UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

BIOCON BIOLOGICS INC.,
Petitioner

v.

REGENERON PHARMACEUTICALS, INC.,
Patent Owner

Inter Partes Review No.: IPR2024-00201

U.S. Patent No. 10,888,601 B2
Filed: April 29, 2019
Issued: January 12, 2021
Inventor: George D. Yancopoulos

Title: USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 10,888,601 B2

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Cases

Statutes

Other Authorities

Regulations

EXHIBIT LIST

Exhibit	Description
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
	(September 28, 2008), https://investor.regeneron.com/news-releases/news-release-details/vegf-trap-eye-final-phase-2-results-age-related-macular ("September 28, 2008 Press Release")
1012	Certified Prosecution History of U.S. Patent No. 10,888,601 ("'601 patent PH")
1013	Adis R&D Profile, Aflibercept: AVE 0005, AVE 005, AVE0005, VEGF Trap - Regeneron, VEGF Trap (R1R2), VEGF Trap-Eye. Drugs R D. 2008;9(4):261-269. ("Adis")
1014	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, published April 28 2010, available at https://www.aaojournal.org/article/S0161-6420(10)00243-5/fulltext ("Elman AAO Website)
1015	Lucentis ® Original Approved Labeling (2006), available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/125156s000 0_Lucentis_Prntlbl.pdf
1016	Eylea Label 2023 available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/125387s07 5lbl.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.e du/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")

Exhibit	Description
1020	History of Changes for Study: A Study of rhuFab V2 (Ranibizumab) in Subjects With Subfoveal Choroidal Neovascularization Secondary to Age-Related Macular Degeneration (AMD) (NCT00090623), available at: https://clinicaltrials.gov/ct2/history/NCT00090623?V_1=View#StudyPageTop.
1021	ClinicalTrials.gov Background, available at: https://clinicaltrials.gov/ct2/about-site/background
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")
1028	Halpern MT, Schmier JK, Covert D, Venkataraman K. Resource utilization and costs of age-related macular degeneration. Health Care Financ Rev. 2006;27(3):37-47. ("Halpern 2006").

Exhibit	Description
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")

Exhibit	Description
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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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1044	U.S. Patent App. Pub. US 2007/0190058A1
1045	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 (published online on May 5, 2011). ("Do 2011")
1046	Certified Prosecution History of U.S. Patent No. 10,130,681 B2 ("'681 patent PH")
1047	Eylea Label 2011 available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/125387lbl.pdf
1048	Glenn J. Jaffe, Paul Ashton, P. Andrew Pearson, Intraocular Drug Delivery (2006) ("Jaffe").

Exhibit	Description
1049	Steps for a Safe Intravitreal Injection Technique (2009), available at: https://www.retinalphysician.com/issues/2009/july-aug/steps-for-a-safe-intravitreal-injection-technique
1050	Eylea Label May 2016, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/125387s051lbl.pdf ("Eylea 2016 Label")
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")
1058	Prosecution History of U.S. Patent No. 10,888,601 (submissions post-August 3, 2022)
1059	Petition in *Samsung Bioepis Co., Ltd. v. Regeneron Pharms.*, *Inc.*, IPR2023-00739 (Paper 1) ("Samsung IPR")
1060	Institution Decision in *Samsung Bioepis Co., Ltd. v. Regeneron Pharms.*, *Inc.*, IPR2023-00739 (Paper 9)
1061	Regeneron July 2023 Disclaimer (IPR2023-00739 Ex.2002)
1062	Exhibit 4P to Pretrial Memorandum in *Regeneron Pharms., Inc. v. Mylan Pharms. Inc.*, No. 22-cv-61 (N.D.W. Va. May 26, 2023)
1063	Docket Navigator, Time to Trial
1064	Patent Owner Preliminary Response in *Samsung Bioepis Co., Ltd. v. Regeneron Pharms.*, *Inc.*, IPR2023-00739 (Paper 6)

Biocon Biologics Inc. ("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 10-12, 17-19, 21, 25-28, and 33[1] (the "Challenged Claims") of U.S. Patent No. 10,888,601 ("'601 patent") (Ex.1001), assigned to Patent Owner, Regeneron Pharmaceuticals, Inc. ("Regeneron" or "PO"). This petition replicates Samsung Bioepis Co., Ltd.'s ("Samsung") petition filed in IPR2023-00739 (the "Samsung IPR"), with the exception of the petitioner-specific mandatory notices and certain sections relating to discretionary denial, and asserts the same grounds of unpatentability of the '601 patent upon which the Patent Trial and Appeal Board (the "Board") has already instituted review in the Samsung IPR. Accordingly, there exists a reasonable likelihood that Petitioner will prevail in demonstrating unpatentability of at least one of the Challenged Claims, and Petitioner respectfully

[1] As the Board's Institution Decision in the Samsung IPR notes, while Samsung originally challenged claims 10-33, 46, and 47, PO has since disclaimed claims 13-16, 20, 22-24, 29-32, and 46-47. Ex.1060, Samsung IPR Institution Decision, 2 n.1. Accordingly, only claims 10-12, 17-19, 21, 25-28, and 33 are currently being challenged in the Samsung IPR, and thus the focus of this petition, being filed for the purpose of seeking joinder with the Samsung IPR, likewise is directed only to claims 10-12, 17-19, 21, 25-28, and 33.

seeks to join the Samsung IPR as set forth in the accompanying motion for joinder filed concurrently. Samsung indicated it does not oppose Petitioner's motion for joinder.

This Petition is timely and proper under 35 U.S.C. § 315(b) (the 1-year time bar "shall not apply to a request for joinder under subsection (c)") and 35 U.S.C. § 315(c).

I. INTRODUCTION

The Challenged Claims are directed to methods of 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. For example, each of the 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 Decl., ¶¶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 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

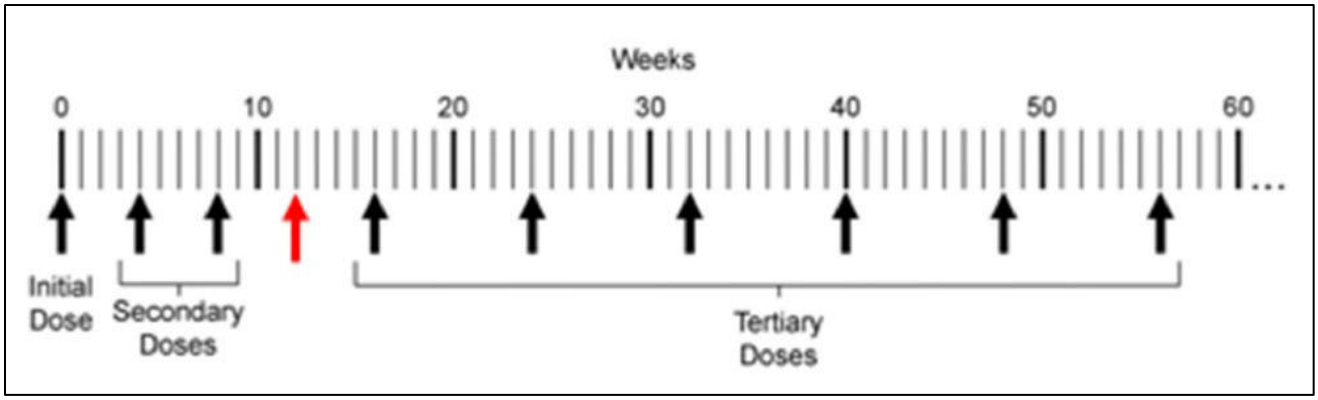
five monthly loading doses for any indication, let alone DR/DME; instead, the only discussion of five doses is part of a list of ***twenty*** other loading/maintenance dosing regimens it discloses for DR/DME, none of which are supported by additional data. *Id.,* 15:35-17:28.

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 Ground 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 some claims of the '601 patent Mylan did not

challenge any of the claims challenged in this petition. The claims previously challenged by Mylan are not directed to methods of treating DR/DME with a regimen beginning with 5 monthly injections. There is no overlap between the Challenged Claims in this petition and those in Mylan's prior petition. Moreover, the compelling merits of the challenges in the Samsung IPR, and the fact that the majority (10 of the 12) of the Challenged Claims have not been the subject of a district court trial, nor will they be before the Final Written Decision in the Samsung IPR, defeat any PO argument for *Fintiv* discretionary denial.

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 (37 C.F.R. § 42.8)

A. REAL PARTIES-IN-INTEREST (37 C.F.R. § 42.8(b)(1))

Petitioner Biocon Biologics Inc., Biocon Limited, Biocon Biologics Limited, Biocon Biologics UK Limited, and Biosimilar Collaborations Ireland Limited are real parties-in-interest ("RPIs") to the current Petition. Biocon Biologics Limited is a subsidiary of Biocon Limited, a publicly traded company. Biocon Biologics UK Limited is a wholly owned subsidiary of Biocon Biologics Limited, and Biosimilar Collaborations Ireland Limited and Biocon Biologics Inc. are wholly owned subsidiaries of Biocon Biologics UK Limited.

Further RPIs include Mylan Pharmaceuticals Inc. ("Mylan") and Johnson &

Johnson. Viatris Inc. and Mylan Inc. are parent companies of Mylan Pharmaceuticals Inc. Accordingly, Viatris Inc., Mylan Inc., and Mylan Pharmaceuticals Inc. are identified as RPIs to the current Petition. Momenta Pharmaceuticals, Inc. and Janssen Research & Development LLC are wholly-owned subsidiaries of Johnson & Johnson, a publicly held company. Momenta Pharmaceuticals, Inc., Janssen Research & Development LLC, and Johnson & Johnson are also RPIs to the current Petition.

No other parties exercised or could have exercised control over this Petition; no other parties funded, directed, and controlled this Petition. *See* Trial Practice Guide, 15-16 (November 2019).

B. RELATED MATTERS (37 C.F.R. § 42.8(b)(2))

Samsung filed a petition requesting *inter partes* review of the Challenged Claims on March 26, 2023. *See* Ex.1059, Samsung IPR Petition. On October 20, 2023, the Board instituted *inter partes* review of the Challenged Claims based on the grounds identified in Samsung's petition. Ex.1060, Samsung IPR Institution Decision.

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, RPI Mylan filed petitions requesting *inter partes* review of those two patents. *See Mylan Pharms. Inc. v. Regeneron Pharms., Inc.*, No. IPR2021-00880 (P.T.A.B.) ("'069 IPR") and *Mylan*

Pharms. Inc. v. Regeneron Pharms., Inc., No. IPR2021-00881 (P.T.A.B.) ("'338 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"). RPI Mylan filed a petition requesting *inter partes* review of the '681 patent on July 1, 2022 (*Mylan Pharms. Inc. v. Regeneron Pharms., Inc.*, IPR2022-01225 (P.T.A.B.)) ("Mylan '681 IPR"). The Mylan '681 IPR was instituted on January 11, 2023. Ex.1054, Mylan '681 IPR Institution Decision ("'681 ID").

Petitioner identifies *Mylan Pharms. Inc. v. Regeneron Pharms., Inc.*, No. IPR2022-01225 (P.T.A.B.) and *Mylan Pharms. Inc. v. Regeneron Pharms., Inc.*, No. IPR2022-01226 (P.T.A.B.). Petitioner also identifies *Mylan Pharms. Inc. v. Regeneron Pharms., Inc.*, No. IPR2021-00880 (P.T.A.B.), *Mylan Pharms. Inc. v. Regeneron Pharms., Inc.*, No. IPR2021-00881 (P.T.A.B.), *Mylan Pharms. Inc. v. Regeneron Pharms., Inc.*, No. IPR2023-00099 (P.T.A.B.), *Regeneron Pharms., Inc. v. Mylan Pharms. Inc.*, No. 2023-1395 (Fed. Cir.), *Regeneron Pharms., Inc. v. Mylan Pharms. Inc.*, No. 2023-1396 (Fed. Cir.), and *Regeneron Pharms., Inc. v. Mylan Pharms. Inc.*, 1:22-cv-00061-TSK (N.D.W. Va.). To the best of Petitioner's knowledge, the following are additional judicial or administrative matters that would

affect, or be affected by, a decision in this proceeding: *Apotex Inc. v. Regeneron Pharmaceuticals, Inc.*, No. IPR2022-01524 (P.T.A.B.), *Samsung Bioepis Co., Ltd. v. Regeneron Pharms., Inc.*, IPR2023-00442 (P.T.A.B.), *Samsung Bioepis Co., Ltd. v. Regeneron Pharms., Inc.*, IPR2023-00884 (P.T.A.B.), *U.S. v. Regeneron Pharms., Inc.*, No. 1:20-cv-11217-FDS (D. Mass.), and *Horizon Healthcare Servs., Inc. v. Regeneron Pharms., Inc.*, No. 1:22-cv-10493-FDS (D. Mass.).

U.S. Patent Nos. 9,254,338 B2; 9,669,069 B2; 10,857,205 B2; 10,828,345 B2; 10,130,681 B2; 11,253,572 B2; 11,559,564; 11,707,506 B2; and 11,730,794; and U.S. Patent Application Nos. 17/072,417; 17/112,063; and 18/496,472 each claim the benefit of the '601 patent's purported priority date.

C. LEAD AND BACK-UP COUNSEL (37 C.F.R. § 42.8(b)(3)-(4))

Petitioner identifies its lead and backup counsel below. A Power of Attorney is filed concurrently herewith under 37 C.F.R. § 42.10(b).

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

Please direct all correspondence to lead and back-up counsel at the contact information above. Petitioner also consents to service by email at:

MYL_REG_IPR@rmmslegal.com. Petitioner intends to file a motion seeking the admission of William A. Rakoczy, Heinz J. Salmen, Eric R. Hunt, Lauren M. Lesko, and Jake R. Ritthamel to appear *pro hac vice* when authorized to do so.

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

The required fees are submitted herewith. The undersigned representative of Petitioner hereby authorizes the Patent Office to charge any additional fees or credit any overpayment to Deposit Account 503626.

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 10-12, 17-19, 21, 25-28, and 33 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 II[2]	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 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

[2] As noted above, only claims 10-12, 17-19, 21, 25-28, and 33 are currently being challenged in the Samsung IPR due to disclaimers that have been filed with regard to the other initially challenged claims. Ex.1060, Samsung IPR Institution Decision, 2 n.1. Accordingly, this petition does not address previously presented Grounds I, IV, and V given that those grounds were directed exclusively to claims that have now been disclaimed by PO.

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. Yancopoulos. *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 '601 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 with 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 13-16, 20, 22-24, and 29-32 have been disclaimed. Ex.1012, 5637; Ex.1061, 1.

Claims 46 and 47, which also were initially challenged by Samsung, have since been disclaimed. Ex.1061, 1.

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.[3] *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 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 PO took terminal disclaimers, the Examiner did not issue an obviousness rejection over that prior art. *Id*.; *see also*, Ex.1002, ¶¶75-78.

On July 11, 2022, PO disclaimed claims 3, 4, 13, 14, 22, 29, and 30 of the '601 patent. Ex.1012, 5637. On July 25, 2023, PO disclaimed claims 15, 16, 20, 23, 24, 31, 32, 46, and 47 of the '601 patent. Ex.1061, 1.

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[3] The applicants also amended the relevant independent Challenged Claims here to recite "in need thereof."

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 (“POSA”):

> 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 notes that in the Samsung IPR, PO did not contest the POSA definition, and the Board has determined that the definition is "reasonable and consistent with the prior art of record." Samsung IPR, Paper 9, 9. Thus, Petitioner proposes the same definition be adopted here. *See also* Ex.1002, ¶¶22-25.

VI. PRIORITY DATE

A. The Challenged Claims Are Not Entitled to a Priority Date Earlier Than July 12, 2013

The Challenged Claims 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 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.[4] *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 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.

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.

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[4] 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.

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

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

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.

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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.

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, 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. 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 '601 patent under 35 U.S.C. § 102(a) and (b); *see also* MPEP § 2128.[6] *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.

[6] 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).

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. 2008) ("PIER Study"), published February 2008, describes the PIER study and is prior art to the '601 patent under § 102(b).[7] *Id.*

E. 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 a 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, 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*.,

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[7] 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.

cl. 18, col. 2:32-36 ("The methods of the present invention can be used to treat…diabetic retinopathy")). For the purposes of this petition, Petitioner does not dispute that statement.[8]

IX. DETAILED GROUNDS FOR INVALIDITY

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. Ground VI addresses dependent claims 17, 25, and 33.

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

Given the PO's disclaimer of claims 46 and 47, this Petition does not address Samsung's initial Ground I.

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

[8] 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.

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.[9]

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-Eye,[10] 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.

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

[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 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").

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* Ex.1002, ¶155. Shams explains that "a treatment schedule comprising an initial

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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).

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 Therapeutic 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.[11] 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. POSAs would have reasonably expected that continuing regular initial dosing beyond a single injection would increase that success. Ex.1002, ¶¶146-158.

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[11] 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).

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

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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.

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.

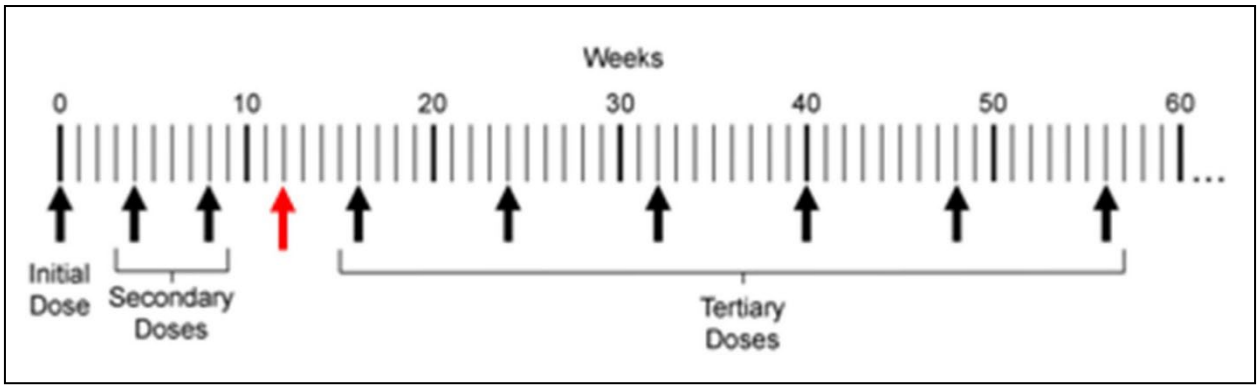
Elman was the most significant study of the treatment of DR/DME via an anti-VEGF agent at the time, and it strongly suggests the use of five initial monthly loading doses, at least for some patients. Ex.1002, ¶¶159-184. In fact, even if substantially less than 78% of patients required a fifth dose, the 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.[13] *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

[13] 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 addition 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 suggest 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

Given the PO's disclaimer of claims 13-16, 20, 22-24, and 29-32, this Petition does not address Samsung's initial Ground IV.

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

Given the PO's disclaimer of claims 13-16, 20, 22-24, and 29-32, this Petition does not address Samsung's initial Ground IV.

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.B, 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.D, 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.D. 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 to 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, PO 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, PO'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 Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1311-12 (Fed. Cir. 2006); *In re Kao*, 639 F.3d 1057, 1068-69

(Fed. Cir. 2011); 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. PO 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. PO 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 *Kao*, 639 F.3d 1068). 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, 7-9 (P.T.A.B. Feb. 13, 2020). The Board considers several nonexclusive factors (the "*Becton Dickinson* Factors") within this framework to

provide useful insight into how to apply each prong, each of which is discussed below. *Id.*, 8-9 n.10; *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8, 17-18 (P.T.A.B. Dec. 15, 2017) (precedential as to § III.C.5, first paragraph).

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 the art and arguments previously considered by the Office. *Becton, Dickinson*, IPR2017-01586, Paper 8, 17; 35 U.S.C.§ 325(d).

PO may argue that the 2009 Press Release was identified on an information disclosure statement along with over 20 other references and marked "considered" by the Examiner. *See* Ex.1012, 70. 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 (P.T.A.B. 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)

General Plastic is indisputably limited to situations where "the same petitioner previously filed a petition ***directed to the same claims of the same patent***." *General Plastic Indus. Co. v. Canon Kabushiki Kaisha*, IPR2016-01357, 2017 WL 3917706, at *4 (P.T.A.B. Sept. 6, 2017) (emphasis added). To the extent PO advances *General Plastic* arguments in this matter, the challenged DME/DR claims in the instant IPR (claims 10-12, 17-19, 21, 25-28, and 33), are different from the AMD treatment claims challenged in Mylan's prior IPR (*Mylan Pharms. Inc. v. Regeneron Pharms., Inc.*, No. IPR2022-01226 (P.T.A.B.)). Accordingly, neither Biocon nor Mylan has previously challenged the claims at issue in the Samsung IPR, a threshold issue from which most of the other *General Plastic* factors flow. Because the *same* claims have not previously been challenged by the *same* party, *General Plastic* Factors 1-5 are not applicable on their face, because there are no "second" or "multiple" petition(s). *See General Plastic*, 2017 WL 3917706 at *4. On Factor 6,

which considers the finite resources of the Board, *id.*, Petitioner notes that the Samsung IPR already has been granted institution and will be proceeding regardless of Biocon's participation, further weighing against denial.

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

Under the Director's recent guidance, at least because of the compelling merits of the challenges in the Samsung IPR, any PO argument applying the factors for *Fintiv* discretionary denial, *Apple Inc. v. Fintiv, Inc.*, IPR2020-00019, Paper 11, 5-6 (P.T.A.B. Mar. 20, 2020), should be rejected.

As to *Fintiv* Factors 1-3, Petitioner does not dispute that trial on claims 11 and 19 of the '601 patent has concluded. However, Regeneron held back all other claims of the '601 patent, including ten claims currently challenged here, strategically electing not to litigate the non-infringement and invalidity of those claims at the June 2023 trial, but to reserve them for a second trial. Ex.1062, 1-2. Regeneron also strategically held back at least 21 other asserted patents from being litigated at the June 2023 trial. Accordingly, it is not clear at this juncture if Regeneron will attempt to assert those 21 patents, as well as all or a selected subset, of the currently Challenged Claims of the '601 patent, in further litigation, leaving a cloud of uncertainty over Biocon's head on 10 of the 12 Challenged Claims.

As of the filing of this petition and motion for joinder, Regeneron has not approached the Court regarding a schedule for the follow-on litigation.

Consequently, there is no trial date, and no follow-on litigation has even begun, meaning that, while a formal stay has not been entered by the district court, the litigation over claims 10, 12, 17, 18, 21, 25-28, and 33 of the '601 patent has, in effect, been stayed. Assuming typical trial court scheduling of just over 30 months, there will not be a trial until well after the Final Written Decision in the Samsung IPR. Ex.1063, 1. While the parties' experts addressed the Challenged Claims in expert discovery of the district court litigation, the invalidity of claims 10, 12, 17, 18, 21, 25-28, and 33 of the '601 patent was never fully developed and litigated in a trial before the trier of fact. Consequently, the parties will still be investing resources over the course of the follow-on litigation, and eventually trial, directed to those claims. Accordingly, at least *Fintiv* Factors 1, 2, and 3 weigh in Petitioner's favor.

As to Factor 4, for avoidance of doubt, Petitioner here stipulates that, to ensure no overlap for the claims-in-common, if the Board institutes this IPR and joins with the Samsung IPR, Petitioner will not pursue at trial in district court litigation (unless a change in law otherwise permits) the specific grounds asserted in the Biocon Petition, or that reasonably could have been asserted in the Biocon Petition, against the currently Challenged Claims; however, this stipulation does not apply to the extent that the Board denies institution for any reason. With such a stipulation, "the PTAB will not discretionarily deny institution." *See, e.g.*, Katherine K. Vidal, Interim Procedure for Discretionary Denials, 7-8 (June 21, 2022) ("Vidal

Memorandum"); *Sotera Wireless, Inc. v. Masimo Corp.*, IPR2020-01019, Paper 12, 18-19 (P.T.A.B. Dec. 1, 2020) (precedential).

As to Factor 5, Petitioner does not dispute that Biocon and Regeneron are parties to the district court litigation.

As to Factor 6, the institution of the Samsung IPR itself presents a compelling merits case, given that PO has not disputed that the claimed drug, the dose, the disease, and the 2Q8 dosing interval are expressly disclosed in the asserted art, including the September 14, 2009 Press Release. PO argues only that the 5 monthly doses of the Challenged Claims are not disclosed. *See, e.g.*, Ex.1064, Samsung IPR POPR, 12-13. But this is routine optimization, Ex.1059, Samsung IPR Petition, 4-5, and neither the specification nor PO presents the 5 monthly doses as a critical or inventive aspect of the regimen. Indeed, as Samsung notes, 5 monthly doses comes from a specification laundry list without blaze marks. *Id.*, 37.

But beyond the fact of institution and PO's inability to dispute the prior art disclosures, additional evidence of compelling merits comes from the unpatentability finding of claims encompassing the same 2Q8 regimen in the '338 patent. Ex.1025, '338 FWD, 45. There, claims drawn to the same 2Q8 dosing regimen were held unpatentable based on the disclosure of the 2Q8 dosing regimen in the prior art. Again, in that IPR, PO did not dispute that the prior art disclosed the 2Q8 dose interval. Further, the '338 patent claims encompass the same subject

matter at issue in the Challenged Claims—"diabetic macular edema" and "diabetic retinopathy" are defined in the specification as "angiogenic eye disorders," and the monthly secondary doses in the '338 patent indisputably include injections "every 4 weeks for the first 5 injections." *Compare, e.g.*, Ex.1056, '338 patent, claim 1, *with* Ex.1001, '601 patent, claim 10. Thus, consistent with the Director's direction that the Board "will not rely on the *Fintiv* factors to discretionarily deny institution … where a petition presents compelling evidence of unpatentability," Vidal Memorandum, 2-3, any effort by PO to seek discretionary denial of Petitioner's petition should be rejected.

XI. CONCLUSION

For the foregoing reasons, Petitioner has established a reasonable likelihood that claims 10-12, 17-19, 21, 25-28, and 33 are unpatentable. Petitioner therefore respectfully requests that *inter partes* review of the '601 patent be granted.

Dated: November 20, 2023

Respectfully Submitted,

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that a true and correct copy of the foregoing **Petition for *Inter Partes* Review of U.S. Patent No. 10,888,601 B2** and **Exhibits 1001-1064** were served on November 20, 2023, via FedEx Priority Overnight on the Patent Owner at the correspondence address of record for U.S. Patent No. 10,888,601 B2 as evidenced in Patent Center:

A&P - Regeneron (Prosecution)
601 Massachusetts Ave., NW
Washington, DC 20001-3743

/Paul J. Molino/
Paul J. Molino (Reg. No. 45,350)

CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(d), the undersigned certifies that this Petition complies with the type-volume limitation of 37 C.F.R. § 42.24(a). The word count application of the word processing program used to prepare this Petition indicates that the Petition contains 9,828 words. This total does not include the tables of contents and authorities, mandatory notices, the caption page, table of exhibits, certificate of service, or this certificate of compliance. 37 C.F.R. § 42.24(a).

Dated: November 20, 2023

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