UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

BIOCON BIOLOGICS, INC. and
BIOCON BIOLOGICS LIMITED,
Petitioners,

v.

REGENERON PHARMACEUTICALS, INC.,
Patent Owner

U.S. Patent No. 12,168,036 to Graham

Issue Date: December 12, 2024

Title: Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins

Post Grant Review No. PGR2026-00039

DECLARATION OF JAY STEWART M.D.

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I, Jay Stewart, M.D., declare as follows:

I. INTRODUCTION

1. I have been retained by the law firm Winston & Strawn LLP on behalf of Biocon Biologics, Inc. and Biocon Biologics Limited, (hereinafter, collectively, "Biocon" or "Petitioner") to provide expert opinions concerning the invalidity of U.S. Patent No. 12,168,036 ("the '036 patent").

2. I understand that Alvotech USA, Inc. and Alvotech hf. (together, "Alvotech") filed a post grant review petition ("Alvotech's petition," Ex. 1069) against claims 1-38 of the '036 patent, and the Patent Trial and Appeal Board instituted Alvotech's petition on March 3, 2026. *See* Ex. 1070, *Alvotech USA, Inc. et al v. Regeneron Pharms. Inc.*, PGR2025-00085, Paper 10 ("Alvotech PGR"). With its PGR petition, I understand that Alvotech submitted a declaration from Dr. Donald Joseph D'Amico, M.D. Ex. 1003 ("D'Amico Declaration"). I have reviewed this declaration in its entirety and, as discussed below, I incorporate it in full here.

3. I understand that Biocon's petition for post grant review requests review and invalidation of the same claims of the '036 patent as the Alvotech PGR and on the same grounds as those put forth in the Alvotech PGR. I further understand that Biocon requests to join the Alvotech PGR. I submit this declaration in support of Biocon's petition for post grant review.

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4. My opinions in this declaration are based on the documents I reviewed along with my professional training, experience and knowledge that I have acquired working in the field of Ophthalmology over the past 22 years. I am being compensated for my services as an expert at my standard consulting rate of $900 per hour. My compensation is in no way contingent on the substance of my opinions or the outcome of this case.

II. BACKGROUND AND QUALIFICATIONS

5. I am an Ophthalmologist specializing in retina and vitreous Diseases. My education and experience are described more fully in my curriculum vitae, which is attached to this declaration as **Exhibit A**. I highlight certain achievements here.

6. I received my Bachelor of Science degree in 1995 from Harvard College and my Medical Degree from Harvard Medical School in 1999. I completed my residency in Ophthalmology from University of California – San Fransico in 2003. I completed a fellowship in Vitreoretinal Diseases and Surgery from the University of Southern California in 2005. I am board certified in Ophthalmology by the American Board of Ophthalmology. I have been board certified since 2004 and licensed to practice in the state of California since 2001.

7. I have over 22 years of clinical experience in ophthalmology, which

is particularly relevant to the issues discussed and incorporated below. I specialize in the care of patients with vitreoretinal surgical diseases and medical retinal diseases including angiogenic eye disorders. More specifically, my expertise includes conditions such as age-related macular degeneration, diabetic retinopathy, ocular trauma, retinal detachment, retinal vascular diseases and uveitis.

8. Over the course of more than two decades of treating patients, I have had the opportunity to utilize different treatment options for patients with vitreoretinal and angiogenic eye disorders, including anti-VEGF intravitreal injections. I have experience treating patients with all the currently available anti-VEGF treatments, including off-label Avastin® (bevacizumab), Lucentis® (ranibizumab), Eylea® (aflibercept, 2 mg and 4 mg) and Eylea HD® (aflibercept, 8 mg), and Vabysmo® (faricimab-svoa 6 mg).

9. I currently practice medicine at the University of California – San Francisco. In this role, I serve as the Subspecialty Medical Director for Retina at UCSF Health and as the Chief of Ophthalmology at Zuckerberg San Francisco General Hospital.

10. I also conduct research regarding age-related macular degeneration, diabetic retinopathy, drug delivery to the eye, and the permeability

and biomechanics of eye tissues, including anti-VEGF treatments for angiogenic eye disorders.

11. I have published 178 peer-reviewed manuscripts and over 100 conference abstracts. I serve as the Editor-in-Chief of the *American Journal of Ophthalmology Case Reports* and as an Associate Editor for *Ophthalmology Science*. Additionally, I perform peer reviews for numerous other journals in the field of ophthalmology.

12. I am a member of the American Academy of Ophthalmology, American Society of Retina Specialists, the Retina Society, and the Macula Society. I was awarded the vitreoretinal surgery award from the Ronald G. Michels Fellowship Foundation, which funds outstanding young scholars.

III. PERSON OF ORDINARY SKILL IN THE ART

13. I have been informed that the claims of the ’036 Patent are to be interpreted as a POSA would have understood them at the relevant time, which I have been asked to assume is May 10, 2018.

14. I understand that the D’Amico Declaration defines a POSA as follows:

> A POSA at the time of the invention would have been a multidisciplinary team that included (1) a medical doctor in ophthalmology or a similar field with knowledge of angiogenic eye disorders, including treatments and

> dosing regimens of drugs for intravitreal injection including anti-VEGF drugs, at least several years conducting research on anti-VEGF treatments for angiogenic eye disorders, and familiarity with the pharmacological properties of anti-VEGF treatments; and (2) a Ph.D. in pharmaceutical sciences or a similar field, with at least several years of experience in the development, manufacture, and characterization of therapeutic proteins, including for example, fusion proteins or antibodies.
>
> The POSA in the field of the '036 Patent would have also had access to other individuals typically employed in developing protein active pharmaceutical ingredients and products, including those involved in upstream and downstream manufacturing, analytical chemistry, pharmacokinetics, clinical testing, pharmaceutical packaging, and regulatory affairs.

15. Given my advanced degrees, over 22 years of clinical experience in ophthalmology, and several years of research including anti-VEGF treatments for angiogenic eye disorders, I consider myself to have at least the qualifications of a person of ordinary skill in the art at the time of the alleged invention on May 10, 2018.

IV. MATERIALS CONSIDERED

16. In forming my opinions set forth expressly or incorporated in this declaration, I relied on my knowledge and professional experience as described above. In addition to reviewing the D'Amico Declaration, I also reviewed and considered in whole or in part the materials considered by Dr. D'Amico,

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including the materials listed below:

Exhibit	Description
1001	U.S. Patent No. 12,168,036 (Graham et al.)
1002	File History for U.S. Patent No. 12,168,036
1003	Declaration of Dr. Donald Joseph D'Amico
1004	Declaration of Dr. Robert J. Falconer
1005	U.S. Patent No. 7,608,261 (Furfine)
1006	U.S. Patent No. 8,921,316 (Dix)
1007	U.S. Publication No. 2016/0144025 A1 (Vitti)
1008	Center for Drug Evaluation and Research, "Clinical Pharmacology and Biopharmaceutics Review(s)" App. No. 125387Orig1s000 (2011) ("2011 Eylea® Clinical Review")
1009	Product Information EYLEA® aflibercept (rch), ("AU Eylea® Label")
1010	U.S. Publication No. 2015/0071920 A1 (Larson)
1011	U.S. Publication No. 2017/0232199 A1 (Fiedler)
1013	PTE Application U.S. Patent No. 7,374,758, (App. No. 11/016,503)
1014	Robert L. Avery, MD et al., *INTRAVITREAL INJECTION TECHNIQUE AND MONITORING Updated Guidelines of an Expert Panel,* Retina, J. Retinal and Vitreous Diseases, 34, S1-S18 (2014).
1015	Sahar Awwad et al., *Principles of Pharmacology in the Eye,* 174 Brit. J. Pharmacol. 4205 (2017).
1016	David M. Brown et al., *Intravitreal Aflibercept for Diabetic Macular Edema,* 122 American Acad. of Ophthalmology 2044 (2015).
1017	CATT Research Group, *Ranibizumab and bevacizumab for Neovascular Age-Related Macular Degeneration,* 364 NEJM 1897 (2011).
1018	Nil Celik et al., *Intraocular Pharmacokinetics of Aflibercept and Vascular Endothelial Growth Factor-A,* 56 Investigative Ophthalmology & Visual Science 5574 (2015).

Exhibit	Description
1019	Steven R. Cohen & Thomas W. Gardner, *Diabetic Retinopathy and Diabetic Macular Edema,* 55 Dev. Ophthalmol. 137 (2016).
1020	Arup Das, Paul G. McGuire & Sampathkumar Rangasamy, *Diabetic Macular Edema: Pathophysiology and Novel Therapeutic Targets*, Ophthalmology (2015).
1022	Elia J. Duh, Jennifer K. Sun & Alan W. Stitt, *Diabetic retinopathy: current understanding, mechanisms, and treatment strategies*, JCI Insight (2017).
1023	Elwes et al., *Clinical Outcomes of Switching to Aflibercept Using a pro re nata Treatment Regimen in Patients with Neovascular Age-Related Macular Degeneration Who Incompletely Responded to Ranibizumab*, 18 BMC Ophthalmology (2018).
1024	K Ghasemi Falavarjani & QD Nguyen, *Adverse Events and Complications Associated with Intravitreal Injection of Anti-VEGF Agents: a Review of Literature*, Eye (2013).
1026	Allen C. Ho et al. *Twenty-four-Month Efficacy and Safety of 0.5 mg or 2.0 mg Ranibizumab in Patients with Subfoveal Neovascular Age-Related Macular Degeneration,* 121 Ophthalmology 2181 (2014).
1029	Su-Eon Jin & Sung-Joo Hwang, *Ocular Delivery Systems for the Administration of Antibody Therapeutics*, J. Pharm. 47 Investig. 373 (2017).
1030	Lehman Brothers Presentation, 9th Annual Global Healthcare Conference, Mar. 2006
1031	Joan W. Miller, Saghar Bagheri & Demetrios GF Vavvas, *Advances in Age-related Macular Degeneration Understanding and Therapy,* 10 U.S. Ophthalmic Rev. 119 (2017).
1034	Quan Dong Nguyen, et al., *A Phase I Study of Intravitreal Vascular Endothelial Growth Factor Trap-Eye in Patients with Neovascular Age-Related Macular Degeneration*, 116 Ophthalmology 2141 (2009).
1035	Quan Dong Nguyen, et al., *Evaluation of Very High- and Very Low-Dose Intravitreal Aflibercept in Patients with Neovascular Age-Related Macular Degeneration*, 28 J. Ocular Pharmacology and Therapeutics 581 (2012).

Exhibit	Description
1037	Lorena Perez-Gutierrez & Napoleone Ferrara, *Biology and therapeutic targeting of vascular endothelial growth factor A*, Nature Reviews Molecular Cell Biology (2023).
1039	Michael W. Stewart, *Clinical and Differential Utility of VEGF Inhibitors in Wet Age-Related Macular Degeneration: Focus on Aflibercept,* 6 Clin. Ophthalmol. 1175 (2012).
1041	George Trichonas & Peter K. Kaiser, *Aflibercept for the Treatment of Age-Related Macular Degeneratio*n, 2 Ophthalmol. Ther. 88 (2013).
1042	Rohit Varma, et al., *Prevalence of and Risk Factors for Diabetic Macular Edema in the United States*, 132 JAMA Ophthalmol. 1334 (2014).
1048	Macugen® 2011 Label
1049	Beovu® 2019 Label
1050	Eylea® 2011 Label
1051	Eylea® 2012 Label
1052	Eylea® 2014 Label
1053	Eylea® 2016 Label
1054	Eylea® HD 2024 Label
1055	Lucentis® 2017 Label
1057	Vabysmo® 2022 Label
1058	Assessment Report, Eylea aflibercept, Committee for Medicinal Products for Human Use (CHMP), *European Medicines Agency Science Medicines Health, Sept. 2012*
1059	Center for Drug Evaluation and Research, "Pharmacology Review(s)" App. No. 125387Orig1s000 (2011) ("Eylea Pharmacology Review")
1060	EMA Annex
1061	Loureiro et al., *Intravitreal Injections of Bevacizumab: The Impact of Needle Size in Intraocular Pressure and Pain*, 11 J. Curr. Glaucoma Pract. 38 (2017).

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Exhibit	Description
1062	Napoleone Ferrara, *Vascular endothelial growth factor and age-related macular degeneration: from basic science to therapy*, Nature Medicine (2010).
1063	Roomasa Channa, Michael Smith & Peter A Campochiaro, *Treatment of macular edema due to retinal vein occlusions*, Clinical Ophthalmology (2011).
1064	William Rhoades et al., *Management of macular edema due to central retinal vein occlusion – The role of aflibercept*, Taiwan J. Ophthalmol (2017).
1069	*Alvotech USA Inc. et al v. Regeneron Pharms., Inc.*, PTAB-PGR2025-00085 Paper No. 1.
1070	*Alvotech USA Inc. et al v. Regeneron Pharms., Inc.*, PTAB-PGR2025-00085 Order No. 10.

V. OPINIONS

17. I have reviewed the D'Amico Declaration in full (including Sections I-XIV) and incorporate the declaration in its entirety here. I agree with the opinions and conclusions put forth in the D'Amico Declaration and am prepared to testify further on the background, opinions, and conclusions put forth in the D'Amico Declaration if asked to do so. I adopt the background, opinions and conclusions put forth in the D'Amico Declaration as my own opinion and testimony.

18. Specifically, based on the information put forth in the D'Amico Declaration, I come to the following conclusions:

- Ground 1: A POSA would have been motivated to combine Vitti, the AU Eylea® Label, and Larson with a reasonable expectation of success; and

these references teach, or at least make obvious, the methods recited in Claims 1, 4-38 of the ’036 patent.

- Ground 2: A POSA would have been motivated to combine Regeneron’s Prior Disclosures (Furfine, Dix, and the AU Eylea® Label), Fiedler, and Larson with a reasonable expectation of success; and these references teach, or at least make obvious, the methods recited in Claims 1, 4-38 of the ’036 Patent.

- Ground 4: A POSA would have been motivated to combine Vitti, the AU Eylea® Label, and Larson with the 2011 Eylea Clinical Review; these references teach, or at least make obvious, the methods recited in Claims 2 and 3 of the ’036 Patent.

- Ground 5: A POSA would have been motivated to combine Regeneron’s Prior Disclosures (Furfine, Dix, and the AU Eylea® Label), Fiedler, and Larson with the 2011 Eylea Clinical Review; and these references teach, or at least make obvious, the methods recited in Claims 2 and 3 of the ’036 Patent.

VI. CONCLUSION

19. This declaration is based on my present assessment of material and information currently available to me.

20. I understand that this declaration will be filed as evidence in a contested case before the Patent Trial and Appeal Board of the United States Patent and Trademark Office. I also understand that I may be subject to cross-examination concerning this declaration, and I will appear for cross-examination, if required of me, during the time allotted for cross-examination.

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

Date: March 30, 2026

Jay M. Stewart

Jay Stewart, MD.

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