UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SAMSUNG BIOEPIS CO., LTD.,
Petitioner,

v.

REGENERON PHARMACEUTICALS, INC.,
Patent Owner.

Case IPR2023-00739

U.S. Patent No. 10,888,601

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 10,888,601

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1001	U.S. Patent No. 10,888,601
1002	Expert Declaration of Dr. Edward Chaum in Support of Petition for *Inter Partes* Review of Patent No. 10,888,601, dated March 24, 2023 ("Chaum Decl.")
1003	Edward Chaum *Curriculum Vitae*
1004	Regillo CD, Brown DM, Abraham P, et al. Randomized, double-masked, sham-controlled trial of ranibizumab for neovascular age-related macular degeneration: PIER Study year 1. Am J Ophthalmol. 2008;145(2):239-248. ("PIER Study").
1005	Heier JS, et al., CLEAR-IT 2 Investigators. The 1-year results of CLEAR-IT 2, a phase 2 study of vascular endothelial growth factor trap-eye dosed as-needed after 12-week fixed dosing. Ophthalmology. 2011 Jun;118(6):1098-106. ("Heier 2011")
1006	Elman MJ, et al., Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. Ophthalmology. 2010 Jun;117(6):1064-1077.e35. ("Elman 2010")
1007	Heier JS, et al., Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. Ophthalmology. 2012;119(12):2537-2548. ("Heier 2012")
1008	Dixon JA, Oliver SC, Olson JL, Mandava N. VEGF Trap-Eye for the treatment of neovascular age-related macular degeneration. Expert Opin Investig Drugs. 2009;18(10):1573-1580. ("Dixon")
1009	Press Release, Enrollment Completed in Regeneron and Bayer Healthcare Phase 3 Studies of VEGF Trap-Eye in Neovascular Age-Related Macular Degeneration (Wet AMD) (September 14, 2009), https://newsroom.regeneron.com/news-releases/news-release-details/enrollment-completed-regeneron-and-bayer-healthcare-phase-3 ("2009 Press Release")
1010	WO 2006/047325 Al ("Shams")
1011	Press Release, VEGF Trap-Eye Final Phase 2 Results in Age-Related Macular Degeneration Presented at 2008 Retina Society Meeting

Exhibit	Description
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1015	Lucentis ® Original Approved Labeling (2006), available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/125156s0000_Lucentis_Prntlbl.pdf
1016	Eylea Label 2023 available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/125387s075lbl.pdf
1017	Comparison of Age-related Macular Degeneration Treatments Trials: Lucentis-Avastin Trial (NCT00593450), available at: https://clinicaltrials.gov/ct2/show/NCT00593450
1018	Web Archive of the CATT Patient Eligibility Criteria (July 13, 2010), available at: https://web.archive.org/web/20100713035617/http://www.med.upenn.edu/cpob/studies/documents/CATTEligibilityCriteria_000.pdf ("CATT Study")
1019	Regillo CD, Brown DM, Abraham P, et al. Randomized, double-masked, sham-controlled trial of ranibizumab for neovascular age-related macular degeneration: PIER Study year 1. Am J Ophthalmol. 2008;145(2):239-248, published December 3, 2007, available at https://www.ajo.com/article/S0002-9394(07)00881-1/fulltext ("PIER AJO Website")

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1022	ClinicalTrials.gov About the Results Database, available at: https://clinicaltrials.gov/ct2/about-site/results
1023	Do DV et al., Incorporating the Latest Findings From Clinical Trials Into the Management of Diabetic Retinopathy for the Comprehensive Ophthalmologist (October 25, 2009), available at: https://aao.scientificposters.com/epsView.cfm?xvTgEJiNo9X9FYlsrbBjRKZ9ICSVGWMJbEunzn9LGZqaMHKIw4tNfg%3D%3D ("Do workshop 2009")
1024	Pai A, El Shafei MM, Mohammed OA, Al Hashimi M., Current concepts in intravitreal drug therapy for diabetic retinopathy. Saudi J Ophthalmol. 2010 Oct;24(4):143-9. ("Pai 2010").
1025	Final Written Decision in *Mylan Pharmaceuticals Inc. v. Regeneron Pharmaceuticals, Inc.*, IPR2021-00881 (Paper 94) ("'338 FWD")
1026	U.S. Dep't Health & Human Servs., Nat'l Inst. Health, Nat'l Eye Inst., Diabetic Retinopathy: What You Should Know (Sept. 2015), https://www.nei.nih.gov/sites/default/files/health-pdfs/Diabetic_Retinopathy_What_You_Should_Know.pdf ("NIH DR").
1027	U.S. Dep't Health & Human Servs., Nat'l Inst. Health, Nat'l Eye Inst., Age-Related Macular Degeneration: What You Should Know (Sept. 2015), https://www.nei.nih.gov/sites/default/files/healthpdfs/WYSK_AMD_English_Sept2015_PRINT.pdf ("NIH AMD")
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1029	Holash J, Davis S, Papadopoulos N, et al. VEGF-Trap: a VEGF blocker with potent antitumor effects. Proc Natl Acad Sci U S A. 2002;99(17):11393-11398. ("Holash")
1030	Rudge JS, Thurston G, Davis S, et al. VEGF trap as a novel antiangiogenic treatment currently in clinical trials for cancer and eye diseases, and VelociGene- based discovery of the next generation of angiogenesis targets. Cold Spring Harb Symp Quant Biol. 2005;70:411-418 ("Rudge 2005")
1031	Gomez-Manzano C, Holash J, Fueyo J, et al. VEGF Trap induces antiglioma effect at different stages of disease. Neuro Oncol. 2008;10(6):940-945. ("Gomez-Manzano")
1032	U.S. Patent No. 7,531,173 ("'173 patent")
1033	Rudge JS, Holash J, Hylton D, et al. VEGF Trap complex formation measures production rates of VEGF, providing a biomarker for predicting efficacious angiogenic blockade. Proc Natl Acad Sci U S A. 2007;104(47):18363-18370. ("Rudge 2007")
1034	Li E, Donati S, Lindsley KB, Krzystolik MG, Virgili G. Treatment regimens for administration of anti-vascular endothelial growth factor agents for neovascular age-related macular degeneration. Cochrane Database Syst Rev. 2020;5(5):CD012208. ("Li 2020")
1035	Brown DM, Michels M, Kaiser PK, et al. Ranibizumab versus verteporfin photodynamic therapy for neovascular age-related macular degeneration: Two-year results of the ANCHOR study. Ophthalmology. 2009;116(1):57-65.e5. ("Brown 2009")
1036	Martin DF, Maguire MG, Fine SL, Ying GS, Jaffe GJ, Grunwald JE, et al, Comparison of Age-Related Macular Degeneration Treatments Trial (CATT) Research Group. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. Ophthalmology 2012; 119(7):1388-98 ("Martin")
1037	Chakravarthy U, Harding SP, Rogers CA, Downes SM, Lotery AJ, Wordsworth S, et al, Inhibition of VEGF in Age-related choroidal Neovascularization (IVAN) Study Investigators. Ranibizumab versus bevacizumab to treat neovascular age-related macular degeneration: one-year findings from the IVAN randomized trial. Ophthalmology 2012; 119(7):1399-411 ("Chakravarthy 2012")

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1038	Rosenfeld PJ, Brown DM, Heier JS, Boyer DS, Kaiser PK, Chung CY, et al. Ranibizumab for neovascular age-related macular degeneration. New England Journal of Medicine 2006; 355(14):1419-31 ("Rosenfeld")
1039	Heimann, H. (2007). Chapter 5 Intravitreal Injections: Techniques and Sequelae. In: Holz, F.G., Spaide, R.F. (eds) Medical Retina. Essentials in Ophthalmology. Springer, Berlin, Heidelberg. ("Heimann")
1040	Jager RD, Aiello LP, Patel SC, Cunningham ET Jr. Risks of intravitreous injection: a comprehensive review. Retina. 2004;24(5):676-698. ("Jager")
1041	Pilot Study of Intravitreal Injection of Ranibizumab for Macular Telangiectasia With Neovascularization (NCT00685854) (May 24, 2008), available at: https://clinicaltrials.gov/ct2/history/NCT00685854?V_1=View#StudyPageTop ("MACTEL Study")
1042	Ranibizumab Injections to Treat Macular Telangiectasia Without New Blood Vessel Growth (NCT00685854) (November 7, 2008), available at: https://web.archive.org/web/20081107014243/https://clinicaltrials.gov/ct2/show/NCT00685854 ("MACTEL Study Wayback Machine")
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1051	Scheduling Order (Dkt. 87) entered in *Regeneron Pharmaceuticals, Inc. v. Mylan Pharmaceuticals Inc.*, NDWV-1-22-cv-00061
1052	September 28, 2022 Status Conference Transcript entered in *Regeneron Pharmaceuticals, Inc. v. Mylan Pharmaceuticals Inc.*, NDWV-1-22-cv-00061
1053	Institution Decision in *Mylan Pharmaceuticals Inc. v. Regeneron Pharmaceuticals*, *Inc.*, IPR2022-01226 (Paper 22) ("'601 ID")
1054	Institution Decision in *Mylan Pharmaceuticals Inc. v. Regeneron Pharmaceuticals*, *Inc.*, IPR2022-01225 (Paper 21) ("'681 ID")
1055	Do DV et al., The DA VINCI Study: phase 2 primary results of VEGF Trap-Eye in patients with diabetic macular edema. Ophthalmology. 2011 Sep;118(9):1819-26, available at: https://www.aaojournal.org/article/S0161-6420(11)00177-1/fulltext ("Do 2011 AAO Website")
1056	U.S. Patent No. 9,254,338 ("'338 patent")
1057	WO 2012/097019A1 ("Yancopoulos PCT Application")

I. INTRODUCTION

Samsung Bioepis Co., Ltd. ("Petitioner") petitions for *inter partes* review ("IPR") under 35 U.S.C. §§ 311-319 and 37 C.F.R. §§ 42 et seq., seeking cancellation of claims 10-33 and 46-47 (the "Challenged Claims") of U.S. Patent No. 10,888,601 ("'601 patent") (Ex.1001), assigned to Patent Owner, Regeneron Pharmaceuticals, Inc.

The Challenged Claims are directed to treating diabetic macular edema ("DME"), diabetic retinopathy ("DR"), or DR in a patient with DME by administering aflibercept via a number of initial monthly loading doses, followed by maintenance doses administered every two months. One subset of the Challenged Claims is directed to a dosing regimen with two or more monthly loading doses followed by maintenance doses administered every two months. The other subset of Challenged Claims specify a dosing schedule of five monthly loading doses followed by maintenance doses administered every two months.

The concept of treating DR/DME by administering a number of monthly loading doses followed by less frequent maintenance doses was well-known in the prior art. *See, e.g.* Ex.1005, Heier 2011; Ex.1006, Elman 2010; Ex.1002, Chaum Declaration, ¶¶43-61. During the loading phase, an initial dose followed by sequential monthly doses were given. The purpose of the "initial intensive monthly loading dose phase" was to gain "control of neovascular leakage" by stopping the

growth of new, leaky blood vessels that cause angiogenic eye disorders. Ex.1005, Heier 2011, 1099, 1104. Thus, for most patients, the bulk of improvement generally occurred during this phase. The purpose of the subsequent maintenance phase was to maintain the improved condition while administering fewer doses, thereby reducing "risks of cataract, intraocular inflammation, retinal detachment and endophthalmitis," as well as the "significant time and financial burden" on patients. Ex.1008, Dixon, 1577; *see generally* Ex.1002, ¶¶58-61.

For example, a Regeneron press release from September 14, 2009 ("2009 Press Release") explicitly teaches dividing the treatment period into a "loading" phase and "maintenance" phase. Ex.1009, 2009 Press Release. Specifically, the 2009 Press Release describes administering 2 mg aflibercept to treat DR/DME using a number of different dosing regimens, including one consisting of three monthly loading doses followed by maintenance doses at 8-week intervals. Ex.1009.

As shown in Ground I, the 2009 Press Release thus anticipates Challenged Claims 46 and 47, which recite the general use of loading and maintenance dosing to treat DR/DME, specifying at least two initial monthly loading doses followed by any number of maintenance doses at 8-week intervals. The 2002 Press Release explicitly teaches such a regimen to treat DR/DME.

Additionally, as set out in Ground II, the 2009 Press Release alone or in combination with Shams renders obvious the Challenged Claims that require five

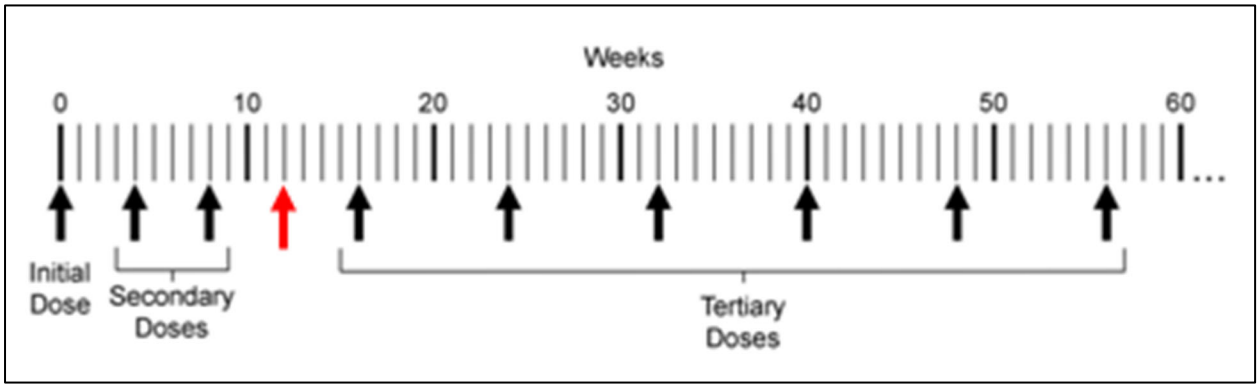
specific loading doses, including independent claims 10, 18, and 26. There is no special benefit taught in the '601 patent to using five loading doses as opposed to two, three, four, six, or more loading doses. The '601 patent states that "[t]he methods of the invention may comprise administering to the patient ***any number*** of secondary and/or tertiary doses of a VEGF antagonist" including "e.g. 2, 3, 4, 5, 6, 7, 8, or more." Ex.1001, 4:13-22. The patent does not contain any data for the use of only five monthly loading doses for any indication, let alone DR/DME; instead, the only discussion of five doses is part of a list of ***twenty*** other loading/maintenance dosing regimens it discloses for DR/DME, none of which are supported by additional data. *Id.,* 15:35-17:28.

Five loading doses is simply the number that works for ***some*** patients, and, importantly, the claims do not require the dosing regimen to apply to all patient populations in a one-size-fits-all approach. Nor could they, as there is no data in the patent supporting such a conclusion. Thus, the claims are directed to a "method for treating diabetic macular edema in ***a patient*** in need thereof," not an entire patient population or a percentage thereof, because that is all the specification describes. There is thus no requirement that a POSA would have been motivated to adopt five initial loading doses for ***all*** patients.

As set out above, the 2009 Press Release describes using ***three*** monthly loading doses followed by 8-week maintenance doses, among other regimens.

Ex.1009. The only difference between this disclosure and the dosing regimen of claims 10, 18, and 26 of the '601 patent is the number of initial monthly doses. While three might be appropriate for some patients, a POSA would have understood that other patients would benefit from additional loading doses, including five monthly loading doses. Indeed, one of the other regimens recited in the 2009 Press Release is PRN ("as needed") dosing after three monthly doses, which requires routine monitoring and reinjection when needed.

Using five monthly loading doses is thus a trivial and routine modification that amounts to the addition of a single monthly injection between the last loading dose and first maintenance dose described in the 2009 Press Release, as shown in the figure below. Ex.1002, ¶¶146-158. The black arrows correspond to the dosing regimen for DR/DME in the 2009 Press Release.



See, Ex.1001, 9. The red arrow corresponds to the addition of one monthly dose, bringing the initial total to five.

A POSA would have found this sort of routine dose optimization obvious for patients still obtaining gains for monthly dosing, and it was also taught in the prior art. The Shams reference explains that "[t]he specific time schedule [for administering doses of an anti-VEGF agent] can be readily determined by a physician having ordinary skill in administering the therapeutic compound ***by routine adjustments***…." Ex.1010, WO2006/047325A1 ("Shams"), 23-24 (emphasis added). It further explains that "the time of administration of the number of first individual and second individual doses as well as subsequent dosages is adjusted to minimize adverse effects while maintaining a maximum therapeutic effect." *Id*.

To the extent Regeneron argues that the use of five initial loading doses for DR/DME was not taught or suggested in the art, Petitioner also presents Ground III. Ground III is based on a combination of the 2009 Press Release with the teachings of a prior art publication, Elman 2010, describing a clinical trial studying the use of ranibizumab to treat DR/DME. In the Elman 2010 trial, one of the subject groups was given four initial monthly loading doses, after which a clinician evaluated the subjects to determine if a fifth monthly dose should be given. Ex.1006, Elman 2010. Elman 2010 reports that ***at least 78% of patients received a fifth loading monthly dose***. *Id.*, 4 (reporting that only 22% of patients did not receive a fifth dose). In view of Elman 2010, a POSA reviewing the 2009 Press Release's description of

using three monthly loading doses would have been motivated to use the five loading doses that were shown by Elman to be efficacious in the vast majority of patients.

Finally, Petitioner presents Grounds IV-VI addressing two sets of dependent limitations, as further set out below.

Discretionary denial is not appropriate here. None of the references cited in Petitioner's grounds were substantively discussed during prosecution, and while Mylan filed a previous petition against the '601 patent, which Petitioner sought to join, Mylan did not challenge any of the claims challenged in this petition. The claims challenged by Mylan are not directed methods of treating DR/DME (referred to herein as the '601 patent's "non-DR/DME claims") and recite a different dosing regimen. There is no overlap between the Challenged Claims in this petition and Mylan's, nor any overlap in the arguments or art presented.

The Board should institute an *inter partes* review of the Challenged Claims and find those claims unpatentable on the grounds presented herein.

II. MANDATORY NOTICES PURSUANT TO 37 C.F.R. § 42.8(A)(1)

A. Real Party-In-Interest (37 C.F.R. § 42.8(b)(1))

The real party-in-interest for Petitioner is Samsung Bioepis Co., Ltd.

B. Related Matters (37 C.F.R. § 42.8(b)(2))

Mylan filed a petition requesting IPR of the '601 patent on July 1, 2022, but that IPR does not involve any of the Challenged Claims here, which are directed to a specific indication (DR/DME) and different dosing regimen. *See* IPR2022-01226

("Mylan IPR"). The Mylan IPR was instituted on January 11, 2023. Ex.1053, '601 ID. Petitioner filed a "copycat" IPR petition on February 10, 2023 copying Mylan's petition and seeking to join Mylan's IPR in a silent understudy role, rather than mount a redundant challenge in this petition to the non-DR/DME claims. *See, Samsung Bioepis Co., Ltd. v. Regeneron Pharmaceuticals, Inc.*, IPR2023-00566, Papers 2-3. The Patent Trial and Appeal Board ("Board") instituted Petitioner's IPR petition and granted its motion for joinder on March 22, 2023 in IPR2023-00566. *Id.*, Paper 10.

The '601 patent is in the same family as U.S. Patent Nos. 9,254,338 ("'338 patent") and 9,669,069 ("'069 patent"). In May 2021, Mylan Pharmaceuticals Inc. filed petitions requesting for *inter partes* review of those two patents. *See* IPR2021-00881 ("'338 IPR") and IPR2021-00880 ("'069 IPR"). The Board instituted review for the '338 and '069 patents and found all challenged claims of those patents unpatentable in Final Written Decisions issued on November 9, 2022. *See* Ex.1025, '338 IPR, Paper 94 ("'338 FWD"); '069 IPR, Paper 89.

The '601 patent is also in the same family as U.S. Patent No. 10,130,681 ("'681 patent"). Mylan filed a petition requesting IPR of the '681 patent on July 1, 2022 (IPR2022-01225) ("Mylan '681 IPR"). The Mylan '681 IPR was instituted on January 11, 2023. Ex.1054, Mylan '681 IPR Institution Decision ("'681 ID").

Petitioner filed a petition against the ’681 patent on January 6, 2023 asserting different grounds of invalidity than in the Mylan ’681 IPR.

To the best of Petitioner’s knowledge, the following are judicial or administrative matters that potentially would affect, or be affected by, a decision in this proceeding: *Regeneron Pharmaceuticals, Inc. v. Mylan Pharmaceuticals Inc.*, NDWV-1-22-cv-00061, *United States v. Regeneron Pharms., Inc.*, No. 1:20-cv-11217-FDS (D. Mass.).

C. Lead and Backup Counsel (37 C.F.R. § 42.8(b)(3)-(4)

Petitioner hereby identifies its lead and backup counsel as follows:

Lead Counsel	Backup Counsel
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Pursuant to 37 C.F.R. § 42.10(b), a Power of Attorney has been filed herewith.

D. Service Information (37 C.F.R. § 42.8(b)(4))

Please send all correspondence to the lead and backup counsel at the addresses shown above. Petitioner consents to service by e-mail at qe-samsungbioepis@quinnemanuel.com.

E. Payment of Fees (37 C.F.R. §§ 42.103 and 42.15(a))

The requisite filing fee of $48,250 (request fee of $21,250, post-institution fee of $27,000) for a Petition for *Inter Partes* Review is submitted herewith. Claims 10-33 and 46-47 of the ’601 patent are being reviewed as part of this Petition. If any additional fees are due during this proceeding, the Office is authorized to charge such fees to Deposit Account No. 505708. Any overpayment or refund of fees may also be deposited in this Deposit Account.

III. GROUNDS FOR STANDING (37 C.F.R. § 42.104(a); 37 C.F.R. §§ 42.101(a)-(c))

Petitioner certifies that the ’601 patent is available for IPR and that Petitioner is not barred or estopped from requesting this review.

IV. IDENTIFICATION OF CHALLENGE AND RELIEF REQUESTED

A. Identification of Challenge (37 C.F.R. § 42.104(b))

Petitioner requests IPR of claims 10-33 and 46-47 of the ’601 patent (“the Challenged Claims”) and that the PTAB cancel those claims as unpatentable.

B. Grounds of Challenge (37 C.F.R. § 42.204(b)(2))

Petitioner respectfully requests that the Board grant institution of IPR on the Challenged Claims based on the following grounds:

Statutory Grounds of Challenge	
Ground I	Claims 46-47 are anticipated and/or rendered obvious under 35 U.S.C. §§ 102 and 103 by the 2009 Press Release
Ground II	Claims 10-12, 18-19, 21, 26-28 are rendered obvious under 35 U.S.C. § 103 by the 2009 Press Release either alone or in view of Shams
Ground III	Claims 10-12, 18-19, 21, 26-28 are rendered obvious under 35 U.S.C. § 103 by the 2009 Press Release in combination with Elman 2010
Ground IV	Claims 13-16, 20, 22-24, and 29-32 are rendered obvious under 35 U.S.C. § 103 by the 2009 Press Release alone, or in combination with Elman 2010, and/or further in view of Do 2011
Ground V	Claims 13-16, 20, 22-24, and 29-32 are anticipated under 35 U.S.C. § 102 by the 2016 Eylea Label

Ground VI	Claims 17, 25, and 33 are rendered obvious under 35 U.S.C. § 103 by the 2009 Press Release alone or in view of Elman 2010 and further in view of the CATT and PIER Studies

V. THE '601 PATENT

A. Overview

The '601 patent is entitled "Using a VEGF Antagonist to Treat Angiogenic Eye Disorders." Ex.1001. The '601 patent issued on January 12, 2021. The '601 patent names as its sole inventor, George D. Yancopoulous. *Id.*

The '601 patent specification discloses that "the methods of the invention comprise sequentially administering multiple doses of a VEGF antagonist" to treat angiogenic eye disorders, i.e., eye disorders caused by or associated with the formation of new blood vessels. *Id.,* 1:30-56, 2:3-31.

Examples 1-6 of the '601 patent describe the results of Phase I, II or III clinical trials using different dosing regimens of "VEGF Receptor-Based Chimeric Molecule (VEGFT)" in subjects with neovascular AMD (Examples 1-4), DME (Example 5), or macular edema secondary to CRVO (Example 6). *See generally id.,* Cols. 7-17. Example 7 of the '681 patent describes additional dosing regimens, but does not contain any test results. *Id.,* 15:35-17:28.

Notably, the specification does not describe the dosing regimen recited in the Challenged Claims outside of a list of twenty other regimens and does not report any results for these regimens. Ex.1001; *see also* Ex.1002, ¶¶70-74.

B. The Challenged Claims

Independent claims 10, 18, and 26 at issue here are directed to methods for treating DME, DR, and DR in a patient DME, respectively. Ex.1001. Each independent claim further recites "intravitreally administering, to said patient, an effective amount of aflibercept which is 2 mg approximately every 4 weeks for the first 5 injections followed by 2 mg approximately once every 8 weeks or once every 2 months." *Id.*; Ex.1002, ¶79.

Dependent claims 11-17, 19-25, and 27-33 recite additional limitations concerning the methods of treatment, including the disease treated, visual acuity results, and exclusion criteria. Ex.1001; Ex.1002, ¶80.

Claims 46 and 47 depend from claim 34 (claim 34 is not challenged here). Ex.1001; Ex.1002, ¶81. Claim 34, which is directed to treating any angiogenic eye disorder, recites the same dosing regimen as claims 10, 18, and 26 but specifies only at least two initial loading doses. *Id.* Claims 46 and 47 specify that the angiogenic eye disorder is diabetic retinopathy and diabetic macular edema, respectively. *Id.*

C. Prosecution History

The ’601 patent issued from U.S. Application No. 16/397,267 (“the ’267 application”), filed on April 29, 2019. Ex.1012, ’601 patent PH.

On May 12, 2020, the Examiner issued a non-final office action rejecting the pending claims on the ground of non-statutory obviousness-type double patenting as being unpatentable over certain claims of the ’338, ’069, and ’681 patents and co-pending U.S. Application No. 16/159,282. *Id.*, 799-805. The Examiner stated that while the specifically claimed dosing regimens were not disclosed, optimizing dosages and dosage schedules was routine experimentation. *Id*.

In a response dated October 21, 2020, the applicants submitted terminal disclaimers to all four of the reference patents.[1] *Id.*, 5583-5585. The claims of all four of these reference patents do not explicitly recite five loading doses for DR/DME, though they do recite “one or more” loading doses. *Id*. The applicants did not argue that providing five loading doses for treating DR or DME specifically was unexpected or otherwise rendered the claims patentable. *Id*.

On November 12, 2020, the Examiner issued a notice of allowance for claims 21-50 and 52-68 (subsequently renumbered). *Id.,* 5594-5602. The Examiner

[1] The applicants also amended the relevant independent Challenged Claims here to recite “in need thereof.”

withdrew the obviousness-type double patenting rejection in view of the terminal disclaimers. *Id*. Despite having available prior art disclosing the same dosing regimen as is recited in the reference patents to which Patent Owner took terminal disclaimers, the Examiner did not issue an obviousness rejection over that prior art. *Id*.; *see also*, Ex.1002, ¶¶75-78.

D. Level of Ordinary Skill in the Art

The ’601 and ’338 patents are in the same family with the same specification. In the Mylan ’338 and ’601 IPRs, the petitioner proposed the following definition for the relevant person of ordinary skill in the art:

> A person of ordinary skill in the art at the time of the invention would have had (1) knowledge regarding the diagnosis and treatment of angiogenic eye disorders, including the administration of therapies to treat said disorders; and (2) the ability to understand results and findings presented or published by others in the field, including the publications discussed herein. Typically, such a person would have an advanced degree, such as an M.D. or Ph.D. (or equivalent, or less education but considerable professional experience in the medical, biotechnological, or pharmaceutical field), with practical academic or medical experience in (i) developing treatments for angiogenic eye disorders (such as AMD), including through the use of VEGF antagonists, or (ii)

> treating of same, including through the use of VEGF antagonists.

Ex.1025, ’338 FWD, 9-10; Pet. 22. In the ’601 ID and ’338 FWD, the Board found that petitioner’s definition was consistent with the proper level of skill. ’601 ID, 15-16; Ex.1025, ’338 FWD, 10; *see also* Ex.1054, 20-21. Petitioner proposes the same definition be adopted here. *See also* Ex.1002, ¶¶22-25.

VI. PRIORITY DATE

A. Claims 10-33 Are Not Entitled to a Priority Date Earlier Than July 12, 2013[2]

Claims 10-33 are entitled to a filing date no earlier than July 12, 2013. The specific claimed dosing regimen of five initial doses for DR/DME—including the recited dosage (2.0 mg), the recited interval between secondary doses and tertiary doses (4 weeks and 8 weeks, respectively), the recited indications (DR/DME), or an “effective” combination of those variables for the treatment of DME/DR—was, at

[2] Petitioner does not challenge that claims 46 and 47 have a priority date of November 21, 2011 for the purposes of this petition only. As set out below in Ground V, to the extent Patent Owner contends that the intended results recited in dependent claims 13-16, 20, 22-24, and 29-32 are entitled to patentable weight and not an inherent result of practicing the method, they are not entitled to a priority date earlier than the ’601 patent’s April 29, 2019 filing date.

best, first described in Application No. 13/940,370, filed on July 12, 2013, which issued as the '338 patent. *Compare,* Ex.1056, '338 patent, *with* Ex.1057, Yancopoulos PCT Application. Accordingly, a POSA would not consider the applicants to be in possession of the claimed invention at least prior to that date.[3] *See also* Ex.1002, ¶¶103-115.

VII. CONSTRUCTION OF THE CHALLENGED CLAIMS

A. "A method for treating…"

For the purposes of this petition only, Petitioner does not contest that the preamble of challenged claims 10, 18, or 26 (and claim 34, from which claims 46 and 47 depend) is limiting, though it reserves the right to do so in separate proceedings. Petitioner proposes that the preamble be given the meaning of "a method for treating…" consistent with the meaning given to that term in the '338 FWD and '601 ID. *See also* Ex.1002, ¶82-91. Petitioner further proposes that the claims not be construed to require a particular level of efficacy. *See,* Ex.1002, ¶82-91.

[3] Petitioner reserves the right to further argue that the current specification, corresponding to July 12, 2013, does not provide adequate written description for the claims.

Specifically, in the ’338 FWD, ’601 ID, and ’681 ID, the Board found that administering a compound—the recited VEGF antagonist—“to [a] patient ***for the purpose*** of improving or providing a beneficial effect on their angiogenic eye disorder” satisfies the “treating” portion of the preamble. Ex.1025, ’338 FWD, 19; *id*., 23; Ex.1053, 9-10; Ex.1054.

Petitioner agrees with that understanding of the term as it appears in the preamble here. *See also* Ex.1002, ¶82-91; Ex.1001, 6:26-7:19; dependent cls. 22-23 (claiming both loss and gain of 15 letters of visual acuity). Administration of aflibercept to a patient for the ***purpose*** of treating them for DR/DME using the recited dosing regimen is sufficient to effectively “treat.” *Id.*

B. “Wherein the patient [loses less than/gains at least] 15 letters of Best Corrected Visual Acuity (BCVA) score” (Claims 13, 15, 22, 23, 29, and 31) / “The method of [claims 15/23/32] wherein Best Corrected Visual Acuity (BCVA) is according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score” (Claims 14, 16, 20, 24, 30, and 32)

Dependent claims 13, 15, 22, 23, 29, and 31 require that the patient [loses less than/gains at least] 15 letters of Best Corrected Visual Acuity (BCVA) score” while claims 14, 16, 20, 24, 30, and 32 add the limitation that the BCVA “is according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.” These dependent claims recite the intended results of administering aflibercept according to the claimed method and therefore are not entitled to patentable weight. Specifically, independent claims 10, 18, and 26, from which all of these claims

depend, recite "comprising intravitreally administering, to said patient, an ***effective amount*** of aflibercept which is 2 mg approximately every 4 weeks for the first 5 injections followed by 2 mg approximately once every 8 weeks or once every 2 months."

The "wherein" clause language does not change or alter the steps of the method. *Id.* Because the independent claims already recite that an "effective amount" will be given if the method is followed (regardless of the effect on a patient), merely specifying in the dependent claim the intended result of providing that "effective amount" cannot provide further structure or definition to the claim. *Id.* The claim has already fully defined what an "effective amount" will be; the recitation in the dependent must thus be merely an intended result inherent in practice of the claim, nothing more. *Id.*

Intended results should not be given patentable weight. *See Syntex (U.S.A.) LLC v. Apotex, Inc.*, 407 F.3d 1371, 1378 (Fed. Cir. 2005) (holding that "in a stabilizing amount" as recited in the body of a claim was non-limiting because it "simply describes the intended result of using the weight to volume rations in the claims); *Bristol-Myers Squibb Co. v. Boehringer Ingelheim Corp*., 86 F. Supp. 2d 433, 443 (D.N.J.) *aff'd in relevant part*, 246 F.3d 1368, 1376 (Fed. Cir. 2001) (holding "reduced hematologic toxicity" not limiting as a matter of claim

construction because it did not "result in a manipulative difference in the steps of the claim.").

Petitioner notes that the claims here are different than the claims in *Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center v. Eli Lilly & Co.*, 849 F.3d 1049 (Fed. Cir. 2017) ("*Los Angeles Biomed*."). In *Los Angeles Biomed.*, the Federal Circuit accorded patentable weight to a claim with two steps, the second of which recited "b) arresting or regressing the at least one of the penile tunical fibrosis and corporal tissue fibrosis, wherein the PDE-5 inhibitor is administered at a dosage up to 1.5 mg/kg/day for not less than 45 days." *Id*., 1060-61. The Federal Circuit held that the "arresting or regressing language" should be given patentable weight for at least two reasons, neither of which apply here.

First, the Federal Circuit reasoned that "[w]hile not dispositive, it is significant that the phrase 'arresting or regressing the [penile] fibrosis' is drafted as part of a separate step of the method…." *Id*., 1061. The Federal Circuit held this distinguished the structure of the claims at issue from past cases where the relevant language appeared in the "structure of patent claims in which statements of general purpose" were made, such as the preamble, and were held to be non-limiting. *Id*.

Second, the Federal Circuit also noted that "[b]ecause the '903 patent claims specify only a maximum dosage level and a minimum treatment period, it is different

from cases in which the claims contain express dosage amounts as material claim limitations, and in which efficacy is 'inherent in carrying out the claim steps.'" *Id*.

Neither of the reasons the Federal Circuit gave for finding the language limiting apply here.

First, as noted above, the relevant language is not recited as "part of a separate step of the method," but rather as part of "wherein" clauses—i.e. "[w]herein the patient [loses less than/gains at least]." "A whereby [or wherein] clause in a method claim is not given weight when it simply expresses the intended result of a process step positively recited" or is otherwise inherent. *Minton v. Nat'l Ass'n. of Sec. Dealers, Inc.*, 336 F.3d 1373, 1381, (Fed. Cir. 2003); *see also Lockheed Martin Corp. v. Space Systems/Loral, Inc.*, 324 F.3d 1308, 1319 (Fed. Cir. 2003) (language only stated an inherent result); *In re Kubin*, 561 F.3d 1351, 1357 (Fed. Cir. 2009) (irrelevant whether prior art disclosed a feature "wherein the polypeptide binds CD48" when feature was necessarily present in protein). Such language must provide structure or acts necessary to define the invention to be a positive limitation. *In re Kubin*, 561 F.3d, 1353.

Here, the language does not define the invention. As discussed above, the independent claims recite "comprising intravitreally administering, to said patient,

an effective amount of aflibercept ***which is***…."[4] The "wherein the patient [loses less than/gains at least]" language appears in the dependent claims. Because the independent claims already specify precisely what "an effective amount" is, the dependent claims merely recite the intended result of providing "an effective amount" as specified in the claim.

Second, and relatedly, unlike the claims in *Los Angeles Biomed*., which specified "only a maximum dosage level and a minimum treatment period," the claims here "contain express dosage amounts as material claim limitations, and in which efficacy is 'inherent in carrying out the claim steps.'" *Id*., 1061. Any requirement of efficacy must be inherent in carrying out the claimed steps as recited in the '601 claims. There is no need to give patentable weight to the language to put a limit on the scope of the claim, as was done in *Los Angeles Biomed*.

C. Exclusion Criteria (Claims 17, 25, and 33)

Dependent claims 17, 25, and 33 recite two exclusion criteria.

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[4] In IPR2022-01524 involving the related '572 patent, the Board gave patentable weight to visual acuity limitations. While Petitioner respectfully disagrees with the Board's analysis of *Los Angeles Biomed*., that analysis is inapplicable here because unlike the '572 patent, the claims here specify the "effective amount" in the body of the claims.

In the ’601 ID, the Board found that the same exclusion criteria recited in the non-DR/DME claims of the ’601 patent are not entitled to patentable weight. Ex.1053, 12-15; *see also* 1054, 18-20. Relying on the two-step test in *Praxair Distrib., Inc. v. Mallinckrodt Hosp. Prods. IP Ltd.*, 890 F.3d 1024, 1032 (Fed. Cir. 2018), the Board found that “there is little question that the exclusion criteria are directed to informational content” under the first step of the *Praxair* analysis. The Board further found that under the second *Praxair* step, the exclusion criteria lacked a functional relationship to the rest of the claims, particularly because “the claims do not expressly recite any positive step to be performed (or negative step *not* to be performed) should a patient meet the exclusion criteria.” Ex.1053, 14; *see also* Ex.1054, 19. Petitioner agrees with that understanding and the same exclusion criteria are not entitled to patentable weight in the Challenged Claims. *See also* Ex.1002, ¶¶99-102.

VIII. OVERVIEW OF THE PRIMARY PRIOR ART REFERENCES

A. The 2009 Press Release

The 2009 Press Release was published on September 14, 2009, and thus constitutes prior art under 35 U.S.C. § 102(a) and (b). The 2009 Press Release reflects its date on its face, was submitted during prosecution and acknowledged by Applicants as prior art, but was never substantively addressed by the Examiner.

The 2009 Press Release discusses VEGF Trap-Eye, also known as aflibercept. Ex.1009; *see also, e.g.*, Ex.1013, Adis; Ex.1008. It discusses a number of clinical trials for various indications of VEGF Trap-Eye, including AMD and DME. As to DME, the press release specifically states that VEGF Trap-Eye is "in Phase 2 development for the treatment of Diabetic Macular Edema (DME)." Ex.1009, 1. It teaches that the trial will involve three different dosing regimens: "VEGF Trap-Eye dosed at 0.5 mg or 2 mg monthly, 2 mg every eight weeks after three monthly loading doses, or 2 mg on an as-needed (PRN) basis after three monthly loading doses." *Id.*; *see also*, Ex.1002, ¶¶116-117.

B. Shams

Shams is a Genentech patent application, titled "Method for treating intraocular neovascular diseases," and generally relates to methods for treating an intraocular neovascular disorder with a VEGF antagonist. Ex.1010. Shams published in 2006 and is prior art under AIA 35 U.S.C. § 102(a) and (b). *Id.*

Shams explains that "a treatment schedule comprising an initial interval of administration of a therapeutic compound [an VEGF antagonist], followed by a subsequent, less frequent interval of administration of the therapeutic compound" allows "one to decrease subsequent doses of the therapeutic compound, while at the same time maintaining the therapeutic efficacy." *Id.*; *see also id.*, 5-6. It further

teaches that the time for each dose can be modified through "routine adjustments to the dosing schedule." *Id.*; *see also*, Ex.1002, ¶¶118-120.

C. Elman 2010

Michael J. Elman, MD, et al., Randomized Trial Evaluating Ranibizumab Plus Prompt or Deferred Laser or Triamcinolone Plus Prompt Laser for Diabetic Macular Edema, Ophthalmology (June 2010) ("Elman 2010") is prior art under AIA 35 U.S.C. § 102(a) and (b).[5] Ex.1006; Ex.1014, Elman AAO Website. It was not cited during the prosecution of the application underlying the '601 patent. Ex.1012.

Elman 2010 describes a Phase 3 trial for ranibizumab for the treatment of DR/DME. Ex.1006; *see also* Ex.1002, ¶¶121-128. At the time of Elman 2010, the VEGF antagonist ranibizumab (Lucentis®) was only approved for treatment of wet AMD. Ex.1006; Ex.1027-28; *see also,* Ex.1002, ¶¶45-49, 121-128. Among its study arms, the Elman 2010 study tested a 52-week treatment protocol under which an initial injection of ranibizumab (at "week 0") was followed by injections at the 4,

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[5] Elman 2010 reflects a publication date of April 27, 2010, with a 2010 copyright. Ex.1006, 1077 ([a]vailable online: April 27, 2010") The entry in Ophthalmology lists its online publication date as April 27, 2010, with publication in Volume 117, Issue 6 in June 2010. Ex.1014, https://www.aaojournal.org/article/S0161-6420(10)00243-5/fulltext.

8, and 12 week visits, for a total of 4 initial injections. Ex.1006, 1066-67, 1077.e1, 1077.e2, 1077.e11. Patients in this arm received either "prompt laser" treatment during the initial dosing period (a standard treatment at the time that used a photocoagulation as part of treatment to remove abnormalities on the retina) or "deferred laser"—use of a photocoagulation laser only at or after 24 weeks if called for by the study protocol. *Id.* The deferred laser group, in particular, is relevant here as the most direct evidence of the effect of an anti-VEGF agent on DR/DME without further complicating variables. *Id.*

As described in Elman 2010, after the required fourth initial monthly dose was given according to the protocol, clinicians thereafter performed an assessment every month (through week 52) in conjunction with a real-time data entry system referred to as a "Retreatment Algorithm." *Id*. This system categorized patients as "success," "improvement," "no improvement," or "failure." *Id*. The designation "depended mainly on visual acuity and OCT [("optical coherence tomography")] measurements." *Id.* Based on that assessment, clinicians were guided as to whether to provide another injection that month or not. *Id.*

According to the Retreatment Algorithm, at the fifth and sixth visits, an injection of ranibizumab was required for patients in the ranibizumab + deferred laser group that were determined to meet the "no improvement" or "failure" criteria. If the "success" criteria was met, an injection was at investigator discretion. *Id*. In

the deferred laser group, this approach resulted in an injection at least 78% of patients receiving a fifth initial monthly doses (i.e. an injection at the fifth visit). *Id*., 1067 (reporting that 22% of patients did not receive a fifth dose).

While Elman 2010 does not specifically report how many patients received an injection at the sixth visit, it does report that for the deferred laser group, the "median number of study drug injections before the 1-year primary outcome visit was… 9 (6, 11) ranibizumab injections (of 13 maximally possible injections)." *Id*. This means that Elman 2010 teaches both that at least 78% of patients received a fifth dose and, if the median is applied to those 78% of patients, they received only four additional doses out of the eight possible doses remaining after their fifth injection. *Id.* While Elman does not provide sufficient data to determine exactly the median number of additional doses for the 78% of patients specifically (as opposed to the full group of deferred laser patients), the data does clearly suggest that DR/DME could be treated by an initial set of at least five monthly doses and then—as shown in other studies of anti-VEGF agents—could be followed by more widely-spaced maintenance dosing. *See also,* Ex.1002, ¶¶121-128.

D. Do 2011

Do DV et al., The DA VINCI Study: Phase 2 Primary Results of VEGF Trap-Eye In Patients With Diabetic Macular Edema ("Do 2011") is prior art under AIA 35 U.S.C. § 102(a) and (b). Ex.1045, Do, 2011, Ophthalmology. 2011

Sep;118(9):1819-26.[6] Do 2011 reports the results of the Phase 2 clinical trial disclosed by the 2009 Press Release. Ex.1045, Endnotes; Ex.1002, ¶189. Do 2011 discloses that after six months of treatment via the dosing regimen described in the 2009 Press Release that 17% of patients achieved at least a 15 letter gain in BCVA. Ex.1045, 4.

E. 2016 Eylea Label

The 2016 Eylea Label was publicly available as of May, 2016, as Regeneron has acknowledged in the '069 IPR. It discloses the dosing regimen recited by the independent claims 10, including 5 monthly loading doses. Ex.1050, 2016 Eylea Label, 1. It further includes efficacy data from the VIVID and VISTA studies evaluating the claimed aflibercept dosing regimen for treating DME and DR showing the percentage of patients that gained at least 15 letters in BCVA. *Id.* at Table 7; *see also*, Ex.1002, ¶¶200-201.

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[6] Do 2011 was published online on May 5, 2011 and in print September 2011. *See* Ex.1045; *see also* Ex. 1055 (https://www.aaojournal.org/article/S0161-6420(11)00177-1/fulltext (showing May (online) and September (print) 2011 publication dates)).

F. CATT and PIER Studies

The ’601 patent claims 17, 25, and 33 recite two exclusion criteria for “(1) active intraocular inflammation” and “(2) active ocular or periocular infection.” Ex.1001. Exclusion of patients with these conditions from receiving treatment via intravitreal injection was routine at the time. *See* Ex.1002, ¶¶129-36.

The table below reproduces the recited exclusion criteria on the left, with the relevant corresponding exclusion criteria from the prior art CATT and PIER studies on the right:

Table 1	
Exclusion Criteria Recited in Claims 17, 25, and 33	**Prior Art Exclusion Criteria for Anti-VEGF Intravitreal Injections Relied on by Petitioner**
“(1) ***active intraocular inflammation***” – i.e. current inflammation within the eye	“***Active*** or recent (within 4 weeks) ***intraocular inflammation*** (grade trace or below) in the study eye.” Ex.1018, CATT Study, 6-7. “***Active intraocular inflammation*** (grade trace or above) in the study eye.” Ex.1004, 248.e3.
“(2) ***active ocular or periocular infection***” – i.e. a current infection anywhere on/in the eye (ocular) or surrounding it within its orbit (periocular)	“***Active*** infectious conjunctivitis, keratitis, scleritis, or endophthalmitis ***in either eye***.” Ex.1018, 6-7. “***Infectious*** conjunctivitis, keratitis, scleritis, or endophthalmitis ***in either eye***.” Ex.1004, 248.e3.

These references were not considered during prosecution of the ’601 patent. Ex.1012.

The University of Pennsylvania sponsored the CATT study, which evaluated bevacizumab and ranibizumab. *See* Ex.1017, NCT00593450; Ex.1002, ¶¶129-136. The web archive of its website provides a document (the “CATT Study”) listing exclusion criteria for CATT as of July 13, 2010. Ex.1018; Ex.1002, ¶¶129-136. Thus, the CATT Study is prior art to the ’681 patent under 35 U.S.C. § 102(a) and (b); *see also* MPEP § 2128.[7] *See also* Ex.1018, 1-2.

The PIER study (NCT00090623) evaluated the efficacy and safety of ranibizumab (Lucentis®) administered monthly for three months and then quarterly. Ex.1004; Ex.1002, ¶¶129-136. Regillo et al., “Randomized, Double-Masked, Sham-Controlled Trial of Ranibizumab for Neovascular Age-related Macular Degeneration: PIER Study Year 1,” Am. J. Ophthalmol., 145(2): 239-248 (Feb.

[7] The CATT study was available and was captured by the Internet Archive as of at least July 13, 2010. Ex.1018 (available at https://web.archive.org/web/20100713035617/http://www.med.upenn.edu/cpob/studies/documents/CATTEligibilityCriteria_000.pdf).

2008) ("PIER Study"), published February 2008, describes the PIER study and is prior art to the '681 patent under § 102(b).[8] *Id.*

G. Prior Art Knowledge Regarding the Relationship Between DR/DME

A POSA would have recognized at the time of the alleged invention that DME is a manifestation of DR, and would have understood that treatment for DME necessarily treats the underlying DR. Ex.1002, ¶¶43-44, 137-140; *see also, e.g.*, Ex.1024, Pai 2010, 2; Ex.1023, Do Workshop 2009; Ex.1026, NIH DR. In fact, the '601 specification states that DME is complication of DR and that DR can be treated by administering anti-VEGF agents in the manner claimed for DME. *See, e.g.* Ex.1001 at 1:38-41 ("DME is the most prevalent cause of moderate vision loss in patients with diabetes and ***is a common complication of diabetic retinopathy***…"); *id*., cl. 18, col. 2:32-36 ("The methods of the present invention can be used to treat…

[8] The PIER Study includes a February 2008 publication date (Ex.1004, 2) and a 2008 copyright, and notes the paper was accepted for publication on Oct. 5, 2007; *see also* Ex.1019, PIER AJO Website (https://www.ajo.com/article/S0002-9394(07)00881-1/fulltext); *see* also Exs.1020-1021.

diabetic retinopathy”)). For the purposes of this petition, Petitioner does not dispute that statement.[9]

IX. DETAILED GROUNDS FOR INVALIDITY

In Ground I, Petitioner challenges claims 46-47, which depend from claim 34. Grounds II-III address claims 10-12, 18-19, 21, 26-28, which include independent claims 10, 18, and 26, followed by analysis of dependent claims 11-12, 19, 21, 27-28. Grounds IV-VI address dependent claims 13-17, 20, 22-25, and 29-33.

A. Ground I: Claims 46-47 are Anticipated and/or Rendered Obvious by the 2009 Press Release

Claims 46 and 47 depend from claim 34 and, unlike the other Challenged Claims, specify only at least two initial monthly loading doses. Independent claim 34 recites an effective dosing regimen for treating a patient with an angiogenic eye disorder in which a “single initial dose” of aflibercept is given, followed by “one or more secondary doses” administered every 4 weeks. Thus, claim 34 requires only at least two initial monthly doses, i.e., the initial dose followed by one secondary dose. Claim 34 also specifies “one or more tertiary doses” administered every 8

[9] Petitioner reserves the right to argue in other proceedings that “treating diabetic retinopathy” in the ’601 patent renders the claims in which it appears invalid under 35 U.S.C. §112 as indefinite or as lacking written description or an enabling disclosure.

weeks. Claims 46 and 47 specify that the angiogenic eye disorder is DR and DME, respectively. Mylan challenged claim 34 in its '601 IPR, but not claims 46 and 47.

The 2009 Press Release reports that "***VEGF Trap-Eye*** is … in Phase 2 development ***for the treatment of Diabetic Macular Edema (DME)***. ***VEGF-Trap dosed at***...***2 mg every eight weeks after three monthly loading doses***…is being compared to focal laser treatment." Ex.1009, 1. Accordingly, the 2009 Press Release's disclosure of the Phase 2 trial for DME anticipates the DME dosing regimen of claim 47, in which an initial loading dose of aflibercept is administered, followed by two secondary doses one month apart, followed by maintenance doses at 8-week intervals. *Id*.; *see also* Ex.1002, ¶¶141-142.

A POSA would have further understood the 2009 Press Release's regimen was "for the treatment" of DME and would be effective, based both on its use in a Phase 2 trial and on past results successfully treating DME with aflibercept. Ex.1002, ¶¶141-142; Ex.1008. And, as discussed by Dr. Chaum and previously found in the '601 ID,[10] VEGF Trap-Eye was another name for aflibercept, and POSAs knew

[10] As the Board noted in the '601 ID, claim 34 describes aflibercept by the structural components of the protein, which were disclosed in the art. '601 ID, 17-18; *see also* Ex.1002, ¶¶50-57. It was understood at the time that VEGF Trap-Eye and aflibercept were the same drug, and the protein's structure is inherent in it. For

its protein structure, which is inherent, as recited in claim 34. *See,* Ex.1002, ¶¶50-57. Thus the 2009 Press Release discloses all recited elements of claim 47.

In addition, as set forth in Section VIII.G, DME is a known symptom of DR, and treating DME necessarily addresses the underlying DR, which is the cause of DME. *See also,* Ex.1002, ¶¶137-140. In other words, treatment of DME via the dosing regimen disclosed in the 2009 Press Release would have necessarily been for the purpose of treating DR, and such treatment was known to be effective. *Id.*, ¶143. Thus, the 2009 Press Release's disclosure of the DME dosing regimen in claim 47 inherently anticipates the DR dosing regimen in claim 46. *Id.*

Alternatively, a POSA would have been found it obvious that the DME dosing regimen disclosed in the 2009 Press Release could be used to treat DR. *See,* Ex.1002,

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instance, Dixon expressly teaches that aflibercept and VEGF Trap-Eye have the "same molecular ***structure***" (Ex.1008, 3), and Adis (Ex.1013) refers to them interchangeably. *See also* Ex.1025, '338 FWD, 34; Ex.1029-31; Ex.1002, ¶¶50-57 (explaining the import of the drugs having the "same molecular structure"). Additionally, Patent Owner has frequently indicated to the Patent Office that they are the same drug. *Compare* Ex.1007, 3-5 (describing VIEW 1/2) with Ex.1008, 4 (describing same); *See also* Ex.1025, '338 FWD (incorporated herein, reviewing Patent Owner's admissions).

¶¶142. A POSA would have been motivated to review the 2009 Press Release in view of POSA's understanding of the relationship between DME and DR as noted in Section VIII.G. *Id.* Based on the 2009 Press Release's discussion of the ongoing clinical trials for DME and AMD utilizing the same dosing regimen, a POSA would have had a reasonable expectation that administering aflibercept according to the disclosed DME dosing regimen would also work for DR. *Id*.

Accordingly, claims 46 and 47 are anticipated and/or rendered obvious by the 2009 Press Release. *See generally*, Ex.1002, ¶¶141-145.

B. Ground II: Claims 10-12, 18-19, 21, 26-28 Are Rendered Obvious by the 2009 Press Release Either Alone or in View of Shams

Independent claims 10, 18, and 26 are similar to claims 46 and 47, but recite treating DR and DME by intravitreally injecting aflibercept using a dosing regimen of ***five*** initial injections of 2 mg (rather than two or more) that are spaced a month apart, followed by maintenance doses spaced eight weeks apart. Ex.1001.[11]

The 2009 Press Release teaches that Regeneron, the Patent Owner and manufacturer of aflibercept, was beginning clinical trials studying the efficacy of aflibercept to treat DME via three different dosing regimens for 2 mg VEGF Trap-

[11] Dependent claims 11-12, 19, 21, and 27-28 are addressed more specifically in Sections IX.B.1-2 below.

Eye,[12] including the use of ***three*** initial injections of 2 mg that are spaced a month apart, followed by maintenance doses spaced eight weeks apart. Ex.1009, 1; Ex.1002, ¶147.

Furthermore, the 2009 Press Release taught that a regimen with more than three loading doses would be safe and tolerable and more likely to improve treatment for at least some patients. *Id.,* ¶¶146-158. Specifically, the 2009 Press Release also disclosed two alternative regimens for the Phase II clinical trial: (1) a regimen of 12 monthly doses of 2 mg aflibercept for the first year of treatment of DME—a standard and proven safe regimen for other anti-VEGF agents; and (2) a regimen of three initial loading doses followed by PRN dosing for treatment of DME. *Id*. In addition to teaching that more than three initial doses would be safe and tolerable, these additional regimens suggest to a POSA that some patients might benefit from more than three loading doses and would provide a reasonable expectation of success for such patients. *Id.*

"[M]onthly dosing of a therapeutically effective amount of VEGF antagonist, followed by less frequent dosing of a therapeutically effective amount of VEGF antagonist" was described in Shams as early as in 2006. Ex.1010, 2; *see also*

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[12] As noted above in fn.10, it was understood at the time that VEGF Trap-Eye and aflibercept were the same drug.

Ex.1002, ¶155. Shams explains that "a treatment schedule comprising an initial interval of administration of a therapeutic compound [an VEGF antagonist], followed by a subsequent, less frequent interval of administration of the therapeutic compound" allows "one to decrease subsequent doses of the therapeutic compound, while at the same time maintaining the therapeutic efficacy." Ex.1010, 22; *see also id*., 5-6. It further explains that "[t]he specific time schedule [for administering doses] can be readily determined by a physician having ordinary skill in administering the therapeutic compound ***by routine adjustments*** of the dosing schedule within the method of the present invention [i.e. loading and maintenance dosing]." *Id*., 23-24 (emphasis added); *see also* Ex.1002, ¶155.

Arriving at five initial doses from the 2009 Press Release would be a product of a POSA's "routine adjustments" to the initial dosing schedule—i.e. a "routine application of a well-known problem-solving strategy." *See* Ex.1002, ¶¶146-158; *see also*, *e.g. Biomarin Pharm. Inc. v. Genzyme Theraputic Prods. Ltd. P'ship*, IPR2013-00534, Paper 81, 8-11 (quoting *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1368 (Fed. Cir. 2007). A POSA would follow such a routine strategy when evaluating the appropriate dosing regimen for an individual patient, based on their clinical judgment, precisely as described in the art as early as 2006. *See* Ex.1002, ¶¶58-61, 146-158.

This basic "problem solving strategy" of evaluating a range of monthly loading doses is taught in Shams (*see* Ex.1010), but it is also mirrored in the '601 patent itself. The '601 patent contains no data particular to the efficacy of five monthly loading doses versus three monthly loading doses—or any such efficacy data on five monthly loading doses at all. The patent explains that "[t]he methods of the invention may comprise administering to the patient any number of secondary and/or tertiary doses of a VEGF antagonist" including "***e.g. 2, 3, 4, 5, 6, 7, 8, or more***." Ex.1001, 4:13-22.

In fact, the '601 patent nowhere identifies five loading doses as the proper or most efficacious number of loading doses for DR/DME (or any other indication). Instead, the use of five loading doses is referenced in the '601 patent only as part of a bare list of ***twenty*** other variations on loading/maintenance dosing regimens that vary the number of initial doses—including two, three, four, five, six, seven, and eight loading doses spaced four weeks apart, as well as a dosing regimen of continuous doses spaced four weeks apart. The patent explains that "[***a***]***ny*** of the foregoing administration regimens may be used for the treatment of…." DME, among a host of angiogenic eye disorders. Ex.1001, 17:16-27.

While the '601 patent's disclosure is thus broad and does not isolate five monthly doses as optimal or as one size fits all (neither do the claims), it does mirror exactly how a POSA would have evaluated the appropriate dosing regimen for an

individual DR/DME patient. A POSA would have considered it obvious to vary the number of initial loading doses disclosed in the art for the treatment of DR/DME before moving to maintenance dosing for individual patients, including the use of five loading doses. Ex.1002, ¶¶58-61, 146-158. In fact, as Dr. Chaum explains, such variation is a normal part of practice in treating DME and other angiogenic diseases: it was and is a routine clinical practice to continue monthly loading doses of anti-VEGF agents until the point at which the dosing interval can be reduced. *Id.*

Notably, claims 10, 18, and 26 recite a method for treating DR/DME "in ***a*** patient in need thereof." Ex.1002, ¶166. To show the obviousness of these claims, there is no requirement that a POSA would have been motivated to adopt five initial loading doses for ***all*** patients. *Id.* The claims do not recite efficacy for a broader population or require that the regimen be more efficacious than other regimens. Nor could the claims contain such limitations: the '601 patent is devoid of ***any*** data on the efficacy of five loading doses, let alone data that could support such a limitation. Ex.1002, ¶154.

Similarly, there is no need to show that other dosing regimens with a different number of monthly doses—such as three, four, six, etc.—were not also obvious. They were, as part of the basic problem solving strategy a POSA would take in treating a patient with DR/DME. Ex.1002, ¶¶146-158. As the Federal Circuit has explained, motivation for making such routine adjustments to a dosing regimen for

treatment of a patient "flows from the 'normal desire of scientists or artisans to improve upon what is already generally known.'" *Pfizer*, 480 F.3d at 1368 (quoting *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003)); *see also* Ex.1002, ¶¶145-158.

Finally, POSAs would have had a reasonable expectation of success in using five initial loading doses instead of the three described in the 2009 Press Release.[13] As an initial matter, the 2009 Press Release's disclosure of a Phase II trial using loading and maintenance dosing of aflibercept to treat DME would provide a POSA with a reasonable expectation of success that such a regimen would work, including the use of maintenance dosing. *Id*. The claimed combination merely adds an additional loading dose, which would only increase a POSA's expectation of success given the proven superiority of monthly dosing in general. *Id*.

Additionally, prior initial testing of only a single injection of aflibercept for DME improved a patient's BVCA by 9 letters with a decrease of 79 µm in retinal thickness as measured by OCT, but then showed regression to only a 3 letter improvement at six weeks without follow up. Ex.1008; Ex.1002, ¶¶146-158.

[13] There is no requirement of certainty; "[f]or obviousness under § 103, all that is required is a reasonable expectation of success." *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988).

POSAs would have reasonably expected that continuing regular initial dosing beyond a single injection would increase that success. Ex.1002, ¶¶146-158.

Thus, independent claims 10, 18, and 26 are rendered obvious.

1. Claims 11/19/27: "The method of [claims 10/18/26] wherein approximately every 4 weeks comprises approximately every 28 days or approximately monthly."

A POSA would have understood that 4 weeks consist of 28 days and that the term is used interchangeably with "monthly." *See also, e.g.,* Ex.1006, 15; Ex.1002, ¶¶180. Therefore, Claims 11, 19 and 29 are rendered obvious.

2. Claims 12/21/28: "The method of [claims 10/18/26] further comprising, after 20 weeks, administering, via intravitreal injection, 2 mg of aflibercept once every 4 weeks."

The requirement of dosing every 4 weeks for the first five injections followed by dosing every 8 weeks starting after week 16 (5 initial doses) in the independent claims is facially inconsistent with dosing "after 20 weeks" every 4 weeks in claims 12, 21, and 28. Ex.1002, ¶¶181-184.

To the extent Patent Owner argues that these claims should be read as requiring dosing every 4 weeks (monthly), the 2009 Press Release discloses such dosing as one arm of the VEGF Trap-Eye Phase 2 clinical trial for DME and renders such claims obvious. *See* Ex.1009; Ex.1002, ¶182.

To the extent Patent Owner argues that these claims should be read as dosing every 4 weeks through week 16, followed by 8 week intervals between doses, and

then dosing every 4 weeks starting at a later point ("after 20 weeks"), such a regimen would be the result of routine experimentation, particularly in patients that show regression. *See, e.g.* Ex.1006; Ex.1008; Ex.1045; Ex.1002, ¶¶157, 183, 191.

Therefore, claims 12, 21, and 28 are, under any interpretation of those claims, rendered obvious. Ex.1002, ¶¶181-184.

C. Ground III: Claims 10-12, 18-19, 21, 26-28 Are Rendered Obvious by the 2009 Press Release in Combination with Elman 2010

The use of five initial loading doses for DR/DME is also obvious over the 2009 Press Release in combination with Elman 2010, which teaches the use of five initial loading doses. Ex.1002, ¶¶159-184.

As set out above, the 2009 Press Release discloses aflibercept, the 2 mg dosing amount, and use of 8-week maintenance dosing to treat DR/DME as recited in claims 10, 18, and 26.[14] The only difference between its disclosure and that of the claims is that the claims recite five initial loading doses, rather than three. Notably, aflibercept had already been tested for treatment of angiogenic eye disorders via four monthly loading doses followed by PRN dosing and six monthly loading doses followed by PRN dosing, thus bracketing the use of five initial loading doses. *See* Ex.1011, September 28, 2008 Press Release (discussing four monthly loading doses

[14] As noted above in fn.10, it was understood at the time that VEGF Trap-Eye and aflibercept were the same drug.

in 12 weeks for treating AMD); Ex.1009 (discussing six monthly loading doses for treating Central Retinal Vein Occlusion).

A POSA would have found it obvious to treat at least some patients with DR/DME by administering ***five*** initial monthly loading doses, instead of three, in view of Elman 2010. Ex.1002, ¶¶159-184. As set out in Section VIII.C, Elman 2010 reports that at least 78% of patients received a fifth initial monthly dose based on a clinical evaluation according to its protocol. Ex.1006, 1067; *see also* Ex.1002, ¶¶154-179.

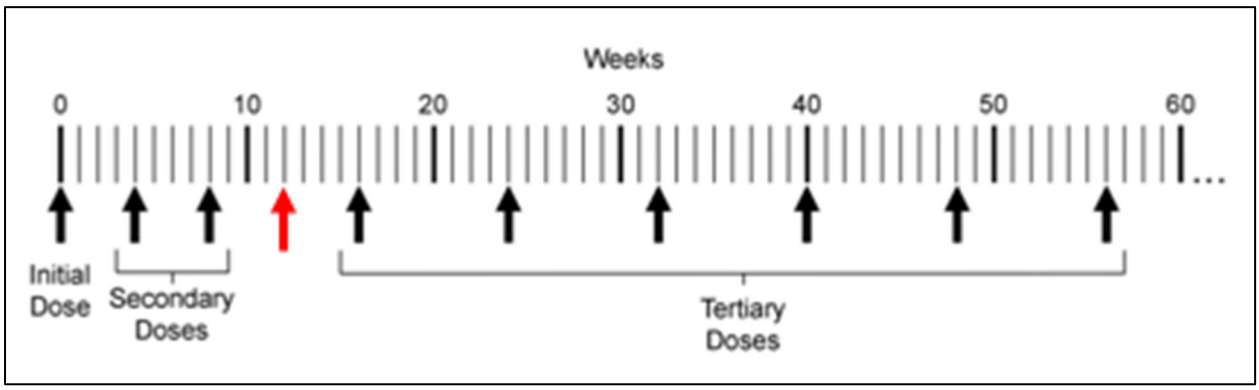
Elman was the most significant study of the treatment of DR/DME via an anti-VEGF agent at the time, and it strongly suggests the use of five initial monthly loading doses, at least for some patients. Ex.1002, ¶¶159-184. In fact, even if substantially less than 78% of patients required a fifth dose, the fact that Elman describes such doses after clinical evaluation would be sufficient to suggest to a POSA—at least for the treatment of some patients, which is all that is required here—the use of five initial loading doses. Ex.1002, ¶¶159-184.

Dependent claims 11-12, 19, 21, and 27-28 are rendered obvious for the same additional reasons discussed in Sections IX.B.1-2.

1. A POSA Would Have Been Motivated to Combine the 2009 Press Release with Elman 2010's Dosing Regimen

A POSA reviewing the 2009 Press Release would have found it natural to adopt, at least for some patients, teachings from the study of another anti-VEGF

agent, ranibizumab, that five monthly loading doses were deemed desirable for at least 78% of patients.[15] *See,* Ex.1002, ¶¶164-172. Modifying the dosing regimen disclosed by the 2009 Press Release required only the most obvious of steps: ensuring a greater likelihood of success in treating at least some patients by adopting a dosing regimen with two additional monthly doses (in effect, a single dose administered between month 3 and 5), as demonstrated by the red arrow below. *Id.*, ¶¶146-158, 164-172; *see also*, Ex.1001, 9.



Id. POSAs would have been further motivated to take this step based on clinical experience and trial results that showed that without sufficient initial monthly dosing, it was more difficult to use the "less frequent" maintenance dosing to sustain "control

[15] Ranibizumab was regularly used as the control or comparison dose in the known clinical trials for aflibercept at the time, including as described in the 2009 Press Release, providing a POSA further motivation to look to Elman 2010's use of ranibizumab to treat DME. *See, e.g.* Exs. 1005-1008.

of neovascular leakage and…. gains in visual acuity….” Ex.1005; Ex.1007; Ex.1002, ¶¶164-172.

A POSA thus would be motivated to use additional initial monthly loading doses at least for some patients, particularly given that the Elman 2010 results reflected the work of clinicians to make in-field assessments of DME patients during the course of treatment. *See generally*, Ex.1002, ¶¶164-172.

Notably, as set out above, to show the obviousness of the claims here, there is no requirement that a POSA would have been motivated to adopt five initial loading doses for ***all*** patients. *Id.* But even if it were, based on the teaching of Elman 2010 that a fifth initial monthly loading dose was desirable for at least 78% of patients in the relevant group, Elman 2010 would make five initial loading doses an obvious starting point for the treatment of all patients, even if in routine practice a POSA would in fact adjust the regimen from there. Ex.1006; Ex.1002, ¶¶164-172.

2. A POSA Would Have Had a Reasonable Expectation of Success in Combining the 2009 Press Release with Elman 2010’s Dosing Regimen

A POSA would have reasonably expected success in making and using the claimed combination. Ex.1002, ¶¶173-179. The 2009 Press Release’s disclosure of a Phase II trial using loading and maintenance dosing of aflibercept to treat DME would provide a POSA with a reasonable expectation of success that such a regimen would work, including the use of maintenance dosing. *Id*. The claimed combination

merely ***adds*** one additional dose to the DME regimen with 3 monthly loading doses followed by 8-week maintenances doses disclosed in the 2009 Press Release. *Id.* The additional of a single dose would only provide an additional visual acuity gain for a patient. Moreover, Elman 2010 already had shown the effectiveness of treating DME via ranibizumab, and aflibercept had already been compared to ranibizumab in clinical trials and shown the same or better effectiveness. *Id.*; Ex.1006; Ex.1008.

Additionally, the dosing regimens taught by the 2009 Press Release suggests that additional initial loading doses (such as five, rather than three) would be safe and tolerable, as one of the Phase II trials was for monthly injections only—a standard and proven safe regimen for other anti-VEGF agents. Ex.1002, ¶174-178; Ex.1009. They further suggest that secondary doses spaced eight weeks apart would be sufficient to maintain the initial gains commonly seen with anti-VEGF agents, as another of the Phase II trials used eight week dosing throughout the trial period. *Id.*; *see also,* Ex.1044, U.S. Patent App. Pub. US 2007/0190058A1.

Accordingly, a POSA would have reasonably expected to succeed in using the claimed combination to treat DME. Ex.1002, ¶¶173-179.

D. Ground IV: Claims 13-16, 20, 22-24, and 29-32 Are Rendered Obvious by the 2009 Press Release Alone, or in Combination with Elman 2010, and/or Further in View of Do 2011

Claims 13-16, 20, 22-24, and 29-32 recite that the patient either loses less than or gains at least 15 letters Best Corrected Visual Acuity (BCVA). Ex.1002, ¶¶185-192.

To the extent these claims are given patentable weight (they should not be (*see* Section VII.B)), a POSA would have found it obvious and expected that at least some patients would achieve 15 letter gains when treated via five initial loading doses followed by 8-week maintenance dosing. Ex.1001. Importantly, the claims do not require the dosing regimen to apply to all patients populations in a one-size-fits-all approach such that ***all*** patients must lose less than or gain at least 15 letters. The claims are directed to a "method for treating diabetic macular edema in ***a*** patient." Ex.1002, ¶186.

As an initial matter, the 2009 Press Release discloses that, in the context of the VIEW 1 study for AMD, which involved the use of three monthly loading doses followed by 8-week dosing intervals, "[m]aintenance of vision is defined as losing fewer than three lines (***equivalent to 15 letters***) on the ETDRS chart." It further states that a secondary endpoint of that study is the "proportion of patients who

gained at least 15 letters of vision at week 52."[16] As to the Phase 2 trial for the treatment of DME, the Press Release explains that the "primary efficacy endpoint evaluation is mean ***improvement*** in visual acuity at six months"—not just maintenance. Ex.1002, ¶187.

A POSA would have found it obvious that the Phase 2 trial for treatment of DME, involving the same number of initial loading doses as the VIEW 1 study, would be expected to produce similar maintenance of vision and improvement ***for at least some patients*** as was expected to be produced in the VIEW 1 study. In other words, there would be nothing unexpected about a patient losing no less than or gaining at least 15 letters of vision (even if others did not). Ex.1002, ¶¶185-192. A POSA further would have expected that ***adding*** additional monthly loading doses via routine adjustment to the dosing regimen disclosed in the 2009 Press Release

[16] The 2009 Press Release further states that "[v]isual acuity is defined as the total number of letters read correctly on the Early Treatment Diabetic Retinopathy Study (ETDRS) chart, a standard chart used in research to measure visual acuity," directly disclosing that element.

would only have improved the number of patients losing no less than or gaining at least 15 letters of vision. *Id.*[17]

A POSA would find this expectation confirmed by Do 2011, which reports the results of the Phase 2 clinical trial disclosed by the 2009 Press Release. Ex.1045, Endnotes; Ex.1002, ¶189. Do 2011 discloses that after six months of treatment via the dosing regimen described in the 2009 Press Release ("2q8" in the chart below) that 17% of patients achieved at least a 15 letter gain, as shown in the chart below:

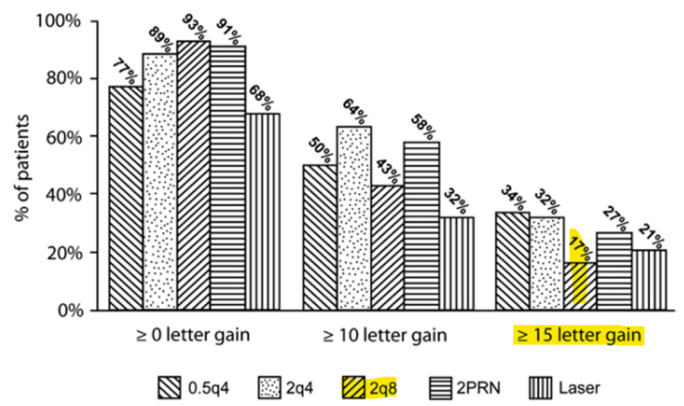


Figure 3. Percentage of patients with changes in BCVA at 6 months by treatment groups (laser and VEGF-Trap-Eye). Last observation carried forward analysis; n=44 (laser; VEGF Trap-Eye 0.5q4, 2q4); n=42 (VEGF Trap-Eye 2q8); n=45 (VEGF Trap-Eye 2PRN). Treatment groups are defined as follows: 0.5q4 = 0.5 mg every 4 weeks; 2q4 = 2 mg every 4 weeks; 2q8 = 2 mg for 3 initial doses then every 8 weeks; 2 PRN = 2 mg for 3 initial doses then as needed. BCVA = best-corrected visual acuity; PRN = as needed; q = every.

Ex.1045, 4.

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[17] This expectation is further supported by data showing, for instance, that a single dose of aflibercept produced a 9 letter gain (Ex.1008, 3) and that ranibizumab, which was expected to be less effective than aflibercept, produced significant gains in DME patients (Ex.1006).

A POSA would find that this data confirms that it was obvious and expected that some patients would gain 15 letters via loading and maintenance dosing. Ex.1002, ¶189. Additionally, as shown above, 32% of patients that received monthly 2mg doses ("2q4") achieved 15 letter gains at six months (i.e. after six total doses). Ex.1002, ¶¶190-191. A POSA would find that this data additionally confirms that additional initial monthly loading doses, including, for instance, five initial loading doses, would further increase the expectation of achieving 15 letter gains in at least some patients. Ex.1002, ¶¶185-192.

1. Alternatively, the Requirements of Claims 13-16, 20, 22-24, and 29-32 Are Inherent in Practicing the Method

Alternatively, the additional limitations of claims 13-16, 20, 22-24, and 29-32 are inherent in practicing the steps recited by the claimed method. *Bristol*, 246 F.3d, 1376; *see also* Ex.1002, ¶193. Where, as here, the limitation at issue is "the natural result of the combination of prior art elements," inherency may supply a missing claim limitation. *Persion Pharm. LLC v. Alvogen Malta Operations Ltd.*, 945 F.3d 1184, 1191 (Fed. Cir. 2019) (citations omitted).

Additionally, post-priority extrinsic evidence can be used to demonstrate what is necessarily present or inherent in a prior art embodiment. *Monsanto Tech. LLC v. E.I. DuPont de Nemours & Co.*, 878 F.3d 1336, 1345 (Fed. Cir. 2018). As set out

below in Section IX.E, the Eylea 2016 label discloses that the claimed acuity gains result from practice of the claimed method. Ex. 1050; *see also* Ex. 1016.

E. Ground V: Claims 13-16, 20, 22-24, and 29-32 Are Anticipated by the 2016 Eylea Label

As discussed in Section VII.B, dependent claims 13-16, 20, 22-24, and 29-32 should not be given patentable weight, as these claims merely recite the inherent, intended result of practicing the claimed method. To the extent these claims are given patentable weight, however, they are not entitled to a priority date earlier than April 29, 2019 filing date—the date these claims were added by preliminary amendment. Ex.1012, 1-60. This is because the specification does not provide written support for the claimed regimen achieving any of the results recited in those claims. Accordingly, these claims are anticipated by the Eylea Label from 2016.[18] Ex.1002, ¶¶194-201.

Notably, the Federal Circuit has previously affirmed the Board's determination that certain challenged claims were not entitled to prior application's priority date due to inadequate written description support in prior application, and held that the prior art in view of later priority date as a result anticipates those challenged claims. *Indivior UK Ltd. v. Dr. Reddy's Lab'ys S.A.*, 18 F.4th 1323, 1326

[18] Petitioner reserves the right to challenge the claims as lacking written description should they be construed to have patentable weight.

(Fed. Cir. 2021); *see also Samsung Elecs. Co., Ltd. v. Acorn Semi, LLC*, No. IPR2020-01205, 2022 WL 131221 (P.T.A.B. Jan. 12, 2022).

1. If the Recited Results Are Given Patentable Weight, Claims 13-16, 20, 22-24, and 29-32 Are Not Entitled to a Priority Date Earlier Than April 29, 2019

Claims 13-16, 20, 22-24, and 29-32 recite "wherein the patient [loses less than/gains at least]" 15 letters of Best Corrected Visual Acuity (BCVA) score (and further specify BVCA is measured according to an ETDRS letter score). The patent does not disclose any such results from practice of the claimed method; in fact, it discloses no results at all for a regimen including five loading doses. The claimed dosing regimen of five initial 2 mg doses followed by 8-week maintenance dosing is only identified in Example 7's listing of twenty different dosing regimens in the specification. Ex.1001, 15:36-17:27. No results are reported for that regimen. Thus, a POSA could not conclude that applicants possessed the invention of a dosing regimen for DR/DME with five initial monthly loading doses that achieved the recited BVCA scores if given patentable weight.

While the patent does report the results of the use of three initial loading doses in Example 5, it does not, unlike Do 2011, report that any patient achieved a 15 letter gain. Instead, the highest reported gain is 13 letters. *See* Ex.1001, Table 2, col. 14:9-54. Thus, if the results of the claimed method are given patentable weight then the

patent fails to disclose possession of the claimed invention and is not entitled to a priority date earlier than April 29, 2019. Ex.1002, ¶¶195-199.

The facts are similar to *Biogen Int'l GMBH v. Mylan Pharms. Inc.*, 18 F.4th 1333, 1343 (Fed. Cir. 2021). There, the relevant dose was "listed only once in the entire specification" without associated results, which the Federal Circuit found "constitutes a significant fact that cuts against Biogen's case, particularly because it appears at the end of one range among a series of ranges…." *Id*. Accordingly, the Federal Circuit concluded that a POSA would not have found guidance in the specification to the specific therapeutic dosage, and thus the patent lacked written description for the alleged results.

Here, the prior art discloses considerably more than the specification as to the claimed method and efficacy thereof. In fact, while Do 2011 teaches that both three initial loading doses and monthly loading doses produced a 15 letter gain in patients with DR/DME, there is no such equivalent disclosure in the '601 patent. It cannot be the case that Do 2011, let alone the rest of the art, does not teach the claimed results, while the specification sufficiently discloses the results. Ex.1002, ¶¶195-199.

2. The 2016 Eylea Label Anticipates Claims 13-16, 20, 22-24, and 29-32 If They Are Not Entitled to a Priority Date Earlier Than 2019

The 2016 Eylea Label discloses the dosing regimen recited by the independent claims: "[t]he 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)." Ex.1050; *see also* Ex.1016, Eylea 2023 Label.

The Label also includes efficacy data from the VIVID and VISTA Studies evaluating the claimed aflibercept dosing regimen for treating DME and DR. Ex.1050. Table 7 shows that ~31% (at Week 100) or ~33% (at Week 52) of patients gained at least 15 letters in BCVA upon administering aflibercept for DME according to the claimed dosing regimen. *Id.,* 22; *see also* Ex.1016, 31. Table 8 shows that 32-38% of patients achieved greater than or equal to 2-Step improvement from baseline in the ETDRS-DRSS score at Week 100 upon administering aflibercept for DR, which include *at least some* with a three-step improvement and 15 letters in BCVA. *Id.,* 24; Ex.1002, ¶¶96, 201 (discussing how to translate step improvement scores to BCVA); *see also*, Ex.1016, 33. These claims are anticipated by the Eylea 2016 Label. Ex.1050, Ex.1016; Ex.1002, ¶¶200-201.

F. Ground VI: Claims 17, 25, and 33 Are Rendered Obvious by the 2009 Press Release Alone or in View of Elman 2010 and Further in View of the CATT and PIER Studies

As set out in Section VII.C, the exclusion criteria should not be given patentable weight. Accordingly, these claims are rendered obvious for the same reasons as set forth in Grounds II and III. Even if the exclusion criteria are given patentable weight, claims 17, 25, and 33 are obvious. The 2009 Press Release does not recite exclusion criteria. The claimed exclusion criteria, however, were well known in the art and are disclosed therein. Ex.1002, ¶¶62-69, 202-208.

Specifically, the CATT and PIER Studies (Exs. 1004, 1017-1018) described above in Section VIII.F, included exclusion criteria for clinical trials of the leading intravitreally injected anti-VEGF treatments that are the same as those claimed by the ’601 patent, as is shown in Table 1 above in Section VIII.F. Applying these exclusion criteria in combination with the methods as described in connection with Grounds III and IV above renders the claimed method obvious.

Moreover, the ’601 patent does not identify anything specifically unique or novel about the combination of the exclusion criteria together or with the claimed method. Ex.1002, ¶¶202-208. Instead, they are merely listed along with 34 other exclusion criteria in the specification, without any further discussion. *Id.*

Finally, POSAs would have been motivated to adopt the exclusion criteria of the CATT and PIER studies and exclude patients from treatment via intravitreal

injection based on active inflammation and active infections in order follow the standard of care, as well as to solve a problem that references such as the 2009 Press Release and Dixon address directly. *See* Ex.1002, ¶¶62-69, 202-208; Ex.1004, 9; Ex.1008-9; Ex.1015; Ex.1047-49.

G. There Are No Secondary Considerations

Finally, though it is not Petitioner's burden, Patent Owner cannot establish secondary considerations that would support a finding of non-obviousness, and particularly it cannot overcome the strong *prima facie* case of obviousness presented in Grounds I-VI. *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1246 (Fed. Cir. 2010); Ex.1002, ¶¶209-214.

No Unexpected Results. As set out in Section VII, the Challenged Claims do not require any particular levels of efficacy. Accordingly, Patent Owner's anticipated argument—asserted during prosecution of related claims in the family (Ex.1046, '681 patent PH, 488-493)—that the less frequent regimen of the Challenged Claims produced "unexpected results" is entirely irrelevant. *Ormco*, 463 F.3d, 1311-12; *Kao*, 639 F.3d, 1068-69; Ex.1002, ¶¶211. Furthermore, as set out in Sections IX.A-F, any results claimed in the '601 patent are obvious and inherent in disclosure of the claimed method.

No Long-Felt, Unmet Need. Patent Owner cannot establish a "need" or show that any such need was "long-felt." Any purported need for the claimed dosing

regimen had been fulfilled long before the ’601 patent was filed. Ex.1002, ¶212. Indeed, POSAs had been implementing such regimens for DME well before the priority date. *Id*. And other successful, intravitreally injected anti-VEGF treatments existed. *Id.*

No Nexus. Patent Owner cannot establish nexus to the “merits of the claimed invention” of the ’601 patent because the art discloses all of the claimed elements. *Novartis AG v. Torrent Pharms. Ltd.*, 853 F.3d 1316, 1330–31 (Fed. Cir. 2017) (citing *In re Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011). There is no “novel combination or arrangement of known individual elements” in the recited limitations—rather, they are routine. Ex.1002, ¶213.

X. DISCRETIONARY DENIAL IS UNWARRANTED

Discretionary denial is unwarranted here.

A. The *Becton Dickinson* Factors Do Not Favor Denial Under 35 U.S.C. § 325(d)

The Board uses a two-part framework to analyze whether denial under § 325(d) is proper. *Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH*, IPR2019-01469, Paper 6, 7 (PTAB Feb. 13, 2020). The Board considers several nonexclusive factors (“*Becton Dickinson* factors”) within this framework to provide useful insight into how to apply each prong, each of which is discussed below. *Id.*, 4; *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8,

17-18 (Dec. 15, 2017) (precedential as to Section III.C.5, first paragraph) ("*Becton, Dickinson*").

1. *Becton Dickinson* Factors (a), (b), and (d)

Petitioner's arguments and prior art here are neither the same nor substantially the same art or arguments previously before the Office during prosecution of the '601 patent.

First, as set out in Section V.C, the Examiner only issued non-statutory double patenting rejections during prosecution and no § 102 or § 103 rejections. Petitioner asserts combinations involving references never expressly considered during prosecution that provide additional, non-cumulative disclosures, including Elman 2010 which was not before the Examiner In other words, the art and arguments presented here were neither "involved" nor "evaluated" during prosecution, and therefore, they are not the same or substantially the same as that previously considered by the Office. *Becton, Dickinson*, IPR2017-01586, Paper 8, 17; 35 U.S.C. § 325(d).

Patent Owner may argue that the 2009 Press Release was identified on an IDS along with over 20 other references and marked "considered" by the Examiner. But, even if 2009 Press Release was considered, it is only one primary reference here. The Examiner did not consider either Shams or Elman 2010, nor the additional arguments presented herein. "The Board has consistently declined exercising its

discretion under Section 325(d) when[, as here] the only fact a Patent Owner can point to is that a reference was disclosed to the Examiner during the prosecution." *Amgen Inc. v. Alexion Pharms., Inc.*, IPR2019-00739, Paper 15, 62 (Aug. 30, 2019).

2. *Becton Dickinson* Factors (c), (e), and (f)

Because Petitioner presents new arguments and combinations herein, analysis of *Becton Dickinson* factors (c), (e), and (f) is unnecessary. Even if the grounds presented herein were considered previously presented to the Office somehow, however, the Examiner made clear errors in evaluating the art.

In particular, as discussed in Section V.C, the Examiner issued obviousness-type double patenting rejections of the DR/DME claims over reference patents describing a dosing regimen consisting of three initial loading doses at four week intervals followed by maintenance doses at eight week intervals. But when the applicants took a terminal disclaimer to overcome those rejections, the Examiner failed to make an obviousness rejection over, for instance, the 2009 Press Release that also disclosed the identical dosing regimen. Applicants thus were allowed the DR/DME claims without ever addressing the substance of the Examiner's obviousness rejection. This was clear error.

As set out in Section IX, the DR/DME claims should be found obvious over the dosing regimen in the 2009 Press Release. The Examiner failed to apply the same (correct) logic applied in evaluating the reference patents to an evaluation of

the prior art, including the 2009 Press Release. Accordingly, discretionary denial is thus not warranted because the Examiner overlooked and failed to consider each reference's disclosures included here, constituting material error.

B. The *General Plastic* Factors Do Not Support Denial Under 35 U.S.C. § 314(a)

In *General Plastic*, the Board articulated a non-exhaustive list of factors to be considered in determining whether to exercise discretion under § 314(a) to deny a petition that challenges the same patent as a previous petition. IPR2016-01357, Paper 19 (PTAB Sept. 6, 2017) (precedential), slip op. 9-10. The *General Plastic* factors were articulated in response to a petitioner that filed serial, harassing petitions against a patent owner. Those factors favor institution.

Here, there is no evidence that Petitioner seeks to harass or unduly burden Patent Owner with its petition. Quite the opposite: this petition challenges only the DR/DME claims that are not subject to IPR right now, and Petitioner chose to join Mylan's IPR as to the non-DR/DME claims by filing an identical petition to Mylan's and taking a silent understudy role. While Petitioner could have challenged the non-DR/DME claims independently, either in this petition or a separate one, creating more burden for Patent Owner, it chose not to do so and instead challenges only those claims not subject to the prior IPR.

Notably, Petitioner cannot control the fact that Mylan chose to challenge only the non-DR/DME claims of the ’601 patent in its IPR. Mylan’s choice not to challenge the DR/DME claims—which may be related to the indications for which Mylan intends to seek (or not seek) regulatory approval—should not be held against Petitioner. Indeed, doing so would be deeply prejudicial, as it would allow one party to effectively block later challenges to certain subject matter in a patent by filing a petition against some claims but not others.

This common sense insight is reflected in the fact that the primary *General Plastic* factor examines “whether the same petitioner previously filed a petition directed to the ***same claims***….” *Qualcomm Inc. v. Monterey Research, LLC*, IPR2020-01493, Paper 11, 15 (March 8, 2021).

This is thus not a case that raises the “potential inequity based on a petitioner’s filing of serial attacks” against a patent—the concern at the heart of *General Plastic*. Instead, Petitioner here has reasonably sought to join the first IPR against the non-DR/DME claims with a copycat petition, rather than filing a new IPR against those claims, while also addressing the separate DR/DME claims that Mylan did not challenge in its petition.

The fact that there is no evidence Petitioner is seeking to burden Patent Owner with serial petitions against the ’601 patent—and, in fact, is seeking to do the opposite by filing a copycat petition as to the non-DR/DME claims—should “weigh[]

especially heavily against a discretionary denial." *See Unified Patents, Inc. v. Certified Measurement, LLC*, IPR2018-00548, Paper 7, 7-8 (Sept. 5, 2018).

1. *General Plastic* Factors 2-5

Absent "extenuating circumstances" such as a showing of coordination between petitioners, once resolution of factor 1 indicates that Petitioner had not previously filed a petition against the same patent claims, factors 2-5 bear little relevance. *Qualcomm*, Paper 11, 15 (March 8, 2021).

There are no such extenuating circumstances here. There was no coordination between Mylan and Petitioner or any other relationship as to the preparation of this petition. Thus factors 2-5, which focus on the petitioner's prior knowledge of the art and of the patent owner's response to it, bear no relevance.

Even if they did, the concerns regarding efficiency and fairness generally addressed by those factors are not present here because Mylan's first petition (and Petitioner's copycat petition) are directed to a different sets of claims—non-DR/DME versus DR/DME. Petitioner did not gain any unfair advantage by waiting to file. To the contrary, all Petitioner has done is simplify the issues by filing a copycat petition on the non-DR/DME claims, and addressing in this petition only the DR/DME claims that are not addressed in Mylan's petition.

Institution is favored under these circumstances, where differences in the issues raised between co-pending petitions mean the "Petitioner could not have

received any insight into the Board's position on the merits of the arguments [in the Petition] in that proceeding…." *The Data Company Technologies Inc, v. Bright Data Ltd.*, IPR2022-00135, Paper 12, 14.

Thus, if considered, factors 2 through 5 also weigh in favor of institution.

2. *General Plastic* Factors 6-7

Factors 6-7 consider the Board's finite resources and requirement to issue a final determination within a year of institution. *Qualcomm*, 18.

Resolving the issues presented by the grounds Petitioner proposes will not require any more of the Board's resources than a standard IPR in which a prior petition has not been filed, and can be done within a year of institution. The Board can address the grounds raised in Petitioner's petition independent of its consideration of Mylan's grounds, which are entirely different.

Factors 6 and 7 thus favor institution.

3. Additional Factors

As some panels have observed, when a subsequent petitioner is different from the previous petitioner, prejudice to the petitioner from a denial and the Patent Owner's litigation activity can be considered. *Microsoft Corp. v. Iron Oak Techs.,* LLC, IPR2019-00107, Paper 8, 53-54, 58 (May 15, 2019).

Petitioner would be prejudiced if institution is denied based on Mylan's petition. Mylan's petition does not address the DR/DME claims, and they directed to a different indication than is addressed in Mylan's petition.

Additionally, multiple petitions have been filed against the '601 patent because of Patent Owner's litigation activity in listing it in the Purple Book for Eylea. This indicates Patent Owner's belief its label for Eylea is covered by the '601 patent. Patent Owner also decided to include the '601 patent in the patents originally asserted against Mylan, including in its "top 6" patents. These factors thus weigh in favor of institution.

C. The *Fintiv* Factors Do Not Support Denial Under 35 U.S.C. § 314(a)

Fintiv sets forth the factors that that the Board weighs in determining whether to exercise discretion to deny institution of the *inter partes* review proceeding under 35 U.S.C. § 314(a) due to a pending district court proceeding. *See Apple Inc. v. Fintiv, Inc.*, Paper 11, 5-6. *Id.*

Here, the *Fintiv* factors do not favor a discretionary denial. Petitioner is not involved in the Patent Owner/Mylan litigation. In that litigation, Regeneron controls what patents and what claims will be asserted according to the Court's Scheduling Order, and Patent Owner will be forced to narrow to *no more than 3 patents and 25 claims* before trial. Ex.1051, Scheduling Order, 2. Further, Patent Owner has represented to the Court that it would be prepared to reduce the number of asserted

claims even further. Ex.1052, September 28, 2022 Status Conference Transcript, 9:9-11.

While Petitioner has no insight into what claims are being asserted from the ’601 patent, it is highly likely that none of the DR/DME claims are being asserted, given that Mylan chose ***not*** to challenge the DR/DME claims in its ’601 IPR. This indicates it is likely that Mylan is pursuing a “carve out” strategy for the DME and DR indications, which would eliminate the possibility that the DR/DME are addressed in that litigation.

Regardless, because Patent Owner has full control of what patent and claims it asserts in the Patent Owner/Mylan litigation, it should not be allowed to argue Petitioner’s petition should be dismissed on discretionary grounds without committing to litigate the ’601 patent and the Challenged Claims in that litigation. Absent such a commitment, any argument from Patent Owner regarding *Fintiv* should be disregarded, because Patent Owner could turn around and dismiss those claims from the litigation, thereby avoiding any challenge.

Moreover, Patent Owner and Mylan may settle their litigation. In that case, Petitioner would have to re-file a petition, delaying its ability to invalidate the claims of the ’601 patent. That would unacceptably delay matters and frustrate one of the primary purposes of IPRs—to provide an expedient alternative to litigation.

1. *Fintiv* Factors 1 and 2

Fintiv Factors 1 and 2 weighs against discretionary denial. Factor 1 concerns "whether the court granted a stay or evidence exists that one may be granted if a proceeding is instituted." *Fintiv,* 5-6. *Fintiv* Factor 2 relates to the "proximity of the court's trial date to the Board's projected statutory deadline [for FWD]." *Id*., 9. Both factors are concerned with duplication of effort and inefficiency.

Here, no motion for stay has been filed in the Mylan Litigation, and trial is scheduled for June 12-23, 2023. Without "specific evidence" of how the court would rule on any stay motion, this factor is neutral. *Sand Revolution II, LLC v. Cont'l Intermodal Grp.—Trucking LLC*, IPR2019-01393, Paper 24, 7 (June 16, 2020) (informative). And, because the DR/DME claims will likely not be addressed at all, concerns about "duplication of effort" and "inefficiency" are minimal to non-existent.

2. *Fintiv* Factor 3

Fintiv Factor 3 considers the "investment in the parallel proceeding by the court and parties." *Fintiv*, Paper 11, 9. This factor weighs in favor of institution. Petitioner has invested no resources into that litigation and "much of the district court's investment relates to ancillary matters untethered to the validity issue itself." *See Sand Revolution II, LLC v. Continental Intermodal Group – Trucking LLC*,

IPR2019-01393, Paper 24, 10–11 (June 16, 2020) (informative). Therefore, Factor 3 favors institution.

3. *Fintiv* Factor 4

Fintiv Factor 4 considers whether "the petition includes the same or substantially the same claims, grounds, arguments, and evidence as presented in the parallel proceeding." *Fintiv*, Paper 11, 12. As an initial matter, because Petitioner and Mylan are unrelated competitors, Petitioner has no control over the Mylan's Litigation and is not aware of any specific overlap between the claims, prior art, and invalidity theories at issue in the parallel proceeding and this IPR.

It is highly likely, however, that the DR/DME claims are not or will not be litigated in the Mylan litigation. Therefore, it is likely that none of the DR/DME claims are "simultaneously adjudicated" in the District Court. Moreover, if institution is denied here on a discretionary basis, Patent Owner will have eliminated this IPR while allowing Patent Owner to later withdraw the majority of the DR/DME claims from the District Court to the extent asserted, shielding those claims from ***any*** invalidity challenge in ***any*** venue.

Factor 4 weighs in favor of institution.

4. *Fintiv* Factor 5

Factor 5 concerns "whether the petitioner and the defendant in the parallel proceeding are the same party." *Fintiv*, Paper 11, 5-6. Petitioner and Mylan are

unrelated competitors, and Petitioner is neither a co-defendant with Mylan nor does it have any control over the Mylan Litigation. Factor 5 weighs in favor of institution. *Fintiv*, IPR2022-00976, Paper 9, 11-12.

5. *Fintiv* Factor 6

The *Fintiv* factors require the Board to take "a holistic view of whether efficiency and integrity of the system are best served by denying or instituting review." *Fintiv*, Paper 11, 6. The Board has explained that if the merits of the petition are strong, institution may "serve the interest of overall system efficiency and integrity because it allows the proceeding to continue in the event that the parallel proceeding settles or fails to resolve the patentability question presented in the PTAB proceeding." *Fintiv*, 15. That holds true here. Petitioner submits that its petition has significant substantive merit because this Petition is premised on clear, understandable prior art that neither the Patent Office nor prior IPRs evaluated, and includes challenges to claims that have never been challenged and will unlikely be addressed in the district court.

XI. CONCLUSION

For the foregoing reasons, Petitioner has established a reasonable likelihood that claims 10-33 and 46-47 are unpatentable. Petitioner therefore respectfully requests that *inter partes* review of the '601 patent be granted.

DATED: March 26, 2023 Respectfully submitted,

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CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(a) and (d), the undersigned hereby certify that the foregoing Petition for *Inter Partes* Review of U.S. Patent No. 10,888,601 complies with the type-volume limitation of 37 C.F.R. § 42.24(a)(1)(i) and (b)(1)(i) permitting a petition of up to 14,000 words because, exclusive of the exempted portions, it contains 13,980 words as counted by the word processing program used to prepare the paper.

Date: March 26, 2023

Respectfully submitted,

By: /Raymond N. Nimrod/

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CERTIFICATE OF SERVICE

In accordance with 37 C.F.R. §§ 42.6(e) and 42.105, I hereby certify that true and correct copies of Petitioner's Power of Attorney, Petition for *Inter Partes* Review of U.S. Patent No. 10,888,601, and Exhibits 1001-1057 will be served on March 27, 2023 via FedEx Priority Overnight on Patent Owner at the correspondence address of record for U.S. Patent No. 10,888,601 as evidenced in in Patent Centers:

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