRS [E] letter score from Baseline	10.7	10.5	1.2	9.4	11.4	0.7	10.7	12.5	0.2	11.1	11.5	0.9
Difference in LS mean [B,C,E] (97.5% CI)	9.1 (6.3, 11.8)	9.3 (6.5, 12.0)		8.2 (5.2, 11.3)	10.7 (7.6, 13.8)		10.45 (7.7, 13.2)	12.19 (9.4, 15.0)		10.1 (7.0, 13.3)	10.6 (7.1, 14.2)	
Proportion of patients who gained at least 15 letters in BCVA [E] from Baseline	33%	32%	9%	31.1%	38.2%	12.1%	31%	42%	8%	33.1%	38.3%	13.0%
Adjusted Difference [D,C,E] (97.5% CI)	24% (13.5, 34.9)	23% (12.6, 33.9)		19.0% (8.0, 29.9)	26.1% (14.8, 37.5)		23% (13.5, 33.1)	34% (24.1, 44.4)		20.1% (9.6, 30.6)	25.8% (15.1, 36.6)	

[A] After treatment initiation with 5 monthly injections

PGR2026-00039
Biocon Ex.1065
Page 518 of 595

[B] LS mean and CI based on an ANCOVA model with baseline BCVA measurement as a covariate and a factor for treatment group. Additionally, region (Europe/Australia vs. Japan) had been included as factor for VIVID^{DME}, and history of MI and/or CVA as a factor for VISTA^{DME}.

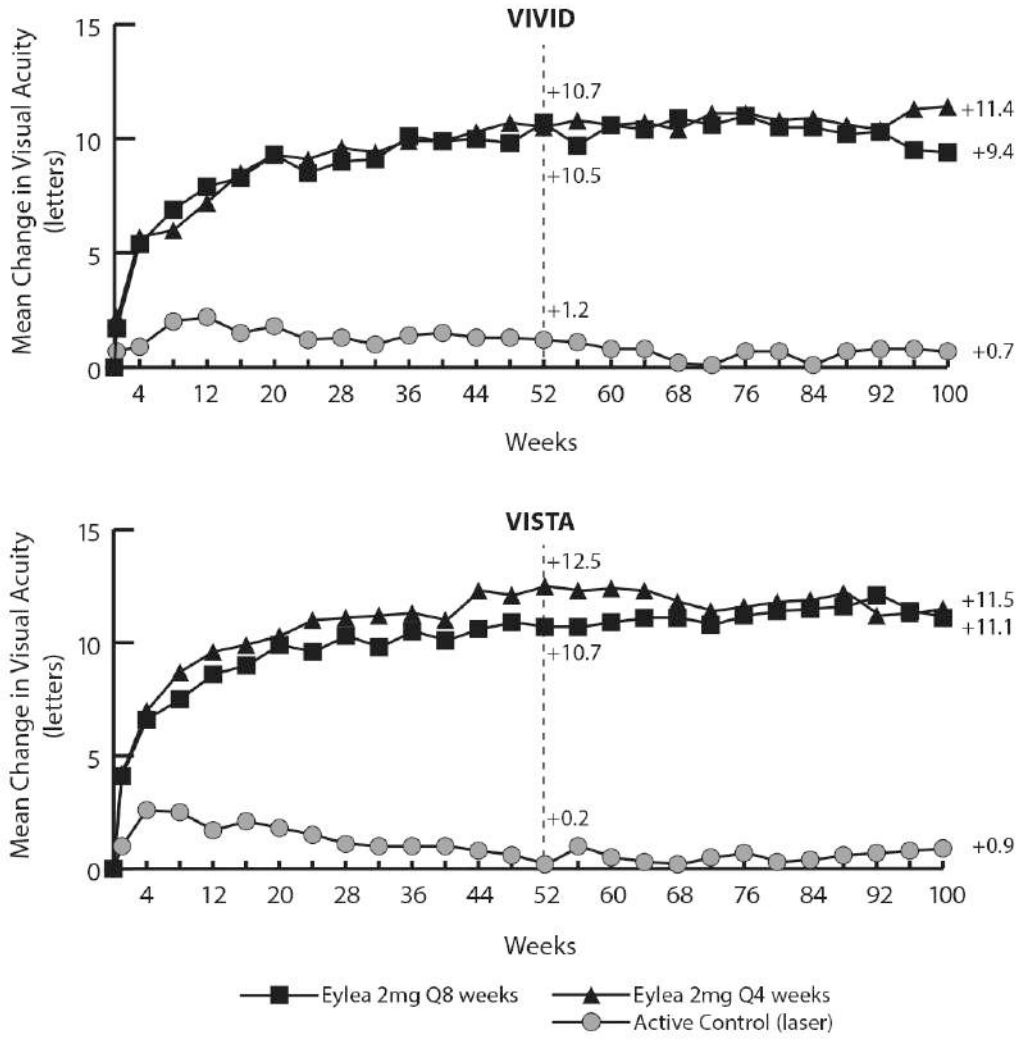
[C] Difference is Eylea group minus active control (laser) group

[D] Difference with confidence interval (CI) and statistical test is calculated using Mantel-Haenszel weighting scheme adjusted by region (Europe/Australia vs. Japan) for VIVID^{DME} and medical history of MI or CVA for VISTA^{DME}

[E] BCVA: Best Corrected Visual Acuity
ETDRS: Early Treatment Diabetic Retinopathy Study
LOCF: Last Observation Carried Forward
LS: Least square means derived from ANCOVA
CI: Confidence interval

PGR2026-00039
Biocon Ex.1065
Page 519 of 595

Figure 4: Mean change in BCVA as Measured by ETDRS Letter Score from Baseline to Week 100 in VIVID[DME] and VISTA[DME] Studies



PGR2026-00039
Biocon Ex.1065
Page 520 of 595

Treatment effects in evaluable subgroups (e.g., age, gender, race, baseline HbA1c, baseline visual acuity, prior anti-VEGF therapy) in each study and in the combined analysis were generally consistent with the results in the overall populations.

In the VIVID^{DME} and VISTA^{DME} studies, 36 (9%) and 197 (43%) patients received prior anti-VEGF therapy, respectively, with a 3-month or longer washout period. Treatment effects in the subgroup of patients who had previously been treated with a VEGF inhibitor prior to study participation were similar to those seen in patients who were VEGF inhibitor naïve prior to study participation.

Patients with bilateral disease were eligible to receive anti-VEGF treatment in their fellow eye if determined to be necessary by the physician. In the VISTA^{DME} study, 217 (70.7%) of Eylea patients received bilateral Eylea injections until week 100; in the VIVID^{DME} study, 97 (35.8%) of Eylea patients received a different anti-VEGF treatment in their fellow eye.

Elderly population

In the DME phase III studies, approximately 47% (268/576) of the patients randomised to treatment with Eylea were 65 years of age or older, and approximately 9% (52/576) were 75 years of age or older. Efficacy and safety outcomes were consistent with the outcomes of the overall population.

Myopic choroidal neovascularisation

The safety and efficacy of Eylea were assessed in a randomised, multi-centre, double-masked, sham-controlled study in treatment-naïve, Asian patients with myopic CNV. Patients were randomly assigned in a 3:1 ratio to receive either 2 mg Eylea intravitreally or sham injections administered once at study start with additional injections given monthly in case of disease persistence or recurrence until week 24, when the primary endpoint was assessed. At week 24, patients initially randomised to sham were eligible to receive the first dose of Eylea. Following this, patients in both groups continued to be eligible for additional injections in case of disease persistence or recurrence.

A total of 121 patients were treated and evaluable for efficacy (90 with Eylea). Their age ranged from 27 to 83 years with a mean of 58 years.

The difference between treatment groups was statistically significant in favour of Eylea for the primary endpoint (change in BCVA) and confirmatory secondary efficacy endpoint (proportion of patients who gained 15 letters in BCVA) at week 24 compared to baseline. Differences for both endpoints were maintained through week 48.

Detailed results from the analysis of the MYRROR study are shown in Table 6 and Figure 5 below.

PGR2026-00039
Biocon Ex.1065
Page 521 of 595

Table 6: Efficacy outcomes at week 24 (primary analysis) and week 48 in MYRROR study (Full Analysis Set with LOCF[A)])

Efficacy Outcomes	**MYRROR**			
	24 Weeks		**48 Weeks**	
	Eylea 2mg (N = 90)	**Sham (N = 31)**	**Eylea 2mg (N = 90)**	**Sham/ Eylea 2mg (N = 31)**
Mean change in BCVA letter score as measured by ETDRS from baseline (SD) [B)]	12.1 (8.3)	-2.0 (9.7)	13.5 (8.8)	3.9 (14.3)
Difference in LS mean [C,D,E)] (95% CI)	14.1 (10.8, 17.4)		9.5 (5.4, 13.7)	
Proportion of patients who gained at least 15 letters in BCVA[B)] from baseline	38.9%	9.7%	50.0%	29.0%
Weighted difference [D,F)] (95% CI)	29.2% (14.4, 44.0)		21.0% (1.9, 40.1)	

A) LOCF: Last Observation Carried Forward

B) BCVA: Best Corrected Visual Acuity
ETDRS: Early Treatment Diabetic Retinopathy Study
SD: Standard Deviation

C) LS mean: Least square means derived from ANCOVA model

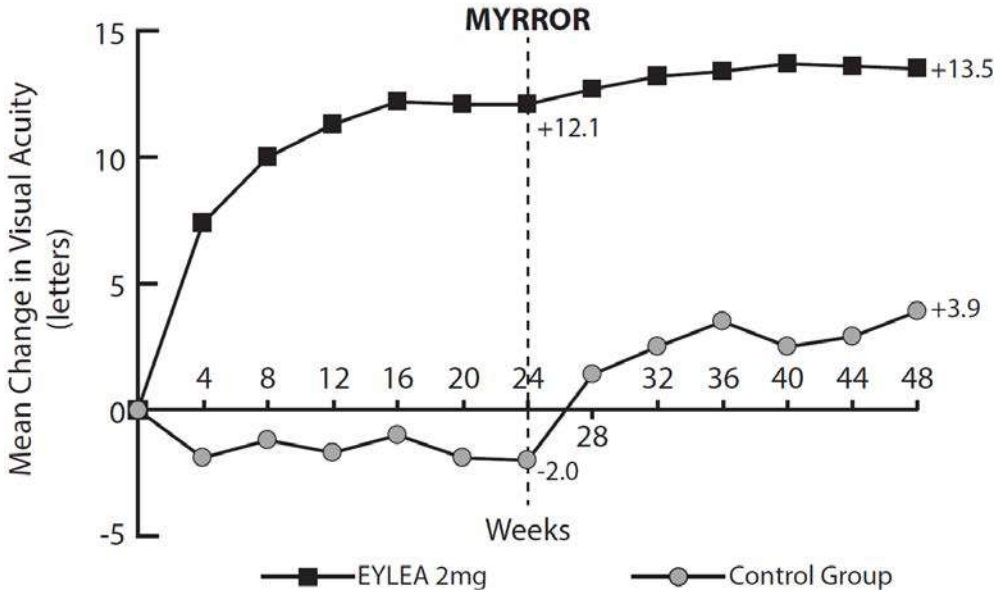
D) CI: Confidence Interval

E) LS mean difference and 95% CI based on an ANCOVA model with treatment group and country (country designations) as fixed effects, and baseline BCVA as covariant.

F) Difference and 95% CI are calculated using Cochran-Mantel-Haenszel (CMH) test adjusted for country (country designations)

PGR2026-00039
Biocon Ex.1065
Page 522 of 595

Figure 5: Mean Change from Baseline to Week 48 in Visual Acuity by Treatment Group for the MYRROR Study (Full Analysis Set, LOCF)



Elderly population

In the myopic CNV study, approximately 36% (33/91) of the patients randomised to treatment with Eylea were 65 years of age or older, and approximately 10% (9/91) were 75 years of age or older.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Eylea in all subsets of the paediatric population in wet AMD, CRVO, BRVO, DME and myopic CNV populations (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Eylea is administered directly into the vitreous to exert local effects in the eye.

Absorption / Distribution
Aflibercept is slowly absorbed from the eye into the systemic circulation after intravitreal administration and is predominately observed in the systemic circulation as an inactive, stable complex with VEGF; however only "free aflibercept" is able to bind endogenous VEGF.

In a pharmacokinetic sub-study in 6 neovascular wet AMD patients with frequent sampling, maximum plasma concentrations of free aflibercept (systemic C_{max}) were low, with a mean of approximately 0.02 microgram/ml (range 0 to 0.054) within 1 to 3 days after a 2 mg intravitreal injection, and were undetectable two weeks following dosage in almost all patients. Aflibercept does not accumulate in the plasma when administered intravitreally every 4 weeks.

The mean maximum plasma concentration of free aflibercept is approximately 50 to 500 times below the aflibercept concentration required to inhibit the biologic activity of systemic VEGF by 50% in animal models, in which blood pressure changes were observed after circulating levels of free aflibercept attained approximately 10 microgram/ml and returned to baseline when levels fell below

PGR2026-00039
Biocon Ex.1065
Page 523 of 595

approximately 1 microgram/ml. It is estimated that after intravitreal administration of 2 mg to patients, the mean maximum plasma concentration of free aflibercept is more than 100-fold lower than the concentration of aflibercept required to half-maximally bind systemic VEGF (2.91 microgram/ml) in a study of healthy volunteers. Therefore, systemic pharmacodynamic effects such as blood pressure changes are unlikely.

In pharmacokinetic sub-studies in patients with CRVO, BRVO, DME or myopic CNV mean C_{max} of free aflibercept in plasma were similar with values in the range of 0.03 to 0.05 microgram/ml and individual values not exceeding 0.14 microgram/ml. Thereafter, plasma concentrations of free aflibercept declined to values below or close to the lower limit of quantitation generally within one week; undetectable concentrations were reached before the next administration after 4 weeks in all patients.

Elimination
As Eylea is a protein-based therapeutic, no metabolism studies have been conducted.

Free aflibercept binds VEGF to form a stable, inert complex. As with other large proteins, both free and bound aflibercept are expected to be cleared by proteolytic catabolism.

Renal impairment
No special studies in patients with renal impairment have been conducted with Eylea.

Pharmacokinetic analysis of patients in the VIEW2 study, of which 40% had renal impairment (24% mild, 15% moderate, and 1% severe), revealed no differences with respect to plasma concentrations of active drug after intravitreal administration every 4 or 8 weeks.

Similar results were seen in patients with CRVO in the GALILEO study, in patients with DME in the VIVID^{DME} study, and in patients with myopic CNV in the MYRROR study.

5.3 Preclinical safety data

Effects in non-clinical studies on repeated dose toxicity were observed only at systemic exposures considered substantially in excess of the maximum human exposure after intravitreal administration at the intended clinical dose indicating little relevance to clinical use.

Erosions and ulcerations of the respiratory epithelium in nasal turbinates in monkeys treated with aflibercept intravitreally were observed at systemic exposures in excess of the maximum human exposure. The systemic exposure based on C_{max} and AUC for free aflibercept were approximately 200- and 700-fold higher, respectively, when compared to corresponding values observed in humans after an intravitreal dose of 2 mg. At the No Observed Adverse Effect Level (NOAEL) of 0.5 mg/eye in monkeys the systemic exposure was 42- and 56-fold higher based on C_{max} and AUC, respectively.

No studies have been conducted on the mutagenic or carcinogenic potential of aflibercept.

An effect of aflibercept on intrauterine development was shown in embryo-foetal development studies in pregnant rabbits with intravenous (3 to 60 mg/kg) as well as subcutaneous (0.1 to 1 mg/kg) administration. The maternal NOAEL was at the dose of 3 mg/kg or 1 mg/kg, respectively. A developmental NOAEL was not identified. At the 0.1 mg/kg dose, the systemic exposures based on C_{max} and cumulative AUC for free aflibercept were approximately 17- and 10-fold higher, respectively, when compared to corresponding values observed in humans after an intravitreal dose of 2 mg.

Effects on male and female fertility were assessed as part of a 6-month study in monkeys with intravenous administration of aflibercept at doses ranging from 3 to 30 mg/kg. Absent or irregular menses associated with alterations in female reproductive hormone levels and changes in sperm morphology and motility were observed at all dose levels. Based on C_{max} and AUC for free aflibercept

PGR2026-00039
Biocon Ex.1065
Page 524 of 595

observed at the 3 mg/kg intravenous dose, the systemic exposures were approximately 4,900-fold and 1,500-fold higher, respectively, than the exposure observed in humans after an intravitreal dose of 2 mg. All changes were reversible.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Polysorbate 20
Sodium dihydrogen phosphate, monohydrate (for pH adjustment)
Disodium hydrogen phosphate, heptahydrate (for pH adjustment)
Sodium chloride
Sucrose
Water for injection

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store in a refrigerator (2°C to 8°C).
Do not freeze.
Keep the pre-filled syringe in its blister and in the outer carton in order to protect from light.

Prior to usage, the unopened blister of Eylea may be kept at room temperature (below 25°C) for up to 24 hours. After opening the blister, proceed under aseptic conditions.

6.5 Nature and contents of container

90 microlitres of solution in pre-filled syringe (type I glass) marked with a black dosing line, with a plunger stopper (elastomeric rubber) and a Luer lock adaptor with a tip cap (elastomeric rubber). Pack size of 1.

6.6 Special precautions for disposal and other handling

The pre-filled syringe is for single use only.
Do not open the sterile pre-filled blister outside the clean administration room.

Since the pre-filled syringe contains more volume (90 microlitres) than the recommended dose (50 microlitres), a part of the volume contained in the syringe has to be discarded prior to the administration.

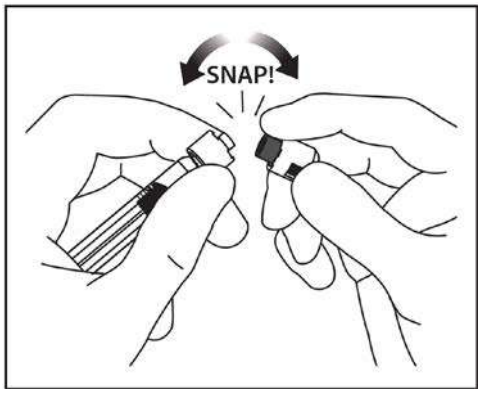
The solution should be inspected visually for any foreign particulate matter and/or discolouration or any variation in physical appearance prior to administration. In the event of either being observed, discard the medicinal product.

For the intravitreal injection, a 30 G x ½ inch injection needle should be used.

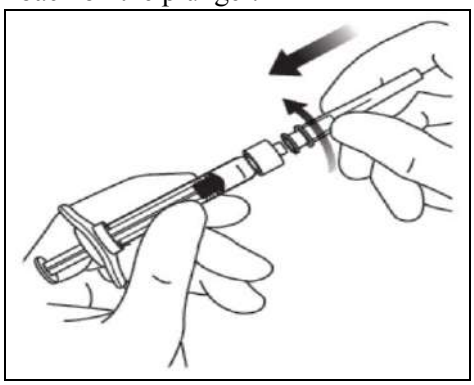
PGR2026-00039
Biocon Ex.1065
Page 525 of 595

Instructions for use of pre-filled syringe:

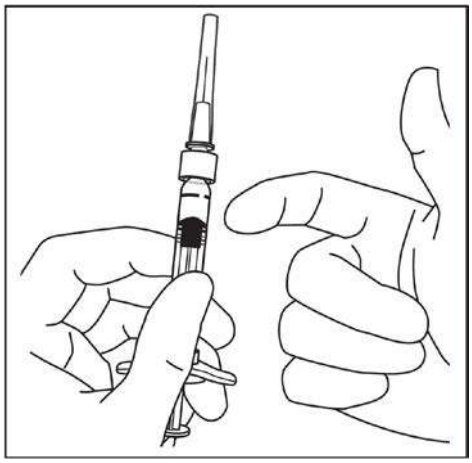
1. When ready to administer Eylea, open the carton and remove the sterilised blister. Carefully peel open the blister ensuring the sterility of its contents. Keep the syringe in the sterile tray until you are ready for assembly.
2. Using aseptic technique, remove the syringe from the sterilised blister.
3. To remove the syringe cap, hold the syringe in one hand while using the other hand to grasp the syringe cap with the thumb and fore finger. Please note: You should snap off (do not turn or twist) the syringe cap.



4. To avoid compromising the sterility of the product, do not pull back on the plunger.
5. Using aseptic technique, firmly twist the injection needle onto the Luer-lock syringe tip.

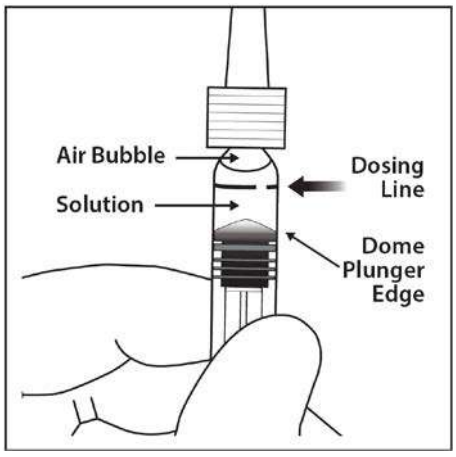


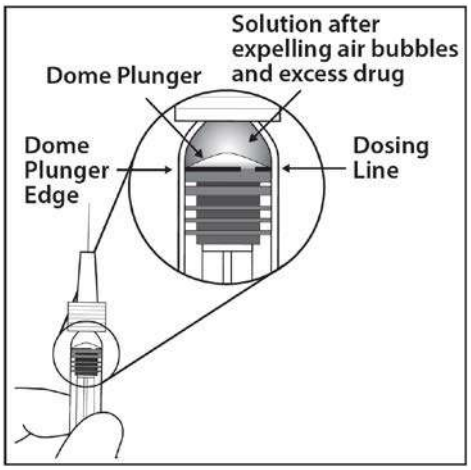
6. Holding the syringe with the needle pointing up, check the syringe for bubbles. If there are bubbles, gently tap the syringe with your finger until the bubbles rise to the top.



PGR2026-00039
Biocon Ex.1065
Page 526 of 595

7. To eliminate all bubbles and to expel excess medicinal product, slowly depress the plunger to align the cylindrical base of the dome plunger with the black dosing line on the syringe (equivalent to 50 microlitres).





8. The pre-filled syringe is for single use only.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Bayer Pharma AG
D-13342 Berlin
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/797/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22 November 2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

PGR2026-00039
Biocon Ex.1065
Page 527 of 595

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Eylea 40 mg/ml solution for injection in a vial.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml solution for injection contains 40 mg aflibercept*.

Each vial contains 100 microlitres, equivalent to 4 mg aflibercept. This provides a usable amount to deliver a single dose of 50 microlitres containing 2 mg aflibercept.

*Fusion protein consisting of portions of human VEGF (Vascular Endothelial Growth Factor) receptors 1 and 2 extracellular domains fused to the Fc portion of human IgG1 and produced in Chinese hamster ovary (CHO) K1 cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection)

The solution is a clear, colourless to pale yellow and iso-osmotic solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Eylea is indicated for adults for the treatment of

- neovascular (wet) age-related macular degeneration (AMD) (see section 5.1),
- visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO) (see section 5.1),
- visual impairment due to diabetic macular oedema (DME) (see section 5.1),
- visual impairment due to myopic choroidal neovascularisation (myopic CNV) (see section 5.1).

4.2 Posology and method of administration

Eylea is for intravitreal injection only.

Eylea must only be administered by a qualified physician experienced in administering intravitreal injections.

Posology

wet AMD

The recommended dose for Eylea is 2 mg aflibercept, equivalent to 50 microlitres.

PGR2026-00039
Biocon Ex.1065
Page 528 of 595

Eylea treatment is initiated with one injection per month for three consecutive doses, followed by one injection every two months. There is no requirement for monitoring between injections.

After the first 12 months of treatment with Eylea, the treatment interval may be extended based on visual and/or anatomic outcomes. In this case the schedule for monitoring should be determined by the treating physician and may be more frequent than the schedule of injections.

Macular oedema secondary to RVO (branch RVO or central RVO)

The recommended dose for Eylea is 2 mg aflibercept equivalent to 50 microlitres.
After the initial injection, treatment is given monthly. The interval between two doses should not be shorter than one month.

If visual and anatomic outcomes indicate that the patient is not benefiting from continued treatment, Eylea should be discontinued.

Monthly treatment continues until maximum visual acuity is achieved and/or there are no signs of disease activity. Three or more consecutive, monthly injections may be needed.

Treatment may then be continued with a treat and extend regimen with gradually increased treatment intervals to maintain stable visual and/or anatomic outcomes, however there are insufficient data to conclude on the length of these intervals. If visual and/or anatomic outcomes deteriorate, the treatment interval should be shortened accordingly.

The monitoring and treatment schedule should be determined by the treating physician based on the individual patient's response.

Monitoring for disease activity may include clinical examination, functional testing or imaging techniques (e.g. optical coherence tomography or fluorescein angiography).

Diabetic macular oedema

The recommended dose for Eylea is 2 mg aflibercept equivalent to 50 microlitres.

Eylea treatment is initiated with one injection per month for five consecutive doses, followed by one injection every two months. There is no requirement for monitoring between injections.

After the first 12 months of treatment with Eylea, the treatment interval may be extended based on visual and/or anatomic outcomes. The schedule for monitoring should be determined by the treating physician.

If visual and anatomic outcomes indicate that the patient is not benefiting from continued treatment, Eylea should be discontinued.

Myopic choroidal neovascularisation

The recommended dose for Eylea is a single intravitreal injection of 2 mg aflibercept equivalent to 50 microlitres.

Additional doses may be administered if visual and/or anatomic outcomes indicate that the disease persists. Recurrences should be treated as a new manifestation of the disease.

The schedule for monitoring should be determined by the treating physician.

The interval between two doses should not be shorter than one month.

PGR2026-00039
Biocon Ex.1065
Page 529 of 595

Special populations

Hepatic and/or renal impairment
No specific studies in patients with hepatic and/or renal impairment have been conducted with Eylea.

Available data do not suggest a need for a dose adjustment with Eylea in these patients (see section 5.2)

Elderly population
No special considerations are needed. There is limited experience in patients older than 75 years with DME.

Paediatric population
Safety and efficacy have not been established in children and adolescents. There is no relevant use of Eylea in the paediatric population in the indications wet AMD, CRVO, BRVO, DME and myopic CNV.

Method of administration

Intravitreal injections must be carried out according to medical standards and applicable guidelines by a qualified physician experienced in administering intravitreal injections. In general, adequate anaesthesia and asepsis, including topical broad spectrum microbicide (e.g. povidone iodine applied to the periocular skin, eyelid and ocular surface), have to be ensured. Surgical hand disinfection, sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent) are recommended.

The injection needle should be inserted 3.5-4.0 mm posterior to the limbus into the vitreous cavity, avoiding the horizontal meridian and aiming towards the centre of the globe. The injection volume of 0.05 ml is then delivered; a different scleral site should be used for subsequent injections.

Immediately following the intravitreal injection, patients should be monitored for elevation in intraocular pressure. Appropriate monitoring may consist of a check for perfusion of the optic nerve head or tonometry. If required, sterile equipment for paracentesis should be available.

Following intravitreal injection patients should be instructed to report any symptoms suggestive of endophthalmitis (e.g. eye pain, redness of the eye, photophobia, blurring of vision) without delay.

Each vial should only be used for the treatment of a single eye.

The vial contains more than the recommended dose of 2 mg aflibercept. The extractable volume of the vial (100 microlitres) is not to be used in total. The excess volume should be expelled before injecting. Injecting the entire volume of the vial could result in overdose. To expel the air bubble along with excess medicinal product, slowly depress the plunger to align the cylindrical base of the dome plunger with the black dosing line on the syringe (equivalent to 50 microlitres i.e. 2 mg aflibercept).

After injection any unused product must be discarded.

For handling of the medicinal product, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance aflibercept or to any of the excipients listed in section 6.1.
Active or suspected ocular or periocular infection.
Active severe intraocular inflammation.

PGR2026-00039
Biocon Ex.1065
Page 530 of 595

4.4 Special warnings and precautions for use

Intravitreal injection-related reactions
Intravitreal injections, including those with Eylea, have been associated with endophthalmitis, intraocular inflammation, rhegmatogenous retinal detachment, retinal tear and iatrogenic traumatic cataract (see section 4.8). Proper aseptic injection techniques must always be used when administering Eylea. In addition, patients should be monitored during the week following the injection to permit early treatment if an infection occurs. Patients should be instructed to report any symptoms suggestive of endophthalmitis or any of the above mentioned events without delay.

Increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including those with Eylea (see section 4.8). Special precaution is needed in patients with poorly controlled glaucoma (do not inject Eylea while the intraocular pressure is ≥ 30 mmHg). In all cases, both the intraocular pressure and the perfusion of the optic nerve head must therefore be monitored and managed appropriately.

Immunogenicity
As this is a therapeutic protein, there is a potential for immunogenicity with Eylea (see section 4.8). Patients should be instructed to report any signs or symptoms of intraocular inflammation, e.g. pain, photophobia, or redness, which may be a clinical sign attributable to hypersensitivity.

Systemic effects
Systemic adverse events including non-ocular haemorrhages and arterial thromboembolic events have been reported following intravitreal injection of VEGF inhibitors and there is a theoretical risk that these may relate to VEGF inhibition. There are limited data on safety in the treatment of patients with CRVO, BRVO, DME or myopic CNV with a history of stroke or transient ischaemic attacks or myocardial infarction within the last 6 months. Caution should be exercised when treating such patients.

Other
As with other intravitreal anti-VEGF treatments for AMD, CRVO, BRVO, DME and myopic CNV the following also applies:

- The safety and efficacy of Eylea therapy administered to both eyes concurrently have not been systematically studied (see section 5.1). If bilateral treatment is performed at the same time this could lead to an increased systemic exposure, which could increase the risk of systemic adverse events.
- Concomitant use of other anti-VEGF (vascular endothelial growth factor)
- There is no data available on the concomitant use of Eylea with other anti-VEGF medicinal products (systemic or ocular).
- Risk factors associated with the development of a retinal pigment epithelial tear after anti-VEGF therapy for wet AMD, include a large and/or high pigment epithelial retinal detachment. When initiating Eylea therapy, caution should be used in patients with these risk factors for retinal pigment epithelial tears.
- Treatment should be withheld in patients with rhegmatogenous retinal detachment or stage 3 or 4 macular holes.
- In the event of a retinal break the dose should be withheld and treatment should not be resumed until the break is adequately repaired**.**
- The dose should be withheld and treatment should not be resumed earlier than the next scheduled treatment in the event of:
    - a decrease in best-corrected visual acuity (BCVA) of ≥30 letters compared with the last assessment of visual acuity;
    - a subretinal haemorrhage involving the centre of the fovea, or, if the size of the haemorrhage is ≥50%, of the total lesion area.

PGR2026-00039
Biocon Ex.1065
Page 531 of 595

- The dose should be withheld within the previous or next 28 days in the event of a performed or planned intraocular surgery.
- Eylea should not be used in pregnancy unless the potential benefit outweighs the potential risk to the foetus (see section 4.6).
- Women of childbearing potential have to use effective contraception during treatment and for at least 3 months after the last intravitreal injection of aflibercept (see section 4.6).
- There is limited experience with treatment of patients with ischaemic CRVO and BRVO. In patients presenting with clinical signs of irreversible ischaemic visual function loss, the treatment is not recommended.

Populations with limited data
There is only limited experience in the treatment of subjects with DME due to type I diabetes or in diabetic patients with an HbA1c over 12% or with proliferative diabetic retinopathy.
Eylea has not been studied in patients with active systemic infections or in patients with concurrent eye conditions such as retinal detachment or macular hole. There is also no experience of treatment with Eylea in diabetic patients with uncontrolled hypertension. This lack of information should be considered by the physician when treating such patients.

In myopic CNV there is no experience with Eylea in the treatment of non-Asian patients, patients who have previously undergone treatment for myopic CNV, and patients with extrafoveal lesions.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Adjunctive use of verteporfin photodynamic therapy (PDT) and Eylea has not been studied, therefore, a safety profile is not established.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
Women of childbearing potential have to use effective contraception during treatment and for at least 3 months after the last intravitreal injection of aflibercept (see section 4.4).

Pregnancy
There are no data on the use of aflibercept in pregnant women.
Studies in animals have shown embryo-foetal toxicity (see section 5.3).

Although the systemic exposure after ocular administration is very low, Eylea should not be used during pregnancy unless the potential benefit outweighs the potential risk to the foetus.

Breastfeeding
It is unknown whether aflibercept is excreted in human milk. A risk to the breast-fed child cannot be excluded.

Eylea is not recommended during breastfeeding. A decision must be made whether to discontinue breastfeeding or to abstain from Eylea therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Fertility
Results from animal studies with high systemic exposure indicate that aflibercept can impair male and female fertility (see section 5.3). Such effects are not expected after ocular administration with very low systemic exposure.

PGR2026-00039
Biocon Ex.1065
Page 532 of 595

4.7 Effects on ability to drive and use machines

Injection with Eylea has a minor influence on the ability to drive and use machines due to possible temporary visual disturbances associated either with the injection or the eye examination. Patients should not drive or use machines until their visual function has recovered sufficiently.

4.8 Undesirable effects

Summary of the safety profile

A total of 3,102 patients constituted the safety population in the eight phase III studies. Among those, 2,501 patients were treated with the recommended dose of 2 mg.

Serious ocular adverse reactions in the study eye related to the injection procedure have occurred in less than 1 in 1,900 intravitreal injections with Eylea and included blindness, endophthalmitis, retinal detachment, cataract traumatic, cataract, vitreous haemorrhage, vitreous detachment, and intraocular pressure increased (see section 4.4).

The most frequently observed adverse reactions (in at least 5% of patients treated with Eylea) were conjunctival haemorrhage (25%), visual acuity reduced (11%), eye pain (10%), cataract (8%), intraocular pressure increased (8%), vitreous detachment (7%), and vitreous floaters (7%).

Tabulated list of adverse reactions

The safety data described below include all adverse reactions from the eight phase III studies in the indications wet AMD, CRVO, BRVO, DME and myopic CNV with a reasonable possibility of causality to the injection procedure or medicinal product.

The adverse reactions are listed by system organ class and frequency using the following convention:

Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥ 1/10,000 to < 1/1,000)

Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness.

PGR2026-00039
Biocon Ex.1065
Page 533 of 595

Table 1: All treatment-emergent adverse drug reactions reported in patients in phase III studies (pooled data of the phase III studies for the indications wet AMD, CRVO, BRVO, DME and myopic CNV)

System Organ Class	Very common	Common	Uncommon	Rare
Immune system disorders			Hypersensitivity***	
Eye disorders	Visual acuity reduced, Conjunctival haemorrhage, Eye pain	Retinal pigment epithelial tear*, Detachment of the retinal pigment epithelium, Retinal degeneration, Vitreous haemorrhage, Cataract, Cataract cortical Cataract nuclear, Cataract subcapsular, Corneal erosion, Corneal abrasion, Intraocular pressure increased, Vision blurred, Vitreous floaters, Vitreous detachment,Injection site pain, Foreign body sensation in eyes, Lacrimation increased, Eyelid oedema, Injection site haemorrhage, Punctate keratitis, Conjunctival hyperaemia, Ocular hyperaemia	Endophthalmitis**, Retinal detachment, Retinal tear, Iritis, Uveitis, Iridocyclitis,Lenticular opacities,Corneal epithelium defect, Injection site irritation, Abnormal sensation in eye, Eyelid irritation, Anterior chamber flare, Corneal oedema,	Blindness, Cataract traumatic, Vitritis, Hypopyon

* Conditions known to be associated with wet AMD. Observed in the wet AMD studies only.

** Culture positive and culture negative endophthalmitis

*** including allergic reactions

Description of selected adverse reactions

In the wet AMD phase III studies, there was an increased incidence of conjunctival haemorrhage in patients receiving anti-thrombotic agents. This increased incidence was comparable between patients treated with ranibizumab and Eylea.

Arterial thromboembolic events (ATEs) are adverse events potentially related to systemic VEGF inhibition. There is a theoretical risk of arterial thromboembolic events following intravitreal use of VEGF inhibitors.

ATEs, as defined by Antiplatelet Trialists' Collaboration (APTC) criteria, include nonfatal myocardial infarction, nonfatal stroke, or vascular death (including deaths of unknown cause).

PGR2026-00039
Biocon Ex.1065
Page 534 of 595

The incidence of ATEs in the phase III wet AMD studies during the 96 weeks study duration was 3.3% (60 out of 1,824) in the combined group of patients treated with Eylea compared to 3.2% (19 out of 595) in patients treated with ranibizumab (see section 5.1). The corresponding numbers in the DME studies during the first 100 weeks were 6.4% (37 out of 578) (Eylea) and 4.2% (12 out of 287) (control group) (see section 5.1).

The incidence of ATEs in the phase III CRVO studies during the 76/100 weeks study duration was 0.6% (2 out of 317) in patients treated with at least one dose of Eylea compared to 1.4% (2 out of 142) in the group of patients receiving only sham treatment (see section 5.1) whilst for the Phase III BRVO study during the 52 weeks study duration it was 0% (0 out of 91) in patients treated with Eylea compared with 2.2% (2 out of 92) in the control group (see section 5.1). One of these patients in the control group had received Eylea rescue treatment.

The incidence of ATEs in the myopic CNV study during the 48 weeks study duration was 1.1% (1 out of 91) (Eylea) compared to 0% (0 out of 31) (control group).

As with all therapeutic proteins, there is a potential for immunogenicity with Eylea.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

In clinical trials doses of up to 4 mg in monthly intervals have been used and isolated cases of overdoses with 8 mg occurred.

Overdosing with increased injection volume may increase intraocular pressure. Therefore, in case of overdose, intraocular pressure should be monitored and if deemed necessary by the treating physician, adequate treatment should be initiated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmologicals / Antineovascularisation agents
ATC code: S01LA05

Aflibercept is a recombinant fusion protein consisting of portions of human VEGF receptor 1 and 2 extracellular domains fused to the Fc portion of human IgG1.

Aflibercept is produced in Chinese hamster ovary (CHO) K1 cells by recombinant DNA technology.

Aflibercept acts as a soluble decoy receptor that binds VEGF-A and PlGF with higher affinity than their natural receptors, and thereby can inhibit the binding and activation of these cognate VEGF receptors.

Mechanism of action
Vascular endothelial growth factor-A (VEGF-A) and placental growth factor (PlGF) are members of the VEGF family of angiogenic factors that can act as potent mitogenic, chemotactic, and vascular permeability factors for endothelial cells. VEGF acts via two receptor tyrosine kinases; VEGFR-1 and VEGFR-2, present on the surface of endothelial cells. PlGF binds only to VEGFR-1, which is also

PGR2026-00039
Biocon Ex.1065
Page 535 of 595

present on the surface of leucocytes. Excessive activation of these receptors by VEGF-A can result in pathological neovascularisation and excessive vascular permeability. PlGF can synergize with VEGF-A in these processes, and is also known to promote leucocyte infiltration and vascular inflammation.

Pharmacodynamic effects

wet AMD

Wet AMD is characterised by pathological choroidal neovascularisation (CNV). Leakage of blood and fluid from CNV may cause retinal thickening or oedema and/or sub-/intra-retinal haemorrhage, resulting in loss of visual acuity.

In patients treated with Eylea (one injection per month for three consecutive months, followed by one injection every 2 months), retinal thickness decreased soon after treatment initiation, and the mean CNV lesion size was reduced, consistent with the results seen with ranibizumab 0.5 mg every month.

In the VIEW1 study there were mean decreases in retinal thickness on optical coherence tomography (OCT) (-130 and -129 microns at week 52 for the Eylea 2 mg every two months and ranibizumab 0.5 mg every month study groups, respectively). Also at the 52 week time point, in the VIEW2 study there were mean decreases in retinal thickness on OCT (-149 and -139 microns for the Eylea 2 mg every two months and ranibizumab 0.5 mg every month study groups, respectively). The reduction of CNV size and reduction in retinal thickness were generally maintained in the second year of the studies.

Macular oedema secondary to CRVO and BRVO

In CRVO and BRVO retinal ischaemia occurs and signals the release of VEGF which in turn destabilises the tight junctions and promotes endothelial cell proliferation. Up-regulation of VEGF is associated with the breakdown of the blood retina barrier and this increased vascular permeability results in retinal oedema, stimulation of endothelial cell growth and neovascularisation.

In patients treated with Eylea (one injection every month for six months) there was consistent, rapid and robust response in morphology (central retinal thickness [CRT] as assessed by OCT). Improvements in mean CRT were maintained through week 24.

In the COPERNICUS and GALILEO studies (CRVO) the mean decrease from baseline in CRT at week 24 was significantly greater in patients treated with Eylea 2 mg every month than in the control group (-457 microns vs. -145 microns in COPERNICUS, and -449 microns vs. -169 microns in GALILEO).

In the VIBRANT study (BRVO) the mean decrease from baseline in CRT at week 24 was significantly greater in patients treated with Eylea 2 mg every month than in the control group (-280 microns vs. -128 microns). This decrease from baseline was maintained to end of study, week 100 in COPERNICUS, week 76 in GALILEO, and week 52 in VIBRANT.

Diabetic macular oedema

Diabetic macular oedema is characterised by increased vasopermeability and damage to the retinal capillaries which may result in loss of visual acuity.

In patients treated with Eylea, the majority of whom were classified as having Type II diabetes, rapid and robust response in morphology (central retinal thickness [CRT]) as assessed by OCT was seen soon after treatment initiation. The mean change in CRT from baseline to week 52 was statistically significant favouring Eylea.

PGR2026-00039
Biocon Ex.1065
Page 536 of 595

In the VIVID-^{DME} and the VISTA-^{DME} studies the mean decreases in CRT at week 52 were -192.4 and -183.1 microns for the 2Q8 Eylea groups and -66.2 and -73.3 microns for the control groups, respectively. At week 100 the decrease was maintained with -195.8 and -191.1 microns for the 2Q8 Eylea groups and -85.7 and -83.9 microns for the control groups, in the VIVID-^{DME} and VISTA-^{DME} studies, respectively.

A ≥ 2 step improvement in DRSS was assessed in a pre-specified manner in VIVID-^{DME} and VISTA-^{DME}. The DRSS score was gradable in 73.7% of the patients in VIVID-^{DME} and 98.3% of the patients in VISTA-^{DME}. At week 52, 27.7% and 29.1% of the Eylea 2Q8 groups, and 7.5% and 14.3% of the control groups experienced a ≥2 step improvement in the DRSS. At week 100, the respective percentages were 32.6% and 37.1% of the Eylea 2Q8 groups and 8.2% and 15.6% of the control groups.

Myopic choroidal neovascularisation

Myopic choroidal neovascularisation (myopic CNV) is a frequent cause of vision loss in adults with pathologic myopia. It develops as a wound healing mechanism consequent to Bruch's membrane ruptures and represents the most vision-threatening event in pathologic myopia.

In patients treated with Eylea in the MYRROR study (one injection given at start of therapy, with additional injections given in case of disease persistence or recurrence), retinal thickness assessed by OCT decreased soon after treatment initiation and the mean CNV lesion size was reduced. The mean change in CRT from baseline to week 24 was statistically significant favouring Eylea (-79 microns and -4 microns for the Eylea 2 mg treatment group and the control group, respectively). The decrease from baseline in retinal thickness in the Eylea 2 mg group was maintained through week 48.

Clinical efficacy and safety

wet AMD

The safety and efficacy of Eylea were assessed in two randomised, multi-centre, double-masked, active-controlled studies in patients with wet AMD. A total of 2,412 patients were treated and evaluable for efficacy (1,817 with Eylea) in the two studies (VIEW1 and VIEW2). In each study, patients were randomly assigned in a 1:1:1:1 ratio to 1 of 4 dosing regimens:

1) Eylea administered at 2 mg every 8 weeks following 3 initial monthly doses (Eylea 2Q8);
2) Eylea administered at 2 mg every 4 weeks (Eylea 2Q4);
3) Eylea administered at 0.5 mg every 4 weeks (Eylea 0.5Q4); and
4) ranibizumab administered at 0.5 mg every 4 weeks (ranibizumab 0.5Q4).

Patient ages ranged from 49 to 99 years with a mean of 76 years.

In the second year of the studies, patients continued to receive the dosage strength to which they were initially randomised but on a modified dosing schedule guided by assessment of visual and anatomic outcomes with a protocol-defined maximum dosing interval of 12 weeks.

In both studies, the primary efficacy endpoint was the proportion of patients in the Per Protocol Set who maintained vision, defined as losing fewer than 15 letters of visual acuity at week 52 compared to baseline.

In the VIEW1 study, at week 52, 95.1% of patients in the Eylea 2Q8 treatment group maintained vision compared to 94.4% patients in the ranibizumab 0.5Q4 group. Eylea treatment was shown to be non-inferior and clinically equivalent to the ranibizumab 0.5Q4 group.

PGR2026-00039
Biocon Ex.1065
Page 537 of 595

In the VIEW2 study, at week 52, 95.6% of patients in the Eylea 2Q8 treatment group maintained vision compared to 94.4% patients in the ranibizumab 0.5Q4 group. Eylea treatment was shown to be non-inferior and clinically equivalent to the ranibizumab 0.5Q4 group.

Detailed results from the combined analysis of both studies are shown in the Table 2 and Figure 1 below.

Table 2: Efficacy outcomes at week 52 (primary analysis) and week 96; combined data from the VIEW1 and VIEW2 studies[B)]

Efficacy Outcome	**Eylea 2Q8** [E)] (Eylea 2 mg every 8 weeks following 3 initial monthly doses) **(**N = **607)**		**Ranibizumab 0.5Q4** (ranibizumab 0.5 mg every 4 weeks) **(**N = **595)**	
	Week 52	Week 96 [G)]	Week 52	Week 96 [G)]
Mean number of injections from baseline	7.6	11.2	12.3	16.5
Mean number of injections during second year (Week 52 to 96)		4.2		4.7
Proportion of patients with maintained visual acuity (< 15 letters of BCVA[A)] loss) (Per Protocol Set)	95.33%[B)]	92.42%	94.42% [B)]	91.60%
Difference[C)] (95% CI)[D)]	0.9% (-1.7, 3.5)[F)]	0.8% (-2.3, 3.8)[F)]		
Mean change in BCVA as measured by ETDRS[A)] letter score from baseline	8.40	7.62	8.74	7.89
Difference in LS [A)] mean change (ETDRS letters)[C)] (95% CI)[D)]	-0.32 (-1.87, 1.23)	-0.25 (-1.98, 1.49)		
Proportion of patients who gained at least 15 letters of vision from baseline	30.97%	33.44%	32.44%	31.60%
Difference[C)] (95% CI)[D)]	-1.5% (-6.8, 3.8)	1.8% (-3.5, 7.1)		

[A)] BCVA: Best Corrected Visual Acuity
ETDRS: Early Treatment Diabetic Retinopathy Study
LS: Least square means derived from ANCOVA

[B)] Full Analysis Set (FAS), Last Observation Carried Forward (LOCF) for all analyses except proportion of patients with maintained visual acuity at week 52 which is Per Protocol Set (PPS)

[C)] The difference is the value of the Eylea group minus the value of the ranibizumab group. A positive value favours Eylea.

[D)] Confidence interval (CI) calculated by normal approximation

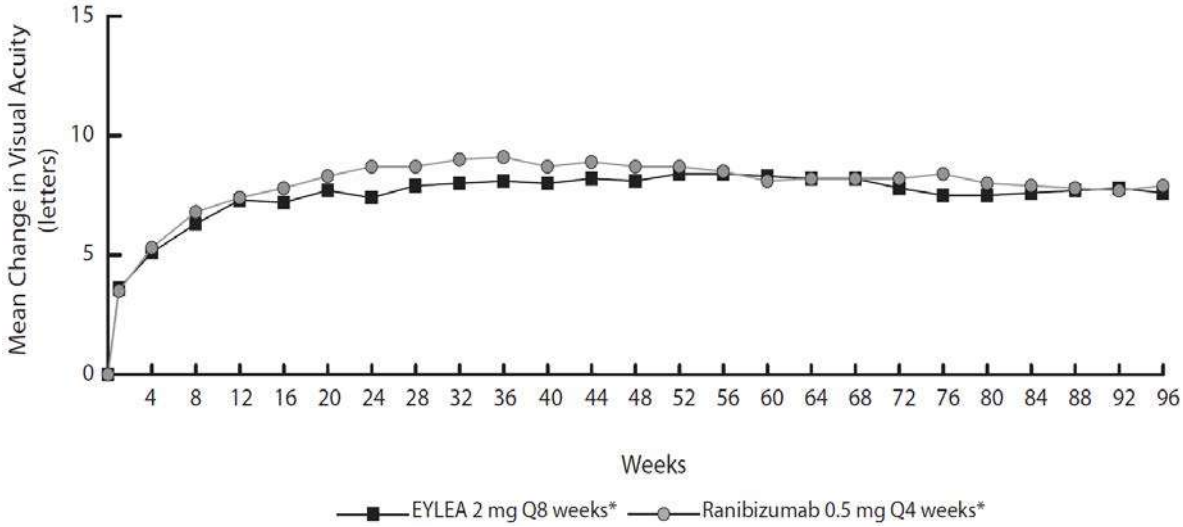
[E)] After treatment initiation with three monthly doses

[F)] A confidence interval lying entirely above -10% indicates a non-inferiority of Eylea to ranibizumab

[G)] Beginning at week 52, all groups were treated using a modified quarterly treatment paradigm where patients could be dosed as frequently as every 4 weeks but not less frequently than every 12 weeks based upon pre-specified retreatment criteria

PGR2026-00039
Biocon Ex.1065
Page 538 of 595

Figure 1. Mean Change in Visual Acuity
from Baseline to Week 96 for the Combined
Data from the View1 and View2 Studies



*) From Baseline to Week 52, Eylea was dosed every 8 weeks following 3 initial monthly doses. From Baseline to Week 52, ranibizumab 0.5 mg was dosed every 4 weeks. Beginning at Week 52, all groups were treated using a modified quarterly treatment paradigm where patients could be dosed as frequently as every 4 weeks but not less frequently than every 12 weeks based upon pre-specified retreatment criteria.

The proportion of patients at week 96 gaining at least 15 letters from baseline was 33.44% in the Eylea 2Q8 group, and 31.60% in the ranibizumab 0.5Q4 group.

In combined data analysis of the VIEW1 and VIEW2 studies Eylea demonstrated clinically meaningful changes from baseline in pre-specified secondary efficacy endpoint National Eye Institute Visual Function Questionnaire (NEI VFQ-25). The magnitude of these changes was similar to that seen in published studies, which corresponded to a 15-letter gain in Best Corrected Visual Acuity (BCVA).

No clinically meaningful differences were found between Eylea and the reference product ranibizumab in changes of NEI VFQ-25 total score and subscales (near activities, distance activities, and vision-specific dependency) at week 52 from baseline.

Decreases in mean CNV area were evident in all dose groups in both studies.

Efficacy results in all evaluable subgroups (e.g. age, gender, race, baseline visual acuity, lesion type, lesion size) in each study and in the combined analysis were consistent with the results in the overall populations.

In the second year of the studies, efficacy was generally maintained through the last assessment at week 96.

In the second year of the studies, 2-4% of patients required all injections on a monthly basis, and a third of patients required at least one injection with a treatment interval of only one month.

Elderly Population

In the clinical studies, approximately 89% (1,616/1,817) of the patients randomised to treatment with Eylea were 65 years of age or older and approximately 63% (1,139/1,817) were 75 years of age or older.

PGR2026-00039
Biocon Ex.1065
Page 539 of 595

Macular oedema secondary to CRVO

The safety and efficacy of Eylea were assessed in two randomised, multi-centre, double-masked, sham-controlled studies in patients with macular oedema secondary to CRVO. A total of 358 patients were treated and evaluable for efficacy (217 with Eylea) in the two studies COPERNICUS and GALILEO. In both studies, patients were randomly assigned in a 3:2 ratio to either 2 mg Eylea administered every 4 weeks (2Q4) or the control group receiving sham injections every 4 weeks for a total of 6 injections.

After 6 monthly injections, patients received treatment only if they met pre-specified retreatment criteria, except for patients in the control group in the GALILEO study who continued to receive sham (control to control) until week 52. Starting from this timepoint all patients were offered treatment if they met pre-specified criteria.

Patient ages ranged from 22 to 89 years with a mean of 64 years.

In both studies, the primary efficacy endpoint was the proportion of patients who gained at least 15 letters in BCVA at week 24 compared to baseline.

Change in visual acuity at week 24 compared to baseline was a secondary efficacy variable in both COPERNICUS and GALILEO studies.

The difference between treatment groups was statistically significant in favour of Eylea in both studies. In both pivotal studies the maximal improvement in visual acuity has been achieved at month 3 with subsequent stabilisation of the effect on visual acuity and central retinal thickness until month 6. The statistically significant difference was maintained through week 52.

Detailed results from the analysis of both studies are shown in the Table 3 and Figure 2 below.

PGR2026-00039
Biocon Ex.1065
Page 540 of 595

Table 3: Efficacy outcomes at week 24, week 52 and week 76/100 (Full Analysis Set with LOCF[C)]) in COPERNICUS and GALILEO studies

Efficacy Outcomes	**COPERNICUS**						**GALILEO**					
	24 Weeks		**52 Weeks**		**100 Weeks**		**24 Weeks**		**52 Weeks**		**76 Weeks**	
	Eylea 2 mg Q4 (N = 114)	**Control (N= 73)**	**Eylea 2 mg (N = 114)**	**Control[E)] (N =73)**	**Eylea [F)] 2 mg (N= 114)**	**Control [E,F)] (N=73)**	**Eylea 2 mg Q4 (N = 103)**	**Control (N = 68)**	**Eylea 2 mg (N = 103)**	**Control (N = 68)**	**Eylea [G)] 2 mg (N = 103)**	**Control [G)] (N = 68)**
Proportion of patients who gained at least 15 letters in BCVA[C)] from baseline	56%	12%	55%	30%	49.1%	23.3%	60%	22%	60%	32%	57.3%	29.4%
Weighted difference[A,B,E)] (95% CI)	44.8% (33.0, 56.6)		25.9% (11.8, 40.1)		26.7% (13.1, 40.3)		38.3% (24.4, 52.1)		27.9% (13.0, 42.7)		28.0% (13.3, 42.6)	
p-value	p < 0.0001		p = 0.0006		p=0.0003		p < 0.0001		p = 0.0004		p=0.0004	
Mean change in BCVA as measured by ETDRS[C)] letter score from baseline (SD)	17.3 (12.8)	-4.0 (18.0)	16.2 (17.4)	3.8 (17.1)	13.0 (17.7)	1.5 (17.7)	18.0 (12.2)	3.3 (14.1)	16.9 (14.8)	3.8 (18.1)	13.7 (17.8)	6.2 (17.7)
Difference in LS mean[A,C,D,E)] (95% CI)	21.7 (17.4, 26.0)		12.7 (7.7, 17.7)		11.8 (6.7, 17.0)		14.7 (10.8, 18.7)		13.2 (8.2, 18.2)		7.6 (2.1, 13.1)	
p-value	p < 0.0001		p < 0.0001		p < 0.0001		p < 0.0001		p < 0.0001		p=0.0070	

A) Difference is Eylea 2 mg Q4 weeks minus control

B) Difference and confidence interval (CI) are calculated using Cochran-Mantel-Haenszel (CMH) test adjusted for region (America vs. rest of the world for COPERNICUS and Europe vs. Asia/Pacific for GALILEO) and baseline BCVA category (> 20/200 and ≤ 20/200)

C) BCVA: Best Corrected Visual Acuity
ETDRS: Early Treatment Diabetic Retinopathy Study
LOCF: Last Observation Carried Forward
SD: Standard deviation
LS: Least square means derived from ANCOVA

D) LS mean difference and confidence interval based on an ANCOVA model with factors treatment group, region (America vs. rest of the world for COPERNICUS and Europe vs. Asia/Pacific for GALILEO) and baseline BCVA category (> 20/200 and ≤ 20/200)

E) In COPERNICUS study, control group patients could receive Eylea on an as-needed basis as frequently as every 4 weeks during week 24 to week 52; patients had visits every 4 weeks.

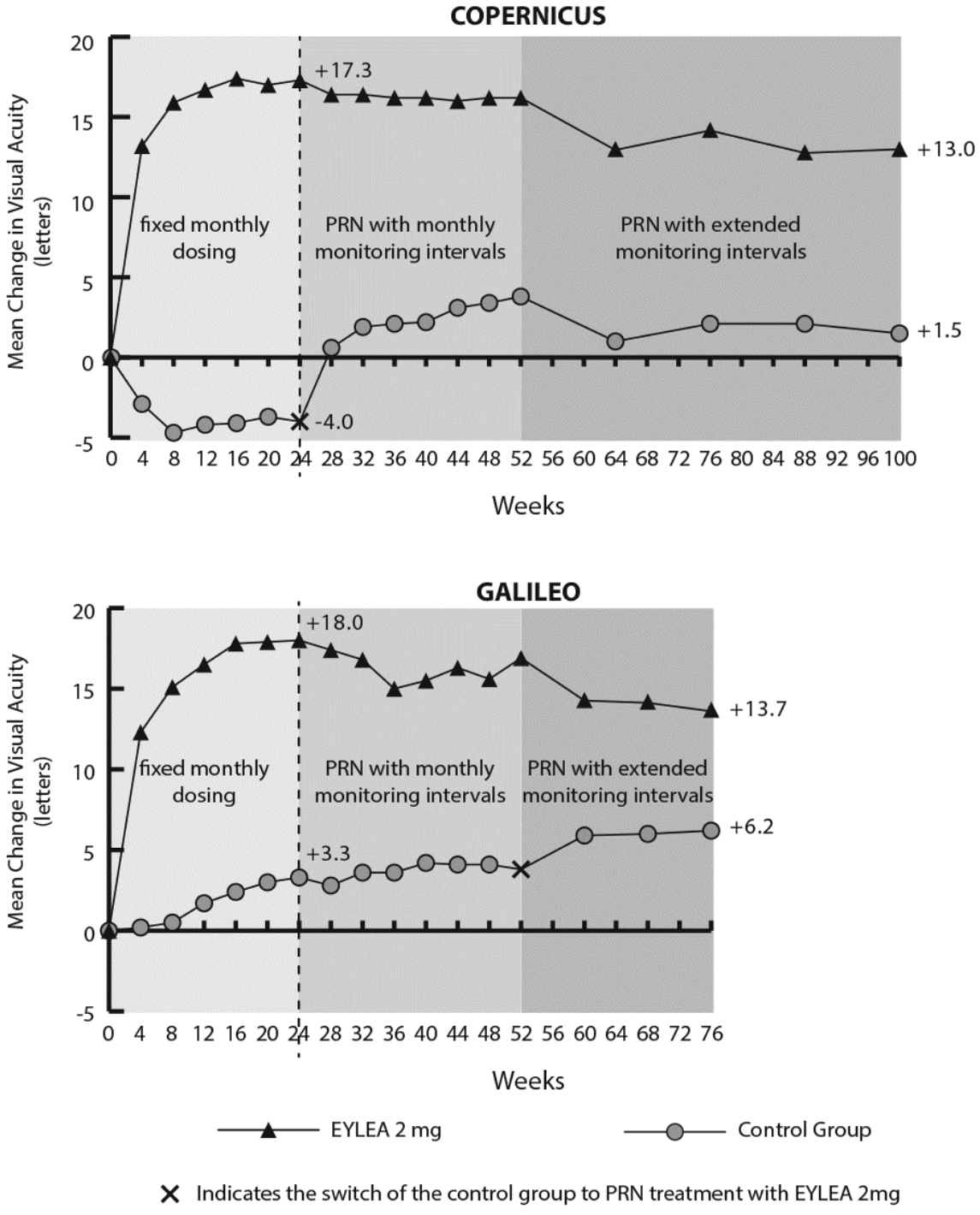
F) In COPERNICUS study, both control group and Eylea 2mg patients received Eylea 2 mg on an as-needed basis as frequently as every 4 weeks starting from Week 52 to Week 96; patients had mandatory quarterly visits but may have been seen as frequently as every 4 weeks if necessary.

PGR2026-00039
Biocon Ex.1065
Page 541 of 595

[G)] In GALILEO study, both control group and Eylea 2mg patients received Eylea 2 mg on an as-needed basis every 8 weeks starting from Week 52 to Week 68; patients had mandatory visits every 8 weeks.

PGR2026-00039
Biocon Ex.1065
Page 542 of 595

Figure 2: Mean change from Baseline to Week 76/100 in Visual Acuity by Treatment Group for the COPERNICUS and GALILEO Studies (Full Analysis Set)



The proportion of perfused patients in the Eylea group was high in the GALILEO study at baseline 86.4%; (n = 89). Perfusion at week 24 primary endpoint was 91.8% (n = 89). The patients were largely able to maintain their perfusion status until week 76, 84.3% (n = 75). The number of perfused patients that started on sham was 79.4% (n = 54) at baseline. Perfusion at week 24 primary endpoint was 85.5% (n = 47). Patients in the sham group were switched to Eylea according to pre-specified criteria

PGR2026-00039
Biocon Ex.1065
Page 543 of 595

at week 52, 83.7% (n = 41) were perfused at this time. The patients were able to maintain their perfusion status until week 76, 84.0% (n = 42).

The proportion of perfused patients in the Eylea group in the COPERNICUS study at baseline was 67.5% (n = 77). Perfusion at week 24 primary endpoint was 87.4% (n = 90). After week 24, patients in the Eylea group were treated according to pre-specified criteria. At week 100, 76.8 % (n = 76) of patients were perfused. The percentage of perfused patients that started on sham was 68.5% (n = 50) at baseline. Perfusion at week 24 primary endpoint was 58.6% (n = 34). Patients in the sham arm were eligible to receive Eylea from week 24. The proportion of perfused patients increased to 83.9% (n = 47) at week 52 and was largely maintained until week 100, 78% (n = 39).

The beneficial effect of Eylea treatment on visual function was similar in the baseline subgroups of perfused and non-perfused patients.

In combined data analysis of the GALILEO and COPERNICUS studies, Eylea demonstrated clinically meaningful changes from baseline in pre-specified secondary efficacy endpoint National Eye Institute Visual Function Questionnaire (NEI VFQ-25). The magnitude of these changes was similar to that seen in published studies, which corresponded to a 15-letter gain in Best Corrected Visual Acuity (BCVA).

Treatment effects in all evaluable subgroups (e.g. age, gender, race, baseline visual acuity, retinal perfusion status, CRVO duration) in each study were in general consistent with the results in the overall populations.

Elderly population

In the CRVO studies, approximately 52% (112/217) of the patients randomised to treatment with Eylea were 65 years of age or older, and approximately 18% (38/217) were 75 years of age or older.

Macular oedema secondary to BRVO

The safety and efficacy of Eylea were assessed in a randomised, multi-centre, double-masked, active-controlled study in patients with macular oedema secondary to BRVO which included Hemi-Retinal Vein Occlusion. A total of 181 patients were treated and evaluable for efficacy (91 with Eylea) in the VIBRANT study. In the study, patients were randomly assigned in a 1:1 ratio to either 2 mg Eylea administered every 8 weeks following 6 initial monthly injections' or laser photocoagulation administered at baseline (laser control group). Patients in the laser control group could receive additional laser photocoagulation (called 'rescue laser treatment') beginning at week 12, if needed. The minimum interval between laser photocoagulation treatments was 12 weeks. Beginning at week 24, patients in the laser treatment group could receive rescue treatment with Eylea 2mg, if needed, administered every 4 weeks for 3 months followed by intravitreal injections every 8 weeks, based on pre-specified criteria.

Patient ages ranged from 42 to 94 years with a mean of 65 years.

In the VIBRANT study, the primary efficacy endpoint was the proportion of patients who gained at least 15 letters in BCVA at week 24 compared to baseline. At week 24, the Eylea group was superior to laser control for the primary endpoint.

Change in visual acuity at week 24 compared to baseline was a secondary efficacy variable in the VIBRANT study. The difference between treatment groups was statistically significant in favour of Eylea. The course of visual improvement was rapid and maximal improvement was achieved at month 3 with subsequent stabilisation of the effect on visual acuity and central retinal thickness until month 6 and subsequent maintenance of the effect until month 12.

PGR2026-00039
Biocon Ex.1065
Page 544 of 595

In the laser group 67 patients received rescue treatment with Eylea beginning at week 24 (Active Control/ Eylea 2mg group). In this treatment group visual acuity improved by about 5 letters from week 24 to 52.

PGR2026-00039
Biocon Ex.1065
Page 545 of 595

Detailed results from the analysis of the VIBRANT study are shown in the Table 4 and Figure 3 below.

Table 4: Efficacy outcomes at week 24 and week 52 (Full Analysis Set with LOCF) in VIBRANT study

Efficacy Outcomes	**VIBRANT**			
	24 weeks		**52 weeks**	
	Eylea 2mg Q4 (N = 91)	**Active Control (laser) (N = 90)**	**Eylea 2mg Q8 (N = 91)[D)]**	**Active Control (laser)/Eylea 2mg[E)] (N = 90)**
Proportion of patients who gained at least 15 letters in BCVA from Baseline (%)	52.7%	26.7%	57.1%	41.1%
Weighted Difference [A,B] (%) (95% CI) p-value	26.6% (13.0, 40.1) p=0.0003		16.2% (2.0, 30.5) p=0.0296	
Mean change in BCVA as measured by ETDRS letter score from Baseline (SD)	17.0 (11.9)	6.9 (12.9)	17.1 (13.1)	12.2 (11.9)
Difference in LS mean [A,C] (95% CI) p-value	10.5 (7.1, 14.0) p<0.0001		5.2 (1.7, 8.7) p=0.0035[F)]	

A) Difference is Eylea 2 mg Q4 weeks minus Laser Control

B) Difference and 95% CI are calculated using Mantel-Haenszel weighting scheme adjusted for region (North America vs. Japan) and baseline BCVA category (> 20/200 and ≤ 20/200)

C) LS mean difference and 95% CI based on an ANCOVA model with treatment group, baseline BCVA category (> 20/200 and ≤ 20/200) and region (North America vs. Japan) as fixed effects, and baseline BCVA as covariate

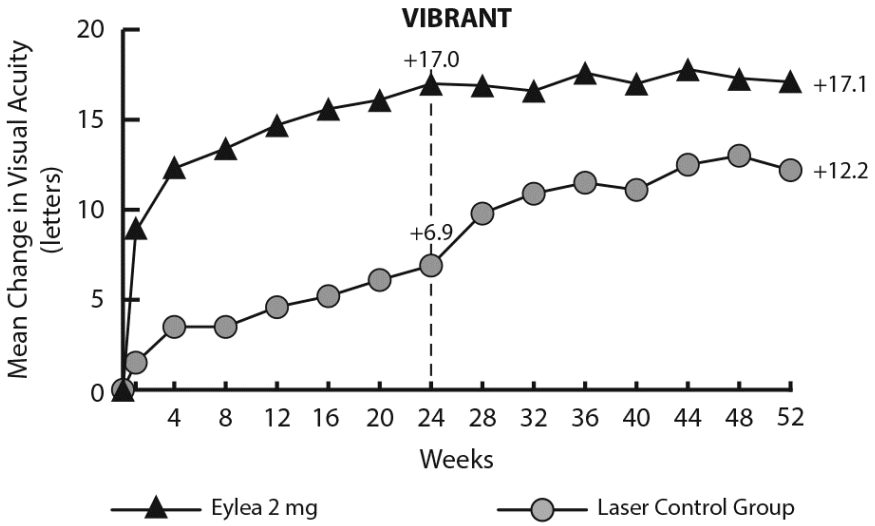
D) From Week 24 on the treatment interval in the Eylea treatment group was extended for all subjects from 4 weeks to 8 weeks through week 48.

E) Beginning at Week 24 subjects in the Laser Group could receive rescue treatment with Eylea, if they met at least one pre-specified eligibility criterion. At total of 67 subjects in this group received Eylea rescue treatment. The fixed regimen for Eylea rescue was three times Eylea 2mg every 4 weeks followed by injections every 8 weeks.

F) Nominal p-value

PGR2026-00039
Biocon Ex.1065
Page 546 of 595

Figure 3: Mean Change in BCVA as Measured by ETDRS Letter Score from Baseline to Week 52 in VIBRANT Study



At baseline, the proportion of perfused patients in the Eylea and laser groups was 60% and 68%, respectively. At week 24 these proportions were 80% and 67%, respectively. In the Eylea group the proportion of perfused patients was maintained through week 52). In the laser group, where patients were eligible for rescue treatment with Eylea from week 24, the proportion of perfused patients increased to 78% by week 52.

Elderly population

In the BRVO study, approximately 58% (53/91) of the patients randomised to treatment with Eylea were 65 years of age or older, and approximately 23% (21/91) were 75 years of age or older.

Diabetic macular oedema

The safety and efficacy of Eylea were assessed in two randomised, multi-centre, double-masked, active-controlled studies in patients with DME. A total of 862 randomised and treated patients were evaluable for efficacy. Of those, 576 were randomised to the Eylea groups in two studies (VIVID^{DME} and VISTA^{DME}). In each study, patients were randomly assigned in a 1:1:1 ratio to 1 of 3 dosing regimens:
1) Eylea administered 2 mg every 8 weeks following 5 initial monthly injections (Eylea 2Q8);
2) Eylea administered 2 mg every 4 weeks (Eylea 2Q4); and
3) macular laser photocoagulation (active control).
Beginning at week 24, patients meeting a pre-specified threshold of vision loss were eligible to receive additional treatment: patients in the Eylea groups could receive laser and patients in the control group could receive Eylea.

Patient ages ranged from 23 to 87 years with a mean of 63 years.

The majority of patients in both studies had Type II diabetes.

PGR2026-00039
Biocon Ex.1065
Page 547 of 595

In both studies, the primary efficacy endpoint was the mean change from baseline in BCVA at Week 52 as measured by ETDRS letter score. Both Eylea 2Q8 and Eylea 2Q4 groups were shown to have efficacy that was statistically significantly superior to the control group. This benefit was maintained through week 100.

Detailed results from the analysis of the VIVID^{DME} and VISTA^{DME} studies are shown in Table 5 and Figure 4 below.

PGR2026-00039
Biocon Ex.1065
Page 548 of 595

Table 5: Efficacy outcomes at week 52 and week 100 (Full Analysis Set with LOCF) in VIVID[DME] and VISTA[DME] studies

Efficacy Outcomes	VIVID[DME]						VISTA[DME]					
	52 Weeks			100 Weeks			52 Weeks			100 Weeks		
	Eylea 2 mg Q8 [A] (N = 135)	Eylea 2 mg Q4 (N = 136)	Active Control (laser) (N = 132)	Eylea 2 mg Q8 [A] (N = 135)	Eylea 2 mg Q4 (N = 136)	Active Control (laser) (N = 132)	Eylea 2 mg Q8 [A] (N = 151)	Eylea 2 mg Q4 (N = 154)	Active Control (laser) (N = 154)	Eylea 2 mg Q8 [A] (N = 151)	Eylea 2 mg Q4 (N = 154)	Active Control (laser) (N = 154)
Mean change in BCVA as measured by ETDRS [E] letter score from Baseline	10.7	10.5	1.2	9.4	11.4	0.7	10.7	12.5	0.2	11.1	11.5	0.9
Difference in LS mean [B,C,E] (97.5% CI)	9.1 (6.3, 11.8)	9.3 (6.5, 12.0)		8.2 (5.2, 11.3)	10.7 (7.6, 13.8)		10.45 (7.7, 13.2)	12.19 (9.4, 15.0)		10.1 (7.0, 13.3)	10.6 (7.1, 14.2)	
Proportion of patients who gained at least 15 letters in BCVA [E] from Baseline	33%	32%	9%	31.1%	38.2%	12.1%	31%	42%	8%	33.1%	38.3%	13.0%
Adjusted Difference [D,C,E] (97.5% CI)	24% (13.5, 34.9)	23% (12.6, 33.9)		19.0% (8.0, 29.9)	26.1% (14.8, 37.5)		23% (13.5, 33.1)	34% (24.1, 44.4)		20.1% (9.6, 30.6)	25.8% (15.1, 36.6)	

[A] After treatment initiation with 5 monthly injections

PGR2026-00039
Biocon Ex.1065
Page 549 of 595

[B] LS mean and CI based on an ANCOVA model with baseline BCVA measurement as a covariate and a factor for treatment group. Additionally, region (Europe/Australia vs. Japan) had been included as factor for VIVID^{DME}, and history of MI and/or CVA as a factor for VISTA^{DME}.

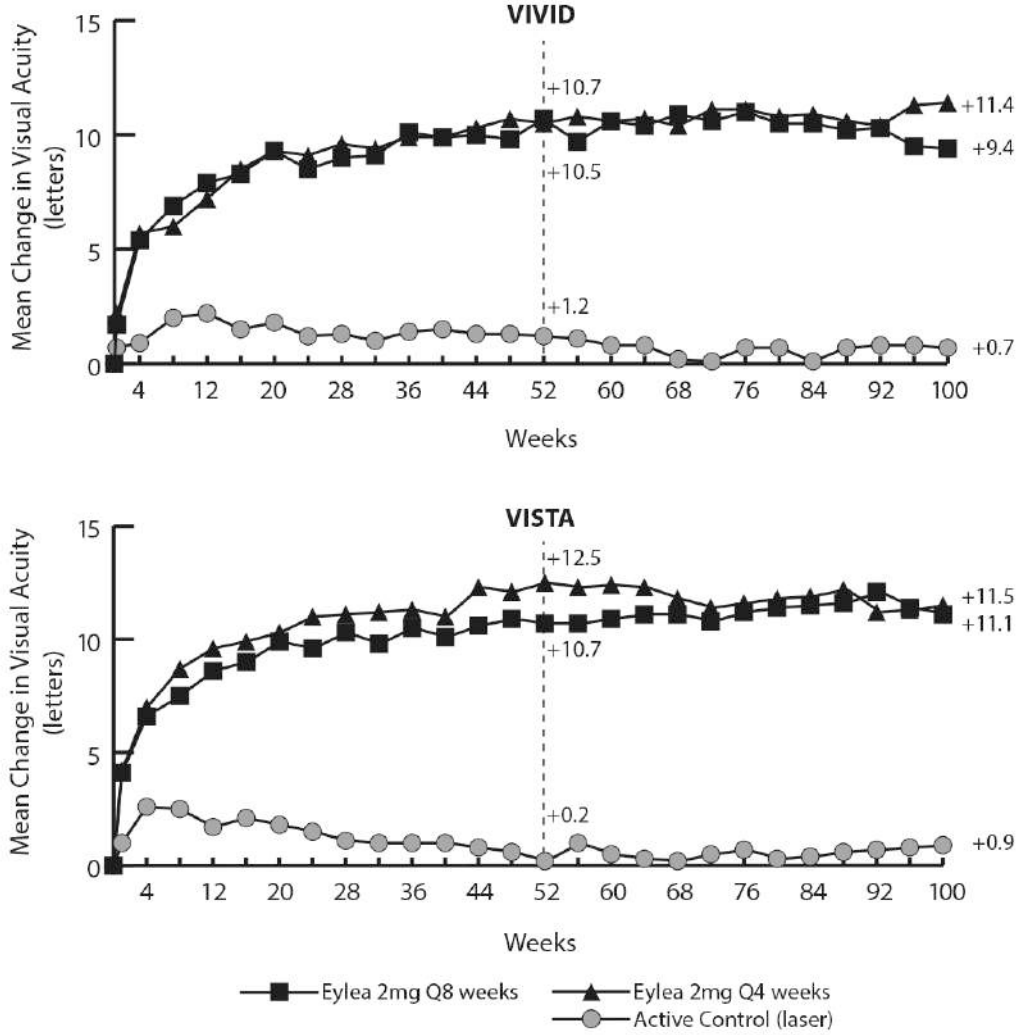
[C] Difference is Eylea group minus active control (laser) group

[D] Difference with confidence interval (CI) and statistical test is calculated using Mantel-Haenszel weighting scheme adjusted by region (Europe/Australia vs. Japan) for VIVID^{DME} and medical history of MI or CVA for VISTA^{DME}

[E] BCVA: Best Corrected Visual Acuity
ETDRS: Early Treatment Diabetic Retinopathy Study
LOCF: Last Observation Carried Forward
LS: Least square means derived from ANCOVA
CI: Confidence interval

PGR2026-00039
Biocon Ex.1065
Page 550 of 595

Figure 4: Mean change in BCVA as Measured by ETDRS Letter Score from Baseline to Week 100 in VIVID^{DME} and VISTA^{DME} Studies



Treatment effects in evaluable subgroups (e.g., age, gender, race, baseline HbA1c, baseline visual acuity, prior anti-VEGF therapy) in each study and in the combined analysis were generally consistent with the results in the overall populations.

In the VIVID^{DME} and VISTA^{DME} studies, 36 (9%) and 197 (43%) patients received prior anti-VEGF therapy, respectively, with a 3-month or longer washout period. Treatment effects in the subgroup of patients who had previously been treated with a VEGF inhibitor prior to study participation were similar to those seen in patients who were VEGF inhibitor naïve prior to study participation.

Patients with bilateral disease were eligible to receive anti-VEGF treatment in their fellow eye if determined to be necessary by the physician. In the VISTA^{DME} study, 217(70.7%) of Eylea patients received bilateral Eylea injections until week 100; in the VIVID^{DME} study, 97(35.8%) of Eylea patients received a different anti-VEGF treatment in their fellow eye.

Elderly population

PGR2026-00039
Biocon Ex.1065
Page 551 of 595

In the DME phase III studies, approximately 47% (268/576) of the patients randomised to treatment with Eylea were 65 years of age or older, and approximately 9% (52/576) were 75 years of age or older. Efficacy and safety outcomes were consistent with the outcomes of the overall population.

Myopic choroidal neovascularisation

The safety and efficacy of Eylea were assessed in a randomised, multi-centre, double-masked, sham-controlled study in treatment-naïve, Asian patients with myopic CNV. Patients were randomly assigned in a 3:1 ratio to receive either 2 mg Eylea intravitreally or sham injections administered once at study start with additional injections given monthly in case of disease persistence or recurrence until week 24, when the primary endpoint was assessed. At week 24, patients initially randomised to sham were eligible to receive the first dose of Eylea. Following this, patients in both groups continued to be eligible for additional injections in case of disease persistence or recurrence.

A total of 121 patients were treated and evaluable for efficacy (90 with Eylea). Their age ranged from 27 to 83 years with a mean of 58 years.

The difference between treatment groups was statistically significant in favour of Eylea for the primary endpoint (change in BCVA) and confirmatory secondary efficacy endpoint (proportion of patients who gained 15 letters in BCVA) at week 24 compared to baseline. Differences for both endpoints were maintained through week 48.

Detailed results from the analysis of the MYRROR study are shown in Table 6 and Figure 5 below.

PGR2026-00039
Biocon Ex.1065
Page 552 of 595

Table 6: Efficacy outcomes at week 24 (primary analysis) and week 48 in MYRROR study (Full Analysis Set with LOCF[A)])

Efficacy Outcomes	**MYRROR**			
	24 Weeks		**48 Weeks**	
	Eylea 2mg (N = 90)	**Sham (N = 31)**	**Eylea 2mg (N = 90)**	**Sham/ Eylea 2mg (N = 31)**
Mean change in BCVA letter score as measured by ETDRS from baseline (SD) [B)]	12.1 (8.3)	-2.0 (9.7)	13.5 (8.8)	3.9 (14.3)
Difference in LS mean [C,D,E)] (95% CI)	14.1 (10.8, 17.4)		9.5 (5.4, 13.7)	
Proportion of patients who gained at least 15 letters in BCVA[B)] from baseline	38.9%	9.7%	50.0%	29.0%
Weighted difference [D, F)] (95% CI)	29.2% (14.4, 44.0)		21.0% (1.9, 40.1)	

A) LOCF: Last Observation Carried Forward

B) BCVA: Best Corrected Visual Acuity
ETDRS: Early Treatment Diabetic Retinopathy Study
SD: Standard Deviation

C) LS mean: Least square means derived from ANCOVA model

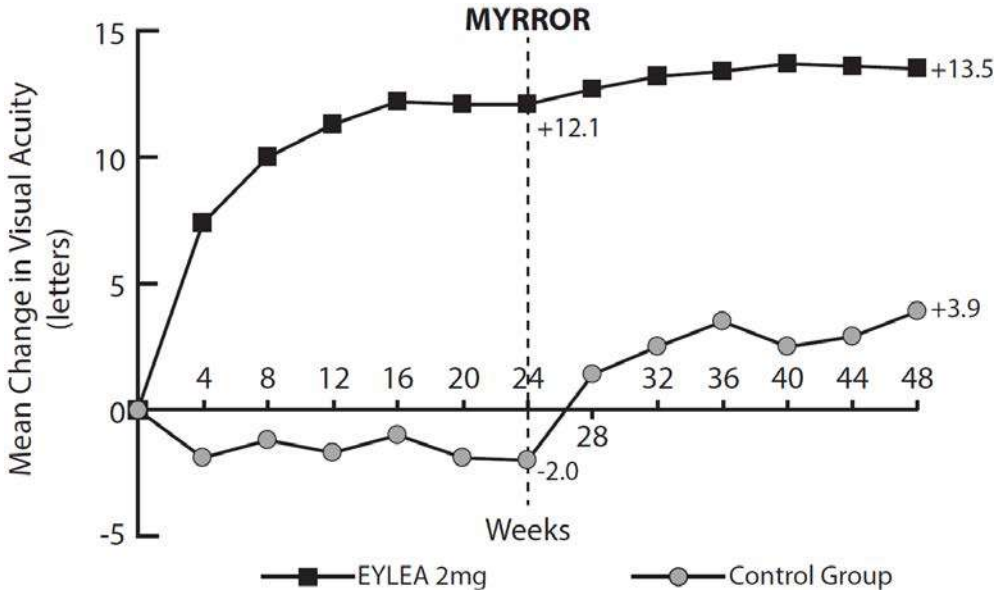
D) CI: Confidence Interval

E) LS mean difference and 95% CI based on an ANCOVA model with treatment group and country (country designations) as fixed effects, and baseline BCVA as covariant.

F) Difference and 95% CI are calculated using Cochran-Mantel-Haenszel (CMH) test adjusted for country (country designations)

PGR2026-00039
Biocon Ex.1065
Page 553 of 595

Figure 5: Mean Change from Baseline to Week 48 in Visual Acuity by Treatment Group for the MYRROR Study (Full Analysis Set, LOCF)



Elderly population

In the myopic CNV study, approximately 36% (33/91) of the patients randomised to treatment with Eylea were 65 years of age or older, and approximately 10% (9/91) were 75 years of age or older.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Eylea in all subsets of the paediatric population in wet AMD, CRVO, BRVO, DME and myopic CNV populations (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Eylea is administered directly into the vitreous to exert local effects in the eye.

Absorption / Distribution
Aflibercept is slowly absorbed from the eye into the systemic circulation after intravitreal administration and is predominately observed in the systemic circulation as an inactive, stable complex with VEGF; however only "free aflibercept" is able to bind endogenous VEGF.

In a pharmacokinetic sub-study in 6 neovascular wet AMD patients with frequent sampling, maximum plasma concentrations of free aflibercept (systemic C_{max}) were low, with a mean of approximately 0.02 microgram/ml (range 0 to 0.054) within 1 to 3 days after a 2 mg intravitreal injection, and were undetectable two weeks following dosage in almost all patients. Aflibercept does not accumulate in the plasma when administered intravitreally every 4 weeks.

The mean maximum plasma concentration of free aflibercept is approximately 50 to 500 times below the aflibercept concentration required to inhibit the biologic activity of systemic VEGF by 50% in animal models, in which blood pressure changes were observed after circulating levels of free aflibercept attained approximately 10 microgram/ml and returned to baseline when levels fell below approximately 1 microgram/ml. It is estimated that after intravitreal administration of 2 mg to patients, the mean maximum plasma concentration of free aflibercept is more than 100-fold lower than the concentration of aflibercept required to half-maximally bind systemic VEGF (2.91 microgram/ml) in a

PGR2026-00039
Biocon Ex.1065
Page 554 of 595

study of healthy volunteers. Therefore, systemic pharmacodynamic effects such as blood pressure changes are unlikely.

In pharmacokinetic sub-studies in patients with CRVO, BRVO, DME or myopic CNV mean C_{max} of free aflibercept in plasma were similar with values in the range of 0.03 to 0.05 microgram/ml and individual values not exceeding 0.14 microgram/ml. Thereafter, plasma concentrations of free aflibercept declined to values below or close to the lower limit of quantitation generally within one week; undetectable concentrations were reached before the next administration after 4 weeks in all patients.

Elimination
As Eylea is a protein-based therapeutic, no metabolism studies have been conducted.

Free aflibercept binds VEGF to form a stable, inert complex. As with other large proteins, both free and bound aflibercept are expected to be cleared by proteolytic catabolism.

Renal impairment
No special studies in patients with renal impairment have been conducted with Eylea.

Pharmacokinetic analysis of patients in the VIEW2 study, of which 40% had renal impairment (24% mild, 15% moderate, and 1% severe), revealed no differences with respect to plasma concentrations of active drug after intravitreal administration every 4 or 8 weeks.

Similar results were seen in patients with CRVO in the GALILEO study, in patients with DME in the VIVID^{DME} study, and in patients with myopic CNV in the MYRROR study.

5.3 Preclinical safety data

Effects in non-clinical studies on repeated dose toxicity were observed only at systemic exposures considered substantially in excess of the maximum human exposure after intravitreal administration at the intended clinical dose indicating little relevance to clinical use.

Erosions and ulcerations of the respiratory epithelium in nasal turbinates in monkeys treated with aflibercept intravitreally were observed at systemic exposures in excess of the maximum human exposure. The systemic exposure based on C_{max} and AUC for free aflibercept were approximately 200- and 700-fold higher, respectively, when compared to corresponding values observed in humans after an intravitreal dose of 2 mg. At the No Observed Adverse Effect Level (NOAEL) of 0.5 mg/eye in monkeys the systemic exposure was 42- and 56-fold higher based on C_{max} and AUC, respectively.

No studies have been conducted on the mutagenic or carcinogenic potential of aflibercept.

An effect of aflibercept on intrauterine development was shown in embryo-foetal development studies in pregnant rabbits with intravenous (3 to 60 mg/kg) as well as subcutaneous (0.1 to 1 mg/kg) administration. The maternal NOAEL was at the dose of 3 mg/kg or 1 mg/kg, respectively. A developmental NOAEL was not identified. At the 0.1 mg/kg dose, the systemic exposures based on C_{max} and cumulative AUC for free aflibercept were approximately 17- and 10-fold higher, respectively, when compared to corresponding values observed in humans after an intravitreal dose of 2 mg.

Effects on male and female fertility were assessed as part of a 6-month study in monkeys with intravenous administration of aflibercept at doses ranging from 3 to 30 mg/kg. Absent or irregular menses associated with alterations in female reproductive hormone levels and changes in sperm morphology and motility were observed at all dose levels. Based on C_{max} and AUC for free aflibercept observed at the 3 mg/kg intravenous dose, the systemic exposures were approximately 4,900-fold and

PGR2026-00039
Biocon Ex.1065
Page 555 of 595

1,500-fold higher, respectively, than the exposure observed in humans after an intravitreal dose of 2 mg. All changes were reversible.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Polysorbate 20
Sodium dihydrogen phosphate, monohydrate (for pH adjustment)
Disodium hydrogen phosphate, heptahydrate (for pH adjustment)
Sodium chloride
Sucrose
Water for injection

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store in a refrigerator (2°C to 8°C).
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

Prior to usage, the unopened vial of Eylea may be kept at room temperature (below 25°C) for up to 24 hours. After opening the vial, proceed under aseptic conditions.

6.5 Nature and contents of container

100 microlitres of solution in a vial (type I glass) with a stopper (elastomeric rubber), and an 18 G filter needle. Pack size of 1.

6.6 Special precautions for disposal and other handling

The vial is for single use only.
Since the vial contains more volume (100 microlitres) than the recommended dose (50 microlitres), a part of the volume contained in the vial has to be discarded prior to the administration.

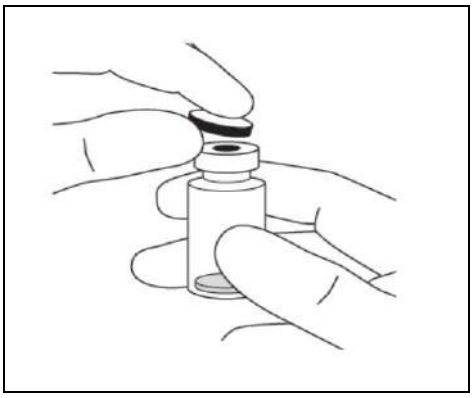
The solution should be inspected visually for any foreign particulate matter and/or discolouration or any variation in physical appearance prior to administration. In the event of either being observed, discard the medicinal product.

For the intravitreal injection, a 30 G x ½ inch injection needle should be used.

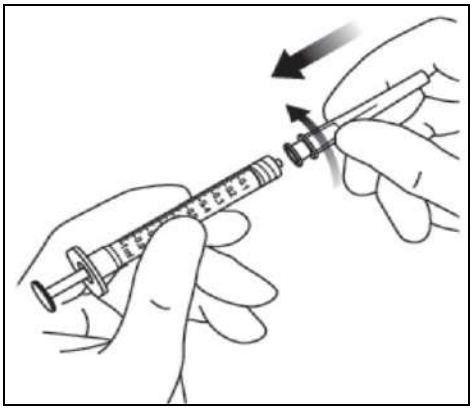
PGR2026-00039
Biocon Ex.1065
Page 556 of 595

Instructions for use of vial:

1. Remove the plastic cap and disinfect the outer part of the rubber stopper of the vial.

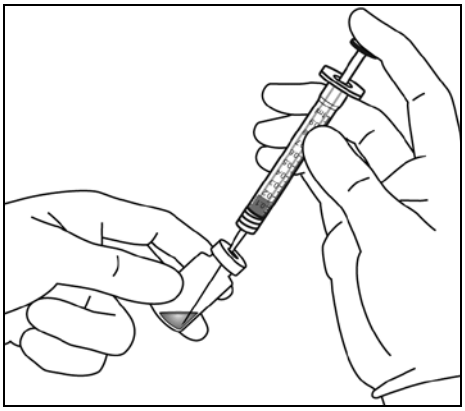


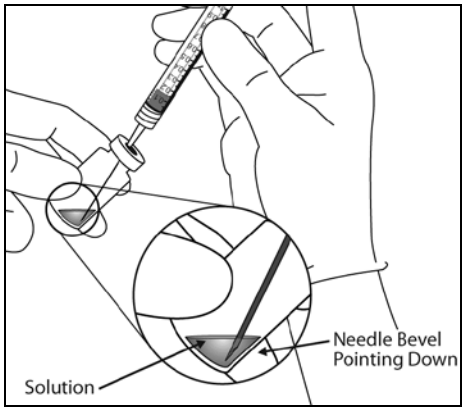
2. Attach the 18 G, 5-micron filter needle supplied in the carton to a 1-ml sterile, Luer-lock syringe.



3. Push the filter needle into the centre of the vial stopper until the needle is completely inserted into the vial and the tip touches the bottom or bottom edge of the vial.

4. Using aseptic technique withdraw all of the Eylea vial contents into the syringe, keeping the vial in an upright position, slightly inclined to ease complete withdrawal. To deter the introduction of air, ensure the bevel of the filter needle is submerged into the liquid. Continue to tilt the vial during withdrawal keeping the bevel of the filter needle submerged in the liquid.

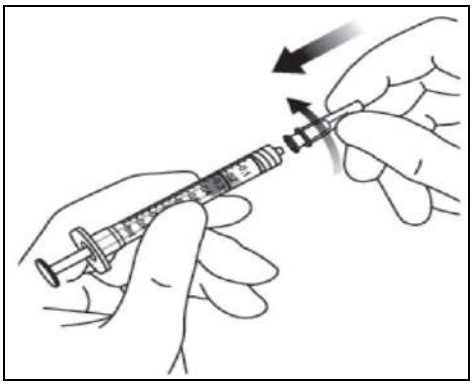




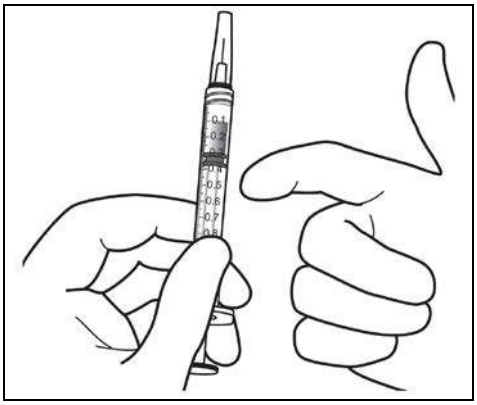
5. Ensure that the plunger rod is drawn sufficiently back when emptying the vial in order to completely empty the filter needle.

6. Remove the filter needle and properly dispose of it.
Note: Filter needle is not to be used for intravitreal injection.

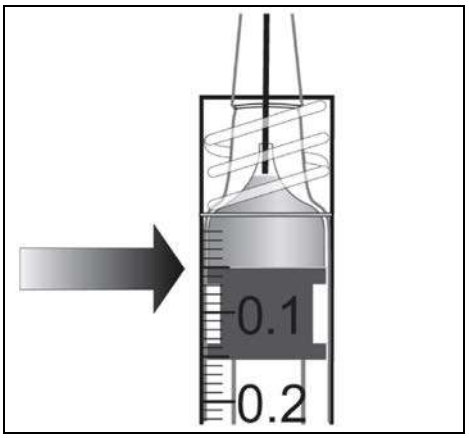
7. Using aseptic technique, firmly twist a 30 G x ½ inch injection needle to the Luer-lock syringe tip.

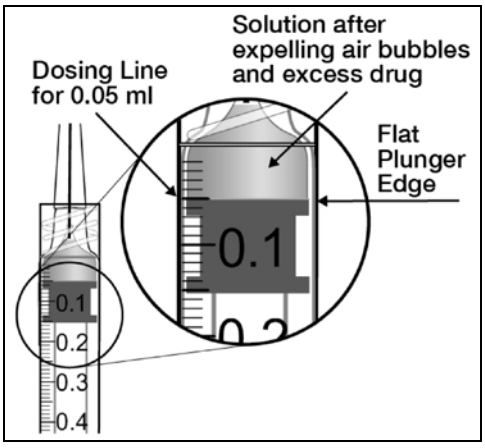


8. Holding the syringe with the needle pointing up, check the syringe for bubbles. If there are bubbles, gently tap the syringe with your finger until the bubbles rise to the top.



9. Eliminate all bubbles and expel excess medicinal product by slowly depressing the plunger so that the plunger tip aligns with the line that marks 0.05 ml on the syringe.





10. The vial is for single use only.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Bayer Pharma AG
D-13342 Berlin
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/797/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22 November 2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

PGR2026-00039
Biocon Ex.1065
Page 559 of 595

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

PGR2026-00039
Biocon Ex.1065
Page 560 of 595

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Regeneron Pharmaceuticals, Inc.
81 Columbia Turnpike
Rensselaer, New York 12144
USA

Name and address of the manufacturers responsible for batch release

Bayer Pharma AG
Müllerstraße 178
13353 Berlin
Germany

GP Grenzach Produktions GmbH
Emil-Barell-Straße 7
79639 Grenzach-Wyhlen
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

PGR2026-00039
Biocon Ex.1065
Page 561 of 595

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

Pharmacovigilance system
The MAH must ensure that the system of pharmacovigilance presented in Module 1.8.1. of the Marketing Authorisation is in place and functioning before and whilst the medicinal product is on the market.

- **Additional risk minimisation measures**

Prior to launch in each Member State the Marketing Authorisation Holder (MAH) shall agree the final educational material with the National Competent Authority.
The MAH shall ensure that, following discussions and agreement with the National Competent Authorities in each Member State where Eylea is marketed, at launch of the new indication myopic choroidal neovascularisation (myopic CNV) and periodically thereafter, all ophthalmological clinics where Eylea is expected to be used are provided with an updated physician information pack containing the following elements:

- Physician information
- Intravitreal injection procedure video
- Intravitreal injection procedure pictogram
- Patient information packs

The physician information should contain the following key elements:

- The Summary of Product Characteristics
- Who should be treated with Eylea
- Sterile techniques, including periocular and ocular disinfection to minimise the risk of infection
- Use of antibiotics
- Use of povidone iodine or equivalent
- Techniques for the intravitreal injection
- The need to expel excess volume of the pre-filled syringe before injecting Eylea to avoid overdose
- Patient monitoring after intravitreal injection
- Key signs and symptoms of intravitreal injection related adverse events including endophthalmitis, increased intraocular pressure, retinal pigment epithelial tear and cataract
- Management of intravitreal injection related adverse events
- Female patients of childbearing potential have to use effective contraception and pregnant women should not use Eylea

The patient information pack should be provided in both the form of a patient information booklet and an audio-CD that contain following key elements:

- Patient information leaflet
- Who should be treated with Eylea
- How to prepare for Eylea treatment
- What are the steps following treatment with Eylea
- Key signs and symptoms of serious adverse events including endophthalmitis, intraocular pressure increased, retinal pigment epithelial tear and cataract
- When to seek urgent attention from their health care provider
- Female patients of childbearing potential have to use effective contraception and pregnant women should not use Eylea

PGR2026-00039
Biocon Ex.1065
Page 562 of 595

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
To perform a post-authorisation randomised study in patients with neovascular (wet) AMD with the primary objective of comparing the standard regime of injections every 8 weeks with a reactive regimen based on visual and anatomic outcomes, based on a CHMP approved protocol.	Final study report submission: 31 December 2018
To perform an interventional post-authorisation efficacy study in patients with diabetic macular oedema with the primary objective of comparing, after the first initial year of Eylea treatment, the standard regime of injections every 8 weeks with alternative treatment regimens, i.e. extended treatment intervals based on visual and anatomic outcomes (PRN and treat-and-extend).	Final study report submission: November 2019

PGR2026-00039
Biocon Ex.1065
Page 563 of 595

ANNEX III

LABELLING AND PACKAGE LEAFLET

PGR2026-00039
Biocon Ex.1065
Page 564 of 595

A. LABELLING

PGR2026-00039
Biocon Ex.1065
Page 565 of 595

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
CARTON
Pre-filled syringe

1. NAME OF THE MEDICINAL PRODUCT

Eylea 40 mg/ml solution for injection in pre-filled syringe

Aflibercept

2. STATEMENT OF ACTIVE SUBSTANCE

Aflibercept

3. LIST OF EXCIPIENTS

Excipients:
Polysorbate 20
Sodium dihydrogen phosphate, monohydrate (for pH adjustment)
Disodium hydrogen phosphate, heptahydrate (for pH adjustment)
Sodium chloride
Sucrose
Water for injection

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled syringe

One pre-filled syringe contains 3.6 mg aflibercept in 90 microlitres (40 mg/ml) in iso-osmotic solution
Delivers a single dose of 2 mg/0.05 ml.
The excess volume should be expelled before injecting

1 pre-filled syringe (3.6 mg/90 microlitres)
Single dose: 2 mg/0.05 ml
Excess volume to be expelled.

5. METHOD AND ROUTE OF ADMINISTRATION

Intravitreal use.
For single use only.
Read the package leaflet before use.
Open the sterile blister in clean administration room only.

PGR2026-00039
Biocon Ex.1065
Page 566 of 595

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in refrigerator (2°C to 8°C).
Do not freeze.
Keep the pre-filled syringe in its blister in the outer carton to protect from light.
Prior to use, the unopened blister may be stored at room temperature (below 25°C) for up to 24 hours.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer Pharma AG
D-13342 Berlin
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/797/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to restricted medical prescription.

15. INSTRUCTIONS ON USE

PGR2026-00039
Biocon Ex.1065
Page 567 of 595

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

PGR2026-00039
Biocon Ex.1065
Page 568 of 595

PARTICULARS TO APPEAR ON THE BLISTER FOIL
Pre-filled syringe

1. NAME OF THE MEDICINAL PRODUCT

Eylea 40 mg/ml solution for injection

Aflibercept

2. STATEMENT OF ACTIVE SUBSTANCE

Aflibercept

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

One pre-filled syringe contains 3.6 mg/90 microlitres (40 mg/ml) in iso-osmotic solution.
Delivers a single dose of 2 mg/0.05 ml.

The excess volume should be expelled before injecting.

5. METHOD AND ROUTE OF ADMINISTRATION

Intravitreal use.
For single use only.
Read the package leaflet before use.
Open the sterile blister in clean administration room only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in refrigerator (2°C to 8°C).
Do not freeze.
Keep the pre-filled syringe in its blister in the outer carton to protect from light.

PGR2026-00039
Biocon Ex.1065
Page 569 of 595

Prior to use, the unopened blister may be stored at room temperature (below 25°C) for up to 24 hours.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer Pharma AG
D-13342 Berlin
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/797/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PGR2026-00039
Biocon Ex.1065
Page 570 of 595

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS LABEL
Pre-filled Syringe

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Eylea 40 mg/ml solution for injection
Aflibercept
Intravitreal use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Single dose = 2 mg/50 microlitres

3.6 mg/90 microlitres

6. OTHER

PGR2026-00039
Biocon Ex.1065
Page 571 of 595

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
CARTON
Vial

1. NAME OF THE MEDICINAL PRODUCT

Eylea 40 mg/ml solution for injection in a vial

Aflibercept

2. STATEMENT OF ACTIVE SUBSTANCE

Aflibercept

3. LIST OF EXCIPIENTS

Excipients:
Polysorbate 20
Sodium dihydrogen phosphate, monohydrate (for pH adjustment)
Disodium hydrogen phosphate, heptahydrate (for pH adjustment)
Sodium chloride
Sucrose
Water for injection

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in a vial

One vial contains 4 mg aflibercept in 100 microlitres (40 mg/ml) in iso-osmotic solution.
Delivers a single dose of 2 mg/0.05 ml.
The excess volume should be expelled before injecting

1 vial (4 mg/0.1 ml)
18G filter needle
Single dose: 2 mg/0.05 ml
Excess volume to be expelled.

5. METHOD AND ROUTE OF ADMINISTRATION

Intravitreal use.
Vial for single use only.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

PGR2026-00039
Biocon Ex.1065
Page 572 of 595

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in refrigerator (2°C to 8°C).
Do not freeze.
Keep the vial in the outer carton to protect from light.
Prior to use, the unopened vial may be stored at room temperature (below 25°C) for up to 24 hours.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer Pharma AG
D-13342 Berlin
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/797/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to restricted medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

PGR2026-00039
Biocon Ex.1065
Page 573 of 595

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS LABEL
Vial

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Eylea 40 mg/ml solution for injection
Aflibercept
Intravitreal use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Single dose = 2 mg/50 microlitres
Extractable content = 4 mg/100 microlitres

6. OTHER

PGR2026-00039
Biocon Ex.1065
Page 574 of 595

B. PACKAGE LEAFLET

PGR2026-00039
Biocon Ex.1065
Page 575 of 595

Package Leaflet: Information for the patient

Eylea 40 mg/ml solution for injection in a pre-filled syringe
Aflibercept

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Eylea is and what it is used for
2. What you need to know before you are given Eylea
3. How you will be given Eylea
4. Possible side effects
5. How to store Eylea
6. Contents of the pack and other information

1. What Eylea is and what it is used for

Eylea is a solution which is injected into the eye to treat eye conditions in adults called

- neovascular (wet) age-related macular degeneration (wet AMD),
- impaired vision due to macular oedema secondary to retinal vein occlusion (branch RVO (BRVO) or central RVO (CRVO)),
- impaired vision due to diabetic macular oedema (DME),
- impaired vision due to myopic choroidal neovascularisation (myopic CNV).

Aflibercept, the active substance in Eylea, blocks the activity of a group of factors, known as Vascular Endothelial Growth Factor A (VEGF-A) and Placental Growth Factor (PlGF).

In patients with wet AMD and myopic CNV, these factors, in excess are involved in the abnormal formation of new blood vessels in the eye. These new blood vessels can cause the leak of blood components into the eye and eventual damage to tissues in the eye responsible for vision.

In patients with CRVO, a blockage occurs in the main blood vessel that transports blood away from the retina. VEGF levels are elevated in response causing the leakage of fluid into the retina and thereby causing a swelling of the macula, (the portion of the retina responsible for fine vision), which is called macular oedema. When the macula swells with fluid, central vision becomes blurry.

In patients with BRVO, one or more branches of the main blood vessel that transports blood away from the retina is blocked. VEGF levels are elevated in response causing the leakage of fluid into the retina and thereby causing macular oedema.

PGR2026-00039
Biocon Ex.1065
Page 576 of 595

Diabetic macular oedema is a swelling of the retina occurring in patients with diabetes due to leaking of fluid from blood vessels within the macula. The macula is the portion of retina responsible for fine vision. When the macula swells with fluid, central vision becomes blurry.

Eylea has been shown to stop the growth of new abnormal blood vessels in the eye which often leak fluid or bleed. Eylea can help to stabilise, and in many cases, improve the vision loss related to wet AMD, CRVO, BRVO, DME and myopic CNV.

2. What you need to know before you are given Eylea

You will not be given Eylea:
- if you are allergic to aflibercept or any of the other ingredients of this medicine (listed in section 6).
- if you have an active or suspected infection in or around the eye (ocular or periocular infection).
- if you have severe inflammation of the eye (indicated by pain or redness).

Warnings and precautions

Talk to your doctor before you are given Eylea:

- if you have glaucoma.
- if you have a history of seeing flashes of light or floaters and if you have a sudden increase of size and number of floaters.
- if surgery was performed or is planned on your eye within the previous or next four weeks.
- if you have a severe form of CRVO or BRVO (ischaemic CRVO or BRVO), treatment with Eylea is not recommended.

Furthermore, it is important for you to know that:

- the safety and efficacy of Eylea when administered to both eyes at the same time has not been studied and if used in this way may lead to an increased risk of experiencing side effects.
- injections with Eylea may cause an increase in eye pressure (intraocular pressure) in some patients within 60 minutes of the injection. Your doctor will monitor this after each injection.
- if you develop an infection or inflammation inside the eye (endophthalmitis) or other complications, you may have eye pain or increased discomfort, worsening eye redness, blurred or decreased vision, and increased sensitivity to light. It is important to have any symptoms diagnosed and treated as soon as possible.
- your doctor will check whether you have other risk factors that may increase the chance of a tear or detachment of one of the layers at the back of the eye (retinal detachment or tear, and retinal pigment epithelial detachment or tear), in which case Eylea must be given with caution.
- Eylea should not be used in pregnancy unless the potential benefit outweighs the potential risk to the unborn child.
- women of childbearing potential have to use effective contraception during treatment and for at least three further months after the last injection of Eylea.

The systemic use of VEGF inhibitors, substances similar to those contained in Eylea, is potentially related to the risk of blood clots blocking blood vessels (arterial thromboembolic events) which may lead to heart attack or stroke. There is a theoretical risk of such events following injection of Eylea into the eye. There are limited data on safety in treating patients with CRVO, BRVO, DME and myopic CNV who have had a stroke or a mini-stroke (transient ischaemic attack) or a heart attack within the last 6 months. If any of these apply to you, Eylea will be given with caution.

There is only limited experience in the treatment of
- patients with DME due to type I diabetes.
- diabetics with very high average blood sugar values (HbA1c over 12%).

PGR2026-00039
Biocon Ex.1065
Page 577 of 595

- diabetics with an eye disease caused by diabetes called proliferative diabetic retinopathy.

There is no experience in the treatment of
- patients with acute infections.
- patients with other eye conditions such as a detachment of the retina or a hole in the macula.
- diabetics with uncontrolled high blood pressure.
- non-Asian patients with myopic CNV.
- patients previously treated for myopic CNV.
- patients with damage outside the central part of the macula (extrafoveal lesions) for myopic CNV.

If any of the above applies to you, your doctor will consider this lack of information when treating you with Eylea.

Children and adolescents
The use of Eylea in children or adolescents under 18 has not been studied because wet AMD, CRVO, BRVO, DME and myopic CNV occur mainly in adults. Therefore, its use in this age group is not relevant.

Other medicines and Eylea
Tell your doctor if you are using, have recently used or might use any other medicines.

Pregnancy and breastfeeding
- Women of childbearing potential have to use effective contraception during treatment and for at least three further months after the last injection of Eylea.

- There is no experience of using Eylea in pregnant women. Eylea should not be used during pregnancy unless the potential benefit outweighs the potential risk to the unborn child. If you are pregnant or planning to become pregnant, discuss this with your doctor before treatment with Eylea.

- Eylea is not recommended during breastfeeding as it is not known whether Eylea passes into human milk. Ask your doctor for advice before starting Eylea treatment.

Driving and using machines
After your injection with Eylea, you may experience some temporary visual disturbances. Do not drive or use machines as long as these last.

Important information about some of the ingredients of Eylea
This medicine contains less than 1 mmol (23 mg) of sodium per dose which means it is essentially "sodium-free".

3. How you will be given Eylea

A doctor experienced in giving eye injections will inject Eylea into your eye under aseptic (clean and sterile) conditions.

The recommended dose is 2 mg aflibercept (50 microlitres).
Eylea is given as an injection into your eye (intravitreal injection).

Before the injection your doctor will use a disinfectant eyewash to clean your eye carefully to prevent infection. Your doctor will also give you a local anaesthetic to reduce or prevent any pain you might have with the injection.

PGR2026-00039
Biocon Ex.1065
Page 578 of 595

wet AMD

Patients with wet AMD will be treated with one injection per month for three consecutive doses, followed by one injection every two months.

After the first 12 months of treatment with Eylea, the treatment interval may be extended based on your doctor's examination.

Unless you experience any problems or are advised differently by your doctor, there is no need for you to see your doctor between the injections.

Macular oedema secondary to RVO (branch RVO or central RVO)

Your doctor will determine the most appropriate treatment schedule for you. You will start your treatment with a series of monthly Eylea injections.

The interval between two injections should not be shorter than one month.

Your doctor may decide to stop treatment with Eylea, if you are not benefiting from continued treatment.

Your treatment will continue with monthly injections until your condition is stable. Three or more monthly injections may be needed.

Your doctor will monitor your response to treatment and may continue your treatment by gradually increasing the interval between your injections to maintain a stable condition. If your condition starts to worsen with a longer treatment interval, your doctor will shorten the interval accordingly.

Based on your response to treatment your doctor will decide on the schedule for follow up examinations and treatments.

Diabetic macular oedema (DME)

Patients with DME will be treated with one injection per month for the first five consecutive doses followed by one injection every two months thereafter.

Unless you experience any problems or are advised differently by your doctor, there is no need for you to see your doctor between the injections.

After the first 12 months of treatment with Eylea, the treatment interval may be extended based on your doctor's examination. Your doctor will decide on the schedule for follow up examinations.

Your doctor may decide to stop treatment with Eylea if it is determined that you are not benefiting from continued treatment.

Myopic CNV

Patients with myopic CNV will be treated with one single injection. You will receive further injections only if your doctor's examinations reveal that your condition has not improved.

The interval between two injections should not be shorter than one month.

If your condition goes away and then comes back, your doctor may re-start the treatment.

Your doctor will decide on the schedule for follow up examinations.

PGR2026-00039
Biocon Ex.1065
Page 579 of 595

If a dose of Eylea is missed
Make a new appointment for an examination and injection.

Stopping treatment with Eylea
Consult your doctor before stopping the treatment.

If you have any further questions about the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Allergic reactions (hypersensitivity) could potentially occur. **These may be serious and require that you contact your doctor immediately.**

With administration of Eylea, there may be some side effects affecting the eyes which are due to the injection procedure. Some of these may be **serious** and include **blindness**, **a serious infection or inflammation inside the eye** (endophthalmitis), **detachment, tear or bleeding of the light-sensitive layer at the back of the eye** (retinal detachment or tear), **clouding of the lens** (cataract), **bleeding in the eye** (vitreous haemorrhage), **detachment of the gel-like substance inside the eye from the retina** (vitreous detachment) and **increase of pressure inside the eye**, see section 2. These serious side effects affecting the eyes occurred in less than 1 in 1,900 injections in clinical studies.

If you experience a sudden decrease in vision, or an increase in pain and redness in your eye after your injection, **contact your doctor immediately**.

List of side effects reported
The following is a list of the side effects reported to be possibly related to the injection procedure or to the medicine. Please do not get alarmed, you might not experience any of these. Always discuss any suspected side effects with your doctor.

Very common side effects *(may affect more than 1 in 10 people):*
- deterioration of eyesight
- bloodshot eye caused by bleeding from small blood vessels in the outer layers of the eye
- eye pain

Common side effects *(may affect up to 1 in 10 people):*
- detachment or tear of one of the layers in the back of the eye, resulting in flashes of light with floaters sometimes progressing to a loss of vision (retinal pigment epithelial tear* /detachment, retinal detachment/tear)
- degeneration of the retina (causing disturbed vision)
- bleeding in the eye (vitreous haemorrhage)
- certain forms of clouding of the lens (cataract)
- damage to the front layer of the eyeball (the cornea)
- increase in eye pressure
- moving spots in vision (floaters)
- detachment of the gel-like substance inside the eye from the retina (vitreous detachment, resulting in flashes of light with floaters)
- a feeling of having something in the eye
- increased tear production
- swelling of the eyelid
- bleeding at the injection site
- redness of the eye

* Conditions known to be associated with wet AMD; observed in wet AMD patients only.

PGR2026-00039
Biocon Ex.1065
Page 580 of 595

Uncommon side effects *(may affect up to 1 in 100 people):*
- allergic reactions (hypersensitivity)
- serious inflammation or infection inside the eye (endophthalmitis)
- inflammation in the iris or other parts of the eye (iritis, uveitis, iridocyclitis, anterior chamber flare)
- abnormal sensation in the eye
- eyelid irritation
- swelling of the front layer of the eyeball (cornea)

Rare side effects *(may affect up to 1 in 1,000 people):*
- blindness
- clouding of the lens due to injury (traumatic cataract)
- inflammation of the gel-like substance inside the eye
- pus in the eye

In the clinical trials, there was an increased incidence of bleeding from small blood vessels in the outer layers of the eye (conjunctival haemorrhage) in patients with wet AMD receiving blood thinners. This increased incidence was comparable between patients treated with ranibizumab and Eylea.

The systemic use of VEGF inhibitors, substances similar to those contained in Eylea, is potentially related to the risk of blood clots blocking blood vessels (arterial thromboembolic events) which may lead to heart attack or stroke. There is a theoretical risk of such events following injection of Eylea into the eye.

As with all therapeutic proteins, there is a possibility for an immune reaction (formation of antibodies) with Eylea.

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Eylea

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the carton and label after EXP. The expiry date refers to the last day of that month.
- Store in a refrigerator (2°C to 8°C). Do not freeze.
- Prior to usage, the unopened blister may be stored at room temperature (below 25°C) for up to 24 hours.
- Keep the pre-filled syringe blister in its outer carton in order to protect from light.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away any medicines you no longer use. These measures will help protect the environment.

PGR2026-00039
Biocon Ex.1065
Page 581 of 595

6. Contents of the pack and other information

What Eylea contains
- The active substance is: aflibercept. One pre-filled syringe contains 90 microlitres, equivalent to 3.6 mg aflibercept. One pre-filled syringe delivers a dose of 2 mg aflibercept in 50 microlitres.
- The other ingredients are: polysorbate 20, sodium dihydrogen phosphate monohydrate (for pH adjustment), disodium hydrogen phosphate heptahydrate (for pH adjustment), sodium chloride, sucrose, water for injection.

What Eylea looks like and contents of the pack
Eylea is a solution for injection (injection) in a pre-filled syringe (3.6 mg/90 microlitres). The solution is colourless to pale yellow.
Pack size of 1.

Marketing Authorisation Holder
Bayer Pharma AG
D-13342 Berlin
Germany

Manufacturer
GP Grenzach Produktions GmbH
Emil-Barell-Straße 7
D-79639 Grenzach-Wyhlen
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België / Belgique / Belgien
Bayer SA-NV
Tél/Tel: +32-(0)2-535 63 11
България
Байер България ЕООД
Тел: +359-(0)2-81 401 01
Česká republika
Bayer s.r.o.
Tel: +420-266 101 111
Danmark
Bayer A/S
Tlf: +45-45 235 000
Deutschland
Bayer Vital GmbH
Tel: +49-(0)214-30 513 48
Eesti
Bayer OÜ
Tel: +372-655 85 65
Ελλάδα
Bayer Ελλάς ABEE
Τηλ: +30-210-618 75 00
España
Bayer Hispania S.L.
Tel: +34-93-495 65 00
Lietuva
UAB Bayer
Tel: +370-5-233 68 68
Luxembourg / Luxemburg
Bayer SA-NV
Tél/Tel: +32-(0)2-535 63 11
Magyarország
Bayer Hungária KFT
Tel: +36-1-487 4100
Malta
Alfred Gera and Sons Ltd.
Tel: +356-21 44 62 05
Nederland
Bayer B.V.
Tel: +31–(0)297-28 06 66
Norge
Bayer AS
Tlf: +47-23 13 05 00
Österreich
Bayer Austria Ges. m. b. H.
Tel: +43-(0)1-711 460
Polska
Bayer Sp. z o.o.
Tel: +48-22-572 35 00

PGR2026-00039
Biocon Ex.1065
Page 582 of 595

France
Bayer HealthCare
Tél (N° vert): +33-(0)800 87 54 54
Hrvatska
Bayer d.o.o.
Tel: + 385-(0)1-6599 900
Ireland
Bayer Limited
Tel: +353-(0)1-2999 313
Ísland
Icepharma hf.
Sími: +354-540 80 00
Italia
Bayer S.p.A.
Tel: +39-02-3978 1
Κύπρος
NOVAGEM Limited
Τηλ: +357-22-48 38 58
Latvija
SIA Bayer
Tel: +371-67 84 55 63

Portugal
Bayer Portugal S.A
Tel: +351-21-416 42 00
România
SC Bayer SRL
Tel: +40-(0)21-528 59 00
Slovenija
Bayer d. o. o.
Tel: +386-(0)1-58 14 400
Slovenská republika
Bayer, spol. s r.o.
Tel: +421-(0)2-59 21 31 11
Suomi/Finland
Bayer Oy
Puh/Tel: +358-(0)20-78521
Sverige
Bayer AB
Tel: +46-(0)8-580 223 00
United Kingdom
Bayer plc
Tel: +44-(0)1635-563000

This leaflet was last revised in {MM/YYYY}

Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu.

<----------

The following information is intended for healthcare professionals only:

Each pre-filled syringe should only be used for the treatment of a single eye.
Do not open the sterile pre-filled blister outside the clean administration room.

The solution should be inspected visually for any foreign particulate matter and/or discolouration or any variation in physical appearance prior to administration. In the event of either being observed, discard the medicinal product.

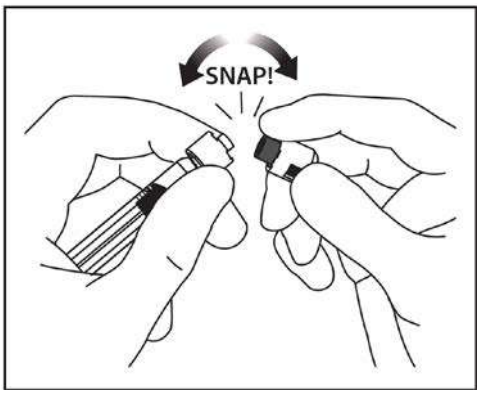
Prior to usage, the unopened blister of Eylea may be kept at room temperature (below 25°C) for up to 24 hours. After opening the blister, proceed under aseptic conditions.
For the intravitreal injection, a 30 G x ½ inch injection needle should be used.

Instructions for use of pre-filled syringe:

1. When ready to administer Eylea, open the carton and remove the sterilized blister. Carefully peel open the blister ensuring the sterility of its contents. Keep the syringe in the sterile tray until you are ready for assembly.
2. Using aseptic technique, remove the syringe from the sterilized blister.

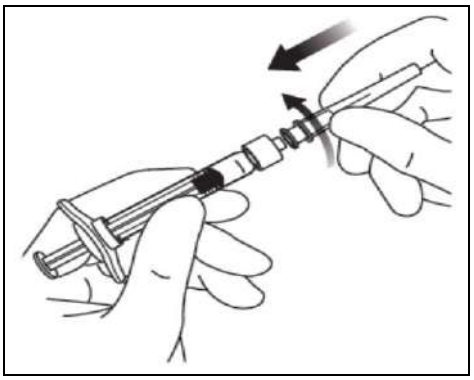
PGR2026-00039
Biocon Ex.1065
Page 583 of 595

3. To remove the syringe cap, hold the syringe in one hand while using the other hand to grasp the syringe cap with the thumb and fore finger. Please note: You should snap off (do not turn or twist), the syringe cap.

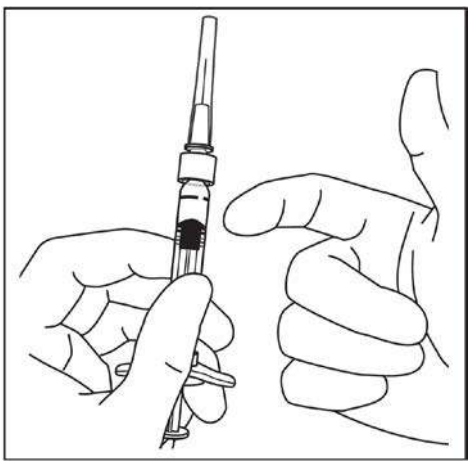


4. To avoid compromising the sterility of the product, do not pull back on the plunger.

5. Using aseptic technique, firmly twist the injection needle onto the Luer-lock syringe tip.

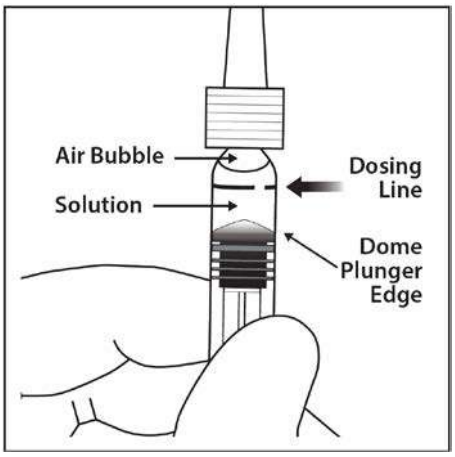


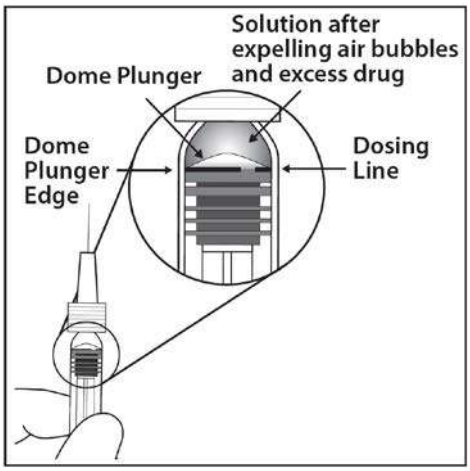
6. Holding the syringe with the needle pointing up, check the syringe for bubbles. If there are bubbles, gently tap the syringe with your finger until the bubbles rise to the top.



7. To eliminate all bubbles and to expel excess medicinal product, slowly depress the plunger to align the cylindrical base of the dome plunger with the black dosing line on the syringe (equivalent to 50 microlitres).

PGR2026-00039
Biocon Ex.1065
Page 584 of 595





8. The pre-filled syringe is for single use only.

   Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

PGR2026-00039
Biocon Ex.1065
Page 585 of 595

Package Leaflet: Information for the patient

Eylea 40 mg/ml solution for injection in a vial
Aflibercept

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Eylea is and what it is used for
2. What you need to know before you are given Eylea
3. How you will be given Eylea
4. Possible side effects
5. How to store Eylea
6. Contents of the pack and other information

1. What Eylea is and what it is used for

Eylea is a solution which is injected into the eye to treat eye conditions in adults called

- neovascular (wet) age-related macular degeneration (wet AMD),
- impaired vision due to macular oedema secondary to retinal vein occlusion (branch RVO (BRVO) or central RVO (CRVO)),
- impaired vision due to diabetic macular oedema (DME),
- impaired vision due to myopic choroidal neovascularisation (myopic CNV).

Aflibercept, the active substance in Eylea, blocks the activity of a group of factors, known as Vascular Endothelial Growth Factor A (VEGF-A) and Placental Growth Factor (PlGF).

In patients with wet AMD and myopic CNV, these factors, in excess are involved in the abnormal formation of new blood vessels in the eye. These new blood vessels can cause the leak of blood components into the eye and eventual damage to tissues in the eye responsible for vision.

In patients with CRVO, a blockage occurs in the main blood vessel that transports blood away from the retina. VEGF levels are elevated in response causing the leakage of fluid into the retina and thereby causing a swelling of the macula, (the portion of the retina responsible for fine vision), which is called macular oedema. When the macula swells with fluid, central vision becomes blurry.

In patients with BRVO, one or more branches of the main blood vessel that transports blood away from the retina is blocked. VEGF levels are elevated in response causing the leakage of fluid into the retina and thereby causing macular oedema.

PGR2026-00039
Biocon Ex.1065
Page 586 of 595

Diabetic macular oedema is a swelling of the retina occurring in patients with diabetes due to leaking of fluid from blood vessels within the macula. The macula is the portion of retina responsible for fine vision. When the macula swells with fluid, central vision becomes blurry.

Eylea has been shown to stop the growth of new abnormal blood vessels in the eye which often leak fluid or bleed. Eylea can help to stabilise, and in many cases, improve the vision loss related to wet AMD, CRVO, BRVO, DME and myopic CNV.

2. What you need to know before you are given Eylea

You will not be given Eylea:
- if you are allergic to aflibercept or any of the other ingredients of this medicine (listed in section 6).
- if you have an active or suspected infection in or around the eye (ocular or periocular infection).
- if you have severe inflammation of the eye (indicated by pain or redness).

Warnings and precautions

Talk to your doctor before you are given Eylea:

- if you have glaucoma.
- if you have a history of seeing flashes of light or floaters and if you have a sudden increase of size and number of floaters.
- if surgery was performed or is planned on your eye within the previous or next four weeks.
- if you have a severe form of CRVO or BRVO (ischaemic CRVO or BRVO), treatment with Eylea is not recommended.

Furthermore, it is important for you to know that:

- the safety and efficacy of Eylea when administered to both eyes at the same time has not been studied and if used in this way may lead to an increased risk of experiencing side effects.
- injections with Eylea may cause an increase in eye pressure (intraocular pressure) in some patients within 60 minutes of the injection. Your doctor will monitor this after each injection.
- if you develop an infection or inflammation inside the eye (endophthalmitis) or other complications, you may have eye pain or increased discomfort, worsening eye redness, blurred or decreased vision, and increased sensitivity to light. It is important to have any symptoms diagnosed and treated as soon as possible.
- your doctor will check whether you have other risk factors that may increase the chance of a tear or detachment of one of the layers at the back of the eye (retinal detachment or tear, and retinal pigment epithelial detachment or tear), in which case Eylea must be given with caution.
- Eylea should not be used in pregnancy unless the potential benefit outweighs the potential risk to the unborn child.
- women of childbearing potential have to use effective contraception during treatment and for at least three further months after the last injection of Eylea.

The systemic use of VEGF inhibitors, substances similar to those contained in Eylea, is potentially related to the risk of blood clots blocking blood vessels (arterial thromboembolic events) which may lead to heart attack or stroke. There is a theoretical risk of such events following injection of Eylea into the eye. There are limited data on safety in treating patients with CRVO, BRVO, DME and myopic CNV who have had a stroke or a mini-stroke (transient ischaemic attack) or a heart attack within the last 6 months. If any of these apply to you, Eylea will be given with caution.

There is only limited experience in the treatment of
- patients with DME due to type I diabetes.
- diabetics with very high average blood sugar values (HbA1c over 12%).

PGR2026-00039
Biocon Ex.1065
Page 587 of 595

- diabetics with an eye disease caused by diabetes called proliferative diabetic retinopathy.

There is no experience in the treatment of
- patients with acute infections.
- patients with other eye conditions such as a detachment of the retina or a hole in the macula.
- diabetics with uncontrolled high blood pressure.
- non-Asian patients with myopic CNV.
- patients previously treated for myopic CNV.
- patients with damage outside the central part of the macula (extrafoveal lesions) for myopic CNV.

If any of the above applies to you, your doctor will consider this lack of information when treating you with Eylea.

Children and adolescents
The use of Eylea in children or adolescents under 18 has not been studied because wet AMD, CRVO, BRVO, DME and myopic CNV occur mainly in adults. Therefore, its use in this age group is not relevant.

Other medicines and Eylea
Tell your doctor if you are using, have recently used or might use any other medicines.

Pregnancy and breastfeeding
- Women of childbearing potential have to use effective contraception during treatment and for at least three further months after the last injection of Eylea.

- There is no experience of using Eylea in pregnant women. Eylea should not be used during pregnancy unless the potential benefit outweighs the potential risk to the unborn child. If you are pregnant or planning to become pregnant, discuss this with your doctor before treatment with Eylea.

- Eylea is not recommended during breastfeeding as it is not known whether Eylea passes into human milk. Ask your doctor for advice before starting Eylea treatment.

Driving and using machines
After your injection with Eylea, you may experience some temporary visual disturbances. Do not drive or use machines as long as these last.

Important information about some of the ingredients of Eylea
This medicine contains less than 1 mmol (23 mg) of sodium per dose which means it is essentially "sodium-free".

3. How you will be given Eylea

A doctor experienced in giving eye injections will inject Eylea into your eye under aseptic (clean and sterile) conditions.

The recommended dose is 2 mg aflibercept (50 microlitres).
Eylea is given as an injection into your eye (intravitreal injection).

Before the injection your doctor will use a disinfectant eyewash to clean your eye carefully to prevent infection. Your doctor will also give you a local anaesthetic to reduce or prevent any pain you might have with the injection.

PGR2026-00039
Biocon Ex.1065
Page 588 of 595

wet AMD

Patients with wet AMD will be treated with one injection per month for three consecutive doses, followed by one injection every two months.

After the first 12 months of treatment with Eylea, the treatment interval may be extended based on your doctor's examination.

Unless you experience any problems or are advised differently by your doctor, there is no need for you to see your doctor between the injections.

Macular oedema secondary to RVO (branch RVO or central RVO)

Your doctor will determine the most appropriate treatment schedule for you. You will start your treatment with a series of monthly Eylea injections.

The interval between two injections should not be shorter than one month.

Your doctor may decide to stop treatment with Eylea, if you are not benefiting from continued treatment.

Your treatment will continue with monthly injections until your condition is stable. Three or more monthly injections may be needed.

Your doctor will monitor your response to treatment and may continue your treatment by gradually increasing the interval between your injections to maintain a stable condition. If your condition starts to worsen with a longer treatment interval, your doctor will shorten the interval accordingly.

Based on your response to treatment your doctor will decide on the schedule for follow up examinations and treatments.

Diabetic macular oedema (DME)

Patients with DME will be treated with one injection per month for the first five consecutive doses followed by one injection every two months thereafter.

Unless you experience any problems or are advised differently by your doctor, there is no need for you to see your doctor between the injections.

After the first 12 months of treatment with Eylea, the treatment interval may be extended based on your doctor's examination. Your doctor will decide on the schedule for follow up examinations.

Your doctor may decide to stop treatment with Eylea if it is determined that you are not benefiting from continued treatment.

Myopic CNV

Patients with myopic CNV will be treated with one single injection. You will receive further injections only if your doctor's examinations reveal that your condition has not improved..

The interval between two injections should not be shorter than one month.

If your condition goes away and then comes back, your doctor may re-start the treatment.

Your doctor will decide on the schedule for follow up examinations.

PGR2026-00039
Biocon Ex.1065
Page 589 of 595

If a dose of Eylea is missed
Make a new appointment for an examination and injection.

Stopping treatment with Eylea
Consult your doctor before stopping the treatment.

If you have any further questions about the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Allergic reactions (hypersensitivity) could potentially occur. **These may be serious and require that you contact your doctor immediately.**

With administration of Eylea, there may be some side effects affecting the eyes which are due to the injection procedure. Some of these may be **serious** and include **blindness**, **a serious infection or inflammation inside the eye** (endophthalmitis), **detachment, tear or bleeding of the light-sensitive layer at the back of the eye** (retinal detachment or tear), **clouding of the lens** (cataract), **bleeding in the eye** (vitreous haemorrhage), **detachment of the gel-like substance inside the eye from the retina** (vitreous detachment) and **increase of pressure inside the eye**, see section 2. These serious side effects affecting the eyes occurred in less than 1 in 1,900 injections in clinical studies.

If you experience a sudden decrease in vision, or an increase in pain and redness in your eye after your injection, **contact your doctor immediately**.

List of side effects reported
The following is a list of the side effects reported to be possibly related to the injection procedure or to the medicine. Please do not get alarmed, you might not experience any of these. Always discuss any suspected side effects with your doctor.

Very common side effects *(may affect more than 1 in 10 people):*
- deterioration of eyesight
- bloodshot eye caused by bleeding from small blood vessels in the outer layers of the eye
- eye pain

Common side effects *(may affect up to 1 in 10 people):*
- detachment or tear of one of the layers in the back of the eye, resulting in flashes of light with floaters sometimes progressing to a loss of vision (retinal pigment epithelial tear* /detachment, retinal detachment/tear)
- degeneration of the retina (causing disturbed vision)
- bleeding in the eye (vitreous haemorrhage)
- certain forms of clouding of the lens (cataract)
- damage to the front layer of the eyeball (the cornea)
- increase in eye pressure
- moving spots in vision (floaters)
- detachment of the gel-like substance inside the eye from the retina (vitreous detachment, resulting in flashes of light with floaters)
- a feeling of having something in the eye
- increased tear production
- swelling of the eyelid
- bleeding at the injection site
- redness of the eye

PGR2026-00039
Biocon Ex.1065
Page 590 of 595

* Conditions known to be associated with wet AMD; observed in wet AMD patients only.

Uncommon side effects *(may affect up to 1 in 100 people):*
- allergic reactions (hypersensitivity)
- serious inflammation or infection inside the eye (endophthalmitis)
- inflammation in the iris or other parts of the eye (iritis, uvetitis, iridocyclitis, anterior chamber flare)
- abnormal sensation in the eye
- eyelid irritation
- swelling of the front layer of the eyeball (cornea)

Rare side effects *(may affect up to 1 in 1,000 people):*
- blindness
- clouding of the lens due to injury (traumatic cataract),
- inflammation of the gel-like substance inside the eye
- pus in the eye

In the clinical trials, there was an increased incidence of bleeding from small blood vessels in the outer layers of the eye (conjunctival haemorrhage) in patients with wet AMD receiving blood thinners. This increased incidence was comparable between patients treated with ranibizumab and Eylea.

The systemic use of VEGF inhibitors, substances similar to those contained in Eylea, is potentially related to the risk of blood clots blocking blood vessels (arterial thromboembolic events) which may lead to heart attack or stroke. There is a theoretical risk of such events following injection of Eylea into the eye.

As with all therapeutic proteins, there is a possibility for an immune reaction (formation of antibodies) with Eylea.

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Eylea

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the carton and label after EXP. The expiry date refers to the last day of that month.
- Store in a refrigerator (2°C to 8°C). Do not freeze.
- Prior to usage, the unopened vial may be stored at room temperature (below 25°C) for up to 24 hours.
- Keep the vial in its outer carton in order to protect from light.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away any medicines you no longer use. These measures will help protect the environment.

PGR2026-00039
Biocon Ex.1065
Page 591 of 595

6. Contents of the pack and other information

What Eylea contains
- The active substance is: aflibercept. One vial contains 100 microlitres, equivalent to 4 mg aflibercept. One vial delivers a dose of 2 mg aflibercept in 50 microlitres.
- The other ingredients are: polysorbate 20, sodium dihydrogen phosphate monohydrate (for pH adjustment), disodium hydrogen phosphate heptahydrate (for pH adjustment), sodium chloride, sucrose, water for injection.

What Eylea looks like and contents of the pack
Eylea is a solution for injection (injection) in a vial (4 mg/100 microlitres). The solution is colourless to pale yellow.
Pack size of 1.

Marketing Authorisation Holder
Bayer Pharma AG
D-13342 Berlin
Germany

Manufacturer
Bayer Pharma AG
Müllerstraße 178
D-13353 Berlin
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België / Belgique / Belgien
Bayer SA-NV
Tél/Tel: +32-(0)2-535 63 11
България
Байер България ЕООД
Тел: +359-(0)2-81 401 01
Česká republika
Bayer s.r.o.
Tel: +420-266 101 111
Danmark
Bayer A/S
Tlf: +45-45 235 000
Deutschland
Bayer Vital GmbH
Tel: +49-(0)214-30 513 48
Eesti
Bayer OÜ
Tel: +372-655 85 65
Ελλάδα
Bayer Ελλάς ABEE
Τηλ: +30-210-618 75 00
España
Bayer Hispania S.L.
Tel: +34-93-495 65 00
Lietuva
UAB Bayer
Tel: +370-5-233 68 68
Luxembourg / Luxemburg
Bayer SA-NV
Tél/Tel: +32-(0)2-535 63 11
Magyarország
Bayer Hungária KFT
Tel: +36-1-487 4100
Malta
Alfred Gera and Sons Ltd.
Tel: +356-21 44 62 05
Nederland
Bayer B.V.
Tel: +31–(0)297-28 06 66
Norge
Bayer AS
Tlf: +47-23 13 05 00
Österreich
Bayer Austria Ges. m. b. H.
Tel: +43-(0)1-711 460
Polska
Bayer Sp. z o.o.
Tel: +48-22-572 35 00

PGR2026-00039
Biocon Ex.1065
Page 592 of 595

France
Bayer HealthCare
Tél (N° vert): +33-(0)800 87 54 54
Hrvatska
Bayer d.o.o.
Tel: + 385-(0)1-6599 900
Ireland
Bayer Limited
Tel: +353-(0)1-2999 313
Ísland
Icepharma hf.
Sími: +354-540 80 00
Italia
Bayer S.p.A.
Tel: +39-02-3978 1
Κύπρος
NOVAGEM Limited
Τηλ: +357-22-48 38 58
Latvija
SIA Bayer
Tel: +371-67 84 55 63

Portugal
Bayer Portugal S.A
Tel: +351-21-416 42 00
România
SC Bayer SRL
Tel: +40-(0)21-528 59 00
Slovenija
Bayer d. o. o.
Tel: +386-(0)1-58 14 400
Slovenská republika
Bayer, spol. s r.o.
Tel: +421-(0)2-59 21 31 11
Suomi/Finland
Bayer Oy
Puh/Tel: +358-(0)20-78521
Sverige
Bayer AB
Tel: +46-(0)8-580 223 00
United Kingdom
Bayer plc
Tel: +44-(0)1635-563000

This leaflet was last revised in {MM/YYYY}

Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu.

<----------

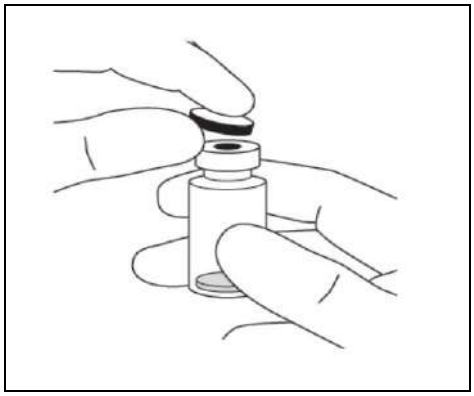
The following information is intended for healthcare professionals only:

Each vial should only be used for the treatment of a single eye.
The solution should be inspected visually for any foreign particulate matter and/or discolouration or any variation in physical appearance prior to administration. In the event of either being observed, discard the medicinal product.

Prior to usage, the unopened vial of Eylea may be kept at room temperature (below 25°C) for up to 24 hours. After opening the vial, proceed under aseptic conditions.
For the intravitreal injection, a 30 G x ½ inch injection needle should be used.

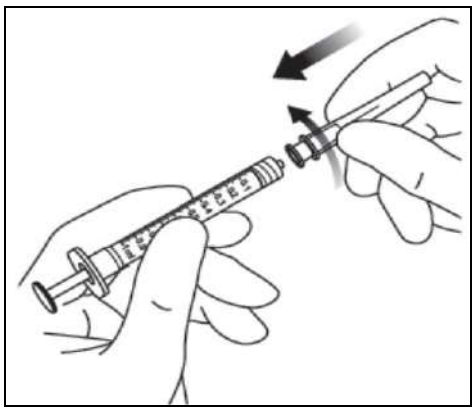
Instructions for use of vial:

1. Remove the plastic cap and disinfect the outer part of the rubber stopper of the vial.

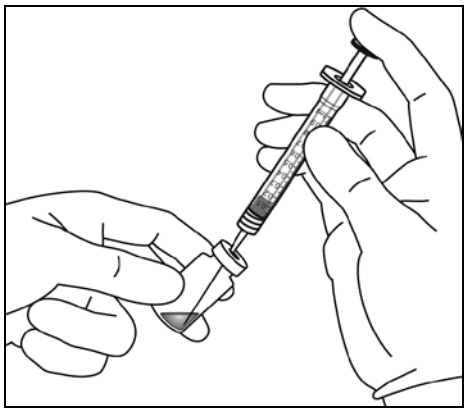


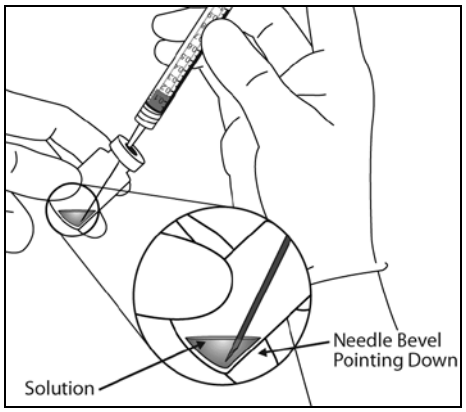
PGR2026-00039
Biocon Ex.1065
Page 593 of 595

2. Attach the 18 G, 5-micron filter needle supplied in the carton to a 1 ml sterile Luer-lock syringe.

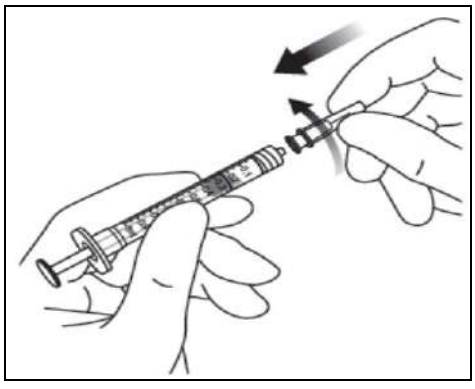


3. Push the filter needle into the centre of the vial stopper until the needle is completely inserted into the vial and the tip touches the bottom or bottom edge of the vial.
4. Using aseptic technique withdraw all of the Eylea vial contents into the syringe, keeping the vial in an upright position, slightly inclined to ease complete withdrawal. To deter the introduction of air, ensure the bevel of the filter needle is submerged into the liquid. Continue to tilt the vial during withdrawal keeping the bevel of the filter needle submerged in the liquid.



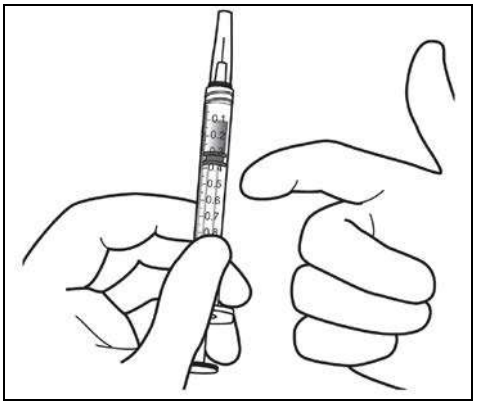


5. Ensure that the plunger rod is drawn sufficiently back when emptying the vial in order to completely empty the filter needle.
6. Remove the filter needle and properly dispose of it.
   Note: Filter needle is not to be used for intravitreal injection.
7. Using aseptic technique, firmly twist a 30 G x ½ inch injection needle onto the Luer-lock syringe tip.

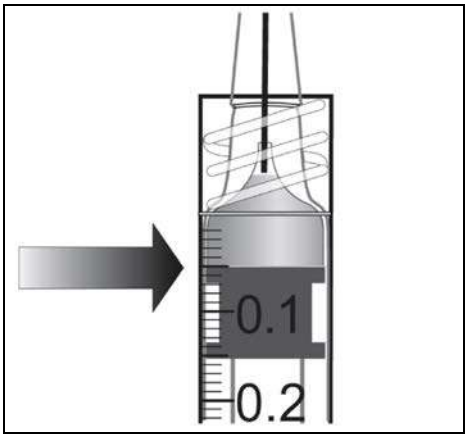


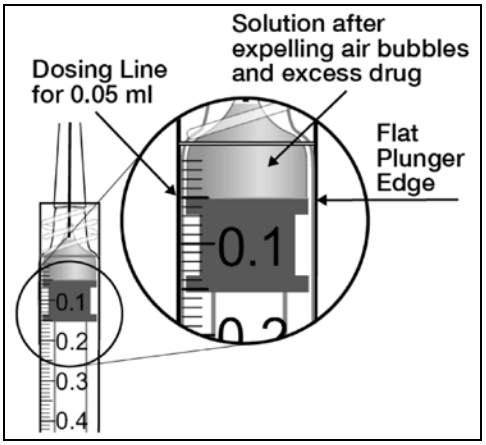
PGR2026-00039
Biocon Ex.1065
Page 594 of 595

8 Holding the syringe with the needle pointing up, check the syringe for bubbles. If there are bubbles, gently tap the syringe with your finger until the bubbles rise to the top.



9. Eliminate all bubbles and expel excess medicinal product by slowly depressing the plunger so that the plunger tip aligns with the line that marks 0.05 ml on the syringe.





10. The vial is for single use only.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

PGR2026-00039
Biocon Ex.1065
Page 595 of 595