

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SAMSUNG BIOEPIS CO., LTD.,
Petitioner,
v.

REGENERON PHARMACEUTICALS, INC.,
Patent Owner.

Patent No. 10,888,601

Inter Partes Review No. IPR2023-00739

PATENT OWNER'S PRELIMINARY RESPONSE

	Page
I. INTRODUCTION	1
II. BACKGROUND	4
A. EYLEA®	4
B. The '601 Patent	8
C. District Court Litigation	9
III. LEVEL OF ORDINARY SKILL IN THE ART	11
IV. CLAIM CONSTRUCTION	11
V. PETITIONER HAS NO REASONABLE LIKELIHOOD OF SUCCESS BECAUSE THE RECITED DOSING REGIMEN IS NOT DISCLOSED OR SUGGESTED BY THE PRIOR ART	11
A. Petitioner Fails to Show That the 2009 Press Release or Shams Would Lead a POSA to the Recited Dosing Regimen (Ground 2).....	11
1. The References Neither Disclose the Recited Dosing Regimen nor Provide Any Reason for a POSA to Adopt That Regimen	12
2. The Relied-Upn Prior Art Teaches Away from the Recited Dosing Regimen	17
3. The “Routine Adjustments” Methodology Petitioner Advocates Does Not Render the Challenged Claims Obvious	22
B. Petitioner Fails to Show That Elman 2010 in Combination with the 2009 Press Release Would Lead a POSA to the Recited Dosing Regimen (Grounds 3 and 6).....	25
1. Petitioner’s References Do Not Disclose, and Instead Teach Away from, the Recited Dosing Regimen	25
2. Petitioner Fails to Show a Motivation to Combine	34
VI. THE <i>FINTIV</i> FACTORS WEIGH AGAINST INSTITUTION.....	37
A. Legal Standard for <i>Fintiv</i> Discretionary Denial.....	39

TABLE OF CONTENTS
(continued)

	Page
1. <i>Fintiv</i> Factors One, Two, Three, Four, and Six Favor Denial	40
2. <i>Fintiv</i> Factor Five Is Neutral.....	44
VII. CONCLUSION.....	45

TABLE OF AUTHORITIES**Page(s)****Cases**

<i>Apotex Inc. v. Novartis AG</i> , IPR2017-00854, 2018 WL 3414289 (P.T.A.B. July 11, 2018).....	21
<i>Apple Inc. v. Fintiv, Inc.</i> , IPR2020-00019, 2020 WL 2126495 (P.T.A.B. Mar. 20, 2020).....	<i>passim</i>
<i>In re Bell</i> , 991 F.2d 781 (Fed. Cir. 1993)	15
<i>Biomarin Pharm. Inc. v. Genzyme Therapeutic Prods. Ltd. P’ship</i> , IPR2013-00534, Paper 81 (P.T.A.B. Feb. 23, 2015).....	23
<i>Commscope Techs. LLC v. Dali Wireless, Inc.</i> , No. IPR2022-01293, 2023 WL 2604001 (P.T.A.B. Mar. 9, 2023).....	41
<i>In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Pat.</i> <i>Litig.</i> , 676 F.3d 1063 (Fed. Cir. 2012)	16, 21
<i>Fitbit, Inc. v. Philips N. Am. LLC</i> , IPR2020-00828, 2020 WL 6470312 (P.T.A.B. Nov. 3, 2020).....	45
<i>Google LLC v. Personalized Media Commc’ns, LLC</i> , IPR2020-00724, 2020 WL 6530785 (P.T.A.B. Nov. 5, 2020).....	45
<i>KSR Int’l Co. v. Teleflex Inc.</i> , 550 U.S. 398 (2007).....	15, 16
<i>In re Kubin</i> , 561 F.3d 1351 (Fed. Cir. 2009)	16
<i>Leo Pharm. Prods., Ltd. v. Rea</i> , 726 F.3d 1346 (Fed. Cir. 2013)	16, 36
<i>Life Spine, Inc. v. Globus Medical, Inc.</i> , IPR2022-01603, Paper 8 (P.T.A.B. June 12, 2023)	14

<i>NHK Spring Co. v. Intri-Plex Techs., Inc.</i> , IPR2018-00752, Paper 8 (P.T.A.B. Sept. 12, 2018).....	38, 41
<i>In re NTP, Inc.</i> , 654 F.3d 1279 (Fed. Cir. 2011)	15
<i>Ortho-McNeil Pharm., Inc. v. Mylan Lab'ys, Inc.</i> , 520 F.3d 1358 (Fed. Cir. 2008)	36
<i>Portney v. CIBA Vision Corp.</i> , 401 F. App'x 526 (Fed. Cir. 2010)	10
<i>Regeneron Pharms., Inc. v. Mylan Pharms. Inc.</i> , 1:22-cv-00061-TSK-JPM (N.D. W. Va.)	37
<i>Samsung Elecs. Co. v. Clear Imaging Rsch., LLC</i> , IPR2020-01399, Paper 13 (P.T.A.B. Feb. 3, 2021).....	42
<i>Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.</i> , 492 F.3d 1350 (Fed. Cir. 2007)	16
<i>TWI Pharms, Inc. v. Merck Serono SA</i> , IPR2023-00050, Paper 8 (P.T.A.B. Mar. 28, 2023)	17
<i>Unigene Lab'ys, Inc. v. Apotex, Inc.</i> , 655 F.3d 1352 (Fed. Cir. 2011)	36
<i>Volvo Penta of the Ams., LLC v. Brunswick Corp.</i> , IPR2022-01366, Paper 15 (P.T.A.B. May 2, 2023)	41
Statutes	
35 U.S.C. § 314(a)	37, 38
42 U.S.C. § 262	9

Exhibit List

Exhibit Description	Exhibit #
U.S. 10,888,601 Patent Disclaimer (July 11, 2022)	2001
U.S. 10,888,601 Patent Disclaimer (July 25, 2023)	2002
Jean-Francois Korobelnik et al., <i>Intravitreal Aflibercept for Diabetic Macular Edema</i> , 121 OPTHALMOLOGY 2247 (2014)	2003
LUCENTIS® Label (rev. Aug. 2012)	2004
Declaration of David M. Brown, M.D., <i>Mylan Pharms. Inc. v. Regeneron Pharms., Inc.</i> , IPR2021-00880, Ex.2050 (Feb. 10, 2022)	2005
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Press Release, Regeneron Announces FDA Acceptance of EYLEA® (aflibercept) Injection Supplemental Biologics License Application for Review for Diabetic Macular Edema Indication (Dec. 18, 2013)	2010
Provisional Application No. 61/432,245 (Jan. 13, 2011)	2011
Mylan Pharmaceuticals Inc.'s Answer, Defenses, and Counterclaims to Plaintiff's Complaint, <i>Regeneron Pharms., Inc. v. Mylan Pharms. Inc.</i> , No. 1:22-cv-00061-TSK-JPM (N.D.W. Va.), ECF No. 47 (filed Aug. 25, 2022)	2012

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Order on Claim Construction, <i>Regeneron Pharms., Inc. v. Mylan Pharms. Inc.</i> , No. 1:22-cv-00061-TSK-JPM (N.D.W. Va.), ECF No. 427 (filed Apr. 19, 2023)	2014
Scheduling Order, <i>Regeneron Pharms., Inc. v. Mylan Pharms. Inc.</i> , No. 1:22-cv-00061-TSK-JPM (N.D.W. Va.), ECF No. 87 (filed Oct. 25, 2022)	2015
Regeneron's Stipulation Regarding Summary Judgment and Case Narrowing, <i>Regeneron Pharms., Inc. v. Mylan Pharms. Inc.</i> , No. 1:22-cv-00061-TSK-JPM (N.D.W. Va.), ECF No. 433 (filed Apr. 27, 2023)	2016
Stipulation and Order Joining Biocon Biologics Inc. as Defendant, <i>Regeneron Pharms., Inc. v. Mylan Pharms. Inc.</i> , No. 1:22-cv-00061-TSK-JPM (N.D.W. Va.), ECF No. 523 (filed June 5, 2023)	2017
Defendant's Opening Post Trial Brief - Issues Where Defendants Bear the Burden of Proof, <i>Regeneron Pharms., Inc. v. Mylan Pharms. Inc.</i> , No. 1:22-cv-00061-TSK-JPM (N.D.W. Va.), ECF No. 576 (filed July 7, 2023)	2018
Order Setting Briefing Schedule, <i>Regeneron Pharms., Inc. v. Mylan Pharms. Inc.</i> , No. 1:22-cv-00061-TSK-JPM (N.D.W. Va.), ECF No. 514 (filed May 30, 2023)	2019
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Irene Barbazetto et al., <i>Dosing Regimen and The Frequency of Macular Hemorrhages in Neovascular Age-Related Macular Degeneration Treated with Ranibizumab</i> , 30 RETINA 1376 (2010)	2021
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I. INTRODUCTION

Samsung’s petition does not demonstrate a reasonable likelihood that any of claims 10–12, 17–19, 21, 25–28, or 33 are invalid.¹ Each of these claims requires treating diabetic macular edema or diabetic retinopathy with a specific dosing regimen of aflibercept: “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 recited regimen”). The prior art does not teach five loading doses, and Petitioner fails to articulate why a POSA would have modified the prior art regimens to arrive at the recited regimen.

Petitioner relies for its primary reference of Grounds 2–3 and 6 on the 2009 Press Release, a prospective disclosure of Regeneron’s DA VINCI clinical

¹ Claims 10–12, 17–19, 21, 25–28, and 33 are the only remaining challenged claims in this proceeding. Although Samsung listed claims 13–14, 22, and 29–30 among the challenged claims in its petition, Patent Owner disclaimed these claims on July 11, 2022, before the petition was filed. Ex.2001. Additionally, to narrow the issues in this proceeding, Patent Owner has disclaimed claims 15–16, 20, 23–24, 31–32, and 46–47. Ex.2002. Because Grounds 1, 4, and 5 related solely to claims that have been disclaimed, Patent Owner does not address those grounds here.

trial. The trial involved four dosing regimens, none of which was the recited regimen. Petitioner argues that a POSA would select a certain regimen from the 2009 Press Release but would then promptly modify it to match the recited dosing regimen, allegedly because the Press Release teaches a POSA that more loading doses will benefit patients. But the 2009 Press Release contains no such teaching, nor does it disclose any results of the DA VINCI trial it describes. Petitioner's arguments are therefore based on hindsight, not the prior art and knowledge of a POSA at the time of the invention.

Petitioner next argues that if the recited dosing regimen is not obvious based on the 2009 Press Release alone, a POSA would combine one of the dosing regimens from the 2009 Press Release with the teachings of either Shams (Ground 2) or Elman 2010 (Grounds 3 and 6). But Petitioner fails to articulate a sufficient reason to combine Shams or Elman 2010 with the 2009 Press Release. Both Shams and Elman 2010 involved ranibizumab, a different drug, and Elman 2010 disclosed fixed dosing followed by individualized, assessment-based dosing, rather than the claimed regimen, which involves fixed dosing throughout. Moreover, Shams does not disclose five fixed loading doses and neither does Elman 2010. Elman 2010 describes a clinical trial protocol that provided for *four* fixed monthly loading doses for all patients. Thereafter, patients could receive monthly loading doses based on an assessment, rather than on a fixed regimen.

Nothing about the protocol suggested the desirability of *even more* initial monthly doses: The protocol involved a transition from fixed to assessment-based dosing after *four* doses, and then after *six* doses provided for a second transition to another assessment-based regimen. By contrast, the claims recite fixed dosing throughout, with a transition from monthly to eight-week dosing after *five* fixed monthly loading doses. Shams similarly does not help Petitioner. Shams discusses the general concept of more-frequent followed by less-frequent dosing, which would not be enough to motivate a POSA to use exactly five monthly doses followed by additional doses every eight weeks, as claimed. This is particularly true in view of the complete disclosure of Shams, which describes a clinical trial that was widely regarded as a failure. Shams discloses as its sole example the dosing regimen of Genentech's PIER trial for ranibizumab (which used three loading doses followed by quarterly dosing, administered to subjects with choroidal neovascularization secondary to age-related macular degeneration). The PIER trial results revealed that this less-frequent dosing regimen was ineffective, and the trial was widely regarded by the priority date of the '601 patent as a failure. The ranibizumab art would not have led a POSA to the claimed dosing regimen.

Finally, discretionary denial is appropriate under *Fintiv*. Two of the challenged claims of the '601 patent were recently tried in the Northern District of West Virginia, and post-trial proceedings are underway. Court proceedings

involve many of the issues Petitioner raises: The trial involves two '601 claims—11 and 19—that are challenged here and that are also representative of other challenged claims in this proceeding. The district court is adjudicating a validity challenge based on Petitioner's primary reference, the 2009 Press Release. The district court's final ruling on these claims, as well as the district court's construction of the exclusion criteria claim limitations that were not tried, will be subject to appeal to the Federal Circuit. A parallel IPR proceeding on the same issues would be a duplicative, wasteful effort.

II. BACKGROUND

A. EYLEA®

Diabetic macular edema (DME) is a common complication of diabetes that leads to vision loss. Chronic high blood sugar in diabetes patients causes damage to small blood vessels throughout the body. Ex.2003, 1. Some of these small blood vessels are found in the back of the eye, surrounding the macula, which is the light-sensitive part of the retina responsible for sharp, direct vision. Ex.2003, 1; Ex.1001, 1:42–44. Damage to the blood vessels in the back of the eye can cause fluid to leak into the macula, resulting in edema, or swelling. Ex.1001, 1:41–42. Macular edema can cause severe vision loss or blindness. Ex.1001, 1:44–45.

Historically, laser photocoagulation was used to manage DME. It could slow or stop vision loss, but few patients saw large gains in their visual acuity with this therapy. Ex.2003, 1.

Researchers discovered that a protein called vascular endothelial growth factor (VEGF) is present at elevated levels in DME patients and contributes to the pathophysiology of DME. Ex.1045, 1. By the late 2000s and early 2010s, several clinical trials were underway to evaluate the efficacy of anti-VEGF agents to treat DME. Ex.1045, 1; Ex.2003, 1. The different trials tested a wide range of dosing regimens and combination therapies, and results varied.

The first such anti-VEGF agent approved to treat DME was Lucentis (ranibizumab), marketed by Genentech. Lucentis is an antibody fragment that binds to VEGF. Ex.1015, 5. Lucentis was approved in 2006 as an intravitreal injection for the treatment of a different condition, age-related macular degeneration (AMD). Ex.1015, 2. FDA approved DME as an additional indication in 2012. Ex.2004, 1.

For AMD and DME, the Lucentis label recommends monthly dosing. Ex.2004, 1. This is because, despite the discomfort, inconvenience, and risks associated with monthly injections into the eye, dosing ranibizumab less frequently produces dramatically lower efficacy. As just one example, in Genentech's PIER study, AMD patients in the treatment arms received ranibizumab every month for

three doses, followed by quarterly doses. Ex.1004, 2. Patients in the treatment arm gained visual acuity during the first three monthly injections but then lost all visual acuity gains after moving to fixed quarterly dosing. Ex.1004, 5 fig. 1. By 2011, the PIER trial was regarded as “highly disappointing,” and a “failure,” Ex.2005 ¶¶ 46–59, and Genentech amended the protocol to allow all patients in the quarterly arms to roll over from quarterly dosing to receiving monthly dosing for the remainder of the two-year study. Ex.2006, 2; Ex.2007, 2. The Lucentis label itself notes that quarterly dosing is “less effective” and “[c]ompared to continued monthly dosing, dosing every 3 months will lead to an approximate 5-letter (1-line) loss of visual acuity benefit, on average, over the following 9 months.” Ex.2004, 1.

Regeneron developed a different anti-VEGF agent, EYLEA® (aflibercept). Aflibercept is not an antibody or antibody fragment but rather a fusion protein made from domains of human VEGF receptors grafted onto an FC portion of an antibody. Ex.1050, 12. FDA first approved EYLEA® in November 2011, for AMD. Ex.1001, 2:51–57.

In 2008, Regeneron began enrolling DME patients in a phase II trial, DA VINCI, “to determine whether different doses and dosing regimens of intravitreal VEGF Trap-Eye are superior to standard macular laser treatment . . . in eyes with DME.” Ex.1045, 2. Subjects were assigned to one of five treatments: “0.5 mg

VEGF Trap-Eye every 4 weeks (0.5q4); 2 mg VEGF Trap-Eye every 4 weeks (2q4); 2 mg VEGF Trap-Eye for 3 initial monthly doses and then every 8 weeks, (2q8); 2 mg VEGF Trap-Eye for 3 initial monthly doses and then on an as-needed (PRN) basis (2 PRN); or macular laser treatment.” Ex.1045, 2. DA VINCI’s primary endpoint was change in best corrected visual acuity (BCVA) from baseline to 24 weeks; a secondary endpoint was change from baseline to 52 weeks. Ex.2008, 4; Ex.2009, 1408 (1615:15–20).

Regeneron obtained the primary, 24-week DA VINCI results by mid-2010, Ex.2009, 1408 (1615:15–24), and Do et al. published these results in May 2011. Ex.1045, 8. At 24 weeks, “[i]n the 2Q8 and 2 PRN arms, the treatment interval for VEGF Trap-Eye administration was prolonged after the loading phase without a trade-off in efficacy, because all VEGF Trap-Eye–treated groups manifested comparable gains in visual acuity versus baseline.” Ex.1045, 6. With these results in hand, Regeneron began planning its phase III trials. As of October 2010, Regeneron planned to test the 2q4 and 2q8 regimens it had used in the DA VINCI trial, Ex.2009, 153 (162:7–9), 1409 (1616:19–25), but it awaited the DA VINCI 52-week data to “provide additional guidance on the number of loading doses,” *id.* 153-154 (162:10–163:3).

Then, in late 2010, Regeneron received the complete 52-week data from the DA VINCI trial. Senior management reviewed the unpublished aggregate and

patient-level data. Ex.2009, 154-55 (163:5–165:13), 1413-14 (1620:6–1621:23).

Dr. George Yancopoulos, co-founder and chief scientific officer, and sole inventor of the '601 patent, made the decision to test in the phase III trial a dosing regimen of *five* loading doses followed by additional doses every eight weeks. *Id.* 1415–16 (1622:15–1623:14), 1096–97 (1234:8–1235:4), 194 (203:5–13), 158–59 (167:25–168:22); Ex.2003, 2.

Regeneron completed its phase III trial, *see generally* Ex.2003 and FDA approved an additional EYLEA® indication for DME in December 2013.

Ex.2010. For DME, the EYLEA® label recommends the dosing regimen recited in the '601 patent: five monthly loading doses followed by additional doses every eight weeks. Ex.1050, 1.

B. The '601 Patent

On January 13, 2011, after the DA VINCI trial ended but before Do 2011 reported the results, Regeneron filed provisional application No. 61/432,245, to which the '601 patent claims priority. Ex.1001, 1:7–20. Example 5 in the provisional application, and in the '601 patent, reports the DA VINCI trial protocol and results. *See* Ex.2011, ¶¶ 61–62; Ex.1001, 14:6–54. The provisional application and '601 patent further disclose administering four secondary doses after the initial dose (*i.e.*, five loading doses) to the patient. Ex.2011, ¶ 18; Ex.1001, 4:17–19.

The '601 patent, which issued on January 12, 2021, claims methods of treating angiogenic eye disorders by administering aflibercept in specific, *fixed* dosing regimens. The remaining challenged claims are drawn to methods of treating diabetic macular edema and the related condition diabetic retinopathy using specific dosing regimens: five monthly loading doses followed by less-frequent dosing, *i.e.*, every eight weeks. The dosing regimen does not vary based on individualized patient assessments.

C. District Court Litigation

Regeneron is litigating the validity of the '601 patent in the Northern District of West Virginia against Defendants Mylan Pharmaceuticals Inc. and Biocon Biologics Inc., under the provisions of the Biologics Price Competition and Innovation Act (BPCIA) (42 U.S.C. §262). *See* Ex.2012, 105 ¶ 122. Regeneron filed its BPCIA complaint on August 2, 2022, but Regeneron and Mylan had been engaged in the BPCIA's "Patent Dance" exchanges since at least January 2022. Ex.2013; Ex.2012, 11–12 ¶ 18.²

On April 19, 2023, the court construed multiple claim limitations in the '601 patent, including the visual acuity and exclusion criteria limitations. Ex. 2014. As required by the scheduling order in the district court litigation, Ex.2015,

² Biocon was added to the litigation in June 2023. Ex.2017.

Regeneron narrowed the number of claims for the June 2023 trial a week after the district court's claim construction order, selecting three claims of the '601 patent at that time. Ex.2016, 2.

Simultaneously, Regeneron stipulated to summary judgement of invalidity with respect to certain claims of the '601 patent (not including the claims selected for trial or challenged in this proceeding) as a procedural vehicle to obtain an appealable decision on the construction of those claims. *See Portney v. CIBA Vision Corp.*, 401 F. App'x 526, 529 (Fed. Cir. 2010) ("This court has generally refrained from granting [petitions for interlocutory review] to resolve claim construction disputes, instead, leaving such matters to be determined after entry of final judgment."); Ex.2016, 1 (Regeneron declining to oppose summary judgment "[s]ubject to all appellate rights, including but not limited to rights of appeal concerning claim construction.").

A trial was held June 12–23. Ultimately, Regeneron selected claims 11 and 19 of the '601 patent to assert in the trial, and the defendants challenged the validity of these claims on several bases including obviousness, with the 2009 Press Release as the primary reference. Ex.2018, 27-28. Patent Owner and Defendants are expected to present closing arguments on August 3, 2023, and thereafter await the district court's judgment. Ex.2019. An expedited appeal is

likely to follow. *See* Ex.2020, 20:11–19 (counsel for Regeneron explaining process by which it will seek to expedite any appeal); Ex.2016].

III. LEVEL OF ORDINARY SKILL IN THE ART

For purposes of this Preliminary Response, Patent Owner has used Petitioner’s definition of the POSA. Patent Owner reserves the right to propose another definition if review is instituted.

IV. CLAIM CONSTRUCTION

For purposes of this Preliminary Response only, Patent Owner does not challenge Petitioner’s proposed constructions, because Petitioner has failed to show a reasonable likelihood of prevailing on any ground, even under its own constructions. Patent Owner reserves the right to propose alternative or additional constructions if review is instituted.

V. PETITIONER HAS NO REASONABLE LIKELIHOOD OF SUCCESS BECAUSE THE RECITED DOSING REGIMEN IS NOT DISCLOSED OR SUGGESTED BY THE PRIOR ART

A. Petitioner Fails to Show That the 2009 Press Release or Shams Would Lead a POSA to the Recited Dosing Regimen (Ground 2)

Each of the claims challenged in this ground requires treating DR or DME using a fixed dosing regimen that consists of (a) five monthly initial injections of 2 mg each, followed by (b) additional doses spread eight weeks apart. None of Petitioner’s references discloses such a regimen, and Petitioner’s hindsight-riddled mixing and matching of different disclosures from the 2009 Press Release and

Shams fails to cure this deficiency. Petitioner also ignores express teachings of the references on which it relies. Neither reference discloses the recited dosing regimen. Neither reference discloses that such a regimen would be desirable. And the Shams reference was known by the priority date to describe a failed regimen when extending dosing intervals beyond one month; Petitioner does not explain why a POSA would have adopted Shams' proposed regimen rather than rejecting it—as POSAs, in fact, did.

1. The References Neither Disclose the Recited Dosing Regimen nor Provide Any Reason for a POSA to Adopt That Regimen

The 2009 Press Release prospectively discloses aspects of the design of a Phase 2 DME trial (DA VINCI) conducted by Regeneron, which contained four arms: (1) VEGF Trap-Eye dosed at 0.5 mg monthly; (2) VEGF Trap-Eye dosed at 2 mg monthly; (3) VEGF Trap-Eye dosed at 2 mg every eight weeks after *three* monthly loading doses; and (4) VEGF Trap-Eye dosed at 2 mg on a *pro re nata* (as-needed) basis after *three* monthly loading doses. Ex.1009, 1.

Petitioner's reliance on the 2009 Press Release suffers from two major flaws. First, none of the four dosing regimens disclosed by the 2009 Press Release is the five-loading-dose regimen required by all the claims challenged in this ground. Second, the 2009 Press Release was issued before the DA VINCI clinical trial began, and therefore, the 2009 Press Release does not disclose the results of

any of the four regimens—much less results that would motivate a POSA to *modify* one of the proposed regimens to *add* loading doses despite the obvious treatment burden, as would be required to arrive at the recited dosing regimen.

In classic hindsight, the Petition also mixes and matches the dosing regimens without articulating a rationale for doing so. Petitioner begins by emphasizing the 2q8 dosing arm of DA VINCI—which administered three monthly doses followed by doses every eight weeks, *see* Pet. at 34–35—but then suggests that the monthly (2q4) and as-needed dosing arms (2 PRN) would “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.” Pet. 35. Petitioner does not explain how these *prospective* arms could provide any such motivation, given that the 2009 Press Release does not report the results for these arms—because no results were available to be reported.

Even if results had been reported, Petitioner does not explain why the 2 PRN regimen (as-needed dosing after three loading doses) would suggest that some patients would benefit from *more* than three loading doses, much less five loading doses. The 2q8 regimen involves *three* loading doses, and so does 2 PRN; combining them does not disclose, let alone motivate, *five* loading doses. Nor does the Petition explain why the 2 PRN regimen, which involves a switch from fixed dosing to individualized patient assessment after three doses, would provide a

motivation to achieve the claimed dosing regimen, which involves fixed dosing throughout the course of treatment.

The addition of the Shams reference into the mix renders Petitioner's ground even more illogical. Shams concerns a different drug, Lucentis (ranibizumab) and does not disclose the recited dosing regimen, let alone any results that a POSA could reasonably expect from implementing such a regimen. Neither Shams nor the 2009 Press Releases discloses five loading doses, and Petitioner has not articulated any reason to modify the dosing regimens of the prior art beyond a hindsight desire to arrive at the invention of the claims. This dooms Petitioner's obviousness argument. *See Life Spine, Inc. v. Globus Medical, Inc.*, IPR2022-01603, Paper 8 at 41 (P.T.A.B. June 12, 2023) (denying institution where record "d[i]d not reveal a reason for making the multiple modifications Petitioner proposes in its combination other than a desire to arrive at device [sic] with all the elements recited in claim").

Petitioner instead relies on Shams for the general concept of "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." Pet. 36 (quoting Ex.1010, 22) (alteration in original). But Petitioner identifies nothing in Shams that would point the way specifically towards the recited dosing regimen. Petitioner admits as

much—it concedes that, by its own logic, “other dosing regimens with a different number of monthly doses—such as three, four, six, *etc.*” were also obvious.

Pet. 38 (emphasis added).

Petitioner’s argument that *any* number of monthly loading doses were obvious is a misapplication of core obviousness law. The Supreme Court has noted that it is not “obvious to try” multiple possibilities unless “there are a finite number of identified, predictable solutions.” *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007). And the Federal Circuit has long cautioned against what Petitioner attempts to do here: “[c]are must be taken to avoid hindsight reconstruction by using ‘the patent in suit as a guide through the maze of prior art references, combining the right references in the right way so as to achieve the result of the claims in suit.’” *In re NTP, Inc.*, 654 F.3d 1279, 1299 (Fed. Cir. 2011) (quoting *Grain Processing Corp. v. Am. Maize-Prods. Co.*, 840 F.2d 902, 907 (Fed. Cir. 1988)); *see also In re Bell*, 991 F.2d 781, 784 (Fed. Cir. 1993) (DNA sequence would not have been obvious in view of prior art reference suggesting a nearly infinite number of possibilities and failing to suggest why among all those possibilities one would seek the claimed sequence). Petitioner fails to identify a finite (let alone predictable) number of options for the numerous variables that can be varied to generate a dosing regimen from the prior art references, including (1) the number of loading doses, (2) how far apart the extended doses are spaced,

(3) the amount of each dose, (4) the identity of the VEGF antagonist, and more.

What Petitioner ignores—but what “obviousness law in general recognizes”—is the “important distinction between combining known options into ‘a finite number of identified, predictable solutions,’ *KSR*, 550 U.S. at 421, and “‘merely throwing metaphorical darts at a board’ in hopes of arriving at a successful result.’” *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1357 (Fed. Cir. 2013) (quoting *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Pat. Litig.*, 676 F.3d 1063, 1071 (Fed. Cir. 2012)). A claim is not obvious where one must “vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result.” *In re Kubin*, 561 F.3d 1351, 1359 (Fed. Cir. 2009); *see also Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1359 (Fed. Cir. 2007) (claims not obvious where there was not “a finite number of identified, predictable solutions” (quoting *KSR*, 550 U.S. at 421)).

Petitioner points to no considerations that would lead a POSA to tweak these various variables in precisely the right way to arrive at the recited dosing regimen. On the contrary, the considerations that a POSA would have to balance point in different directions: For example, adding more monthly loading doses to an extended dosing regimen (such as the 2Q8 arm of DA VINCI), as Petitioner suggests, would result in a greater treatment burden from visits and an increased risk of adverse events. On the other hand, abandoning monthly dosing in favor of

extended dosing runs the risk of reduced efficacy and undertreatment (as evidenced by the failure of the regimen taught in Petitioner’s Shams reference, discussed below), as well as vision-threatening complications such as macular hemorrhage. Ex.2021, 1. The lack of any guidance in the prior art on how to balance these various considerations to arrive at the specific regimen recited in the claims reflects the use impermissible hindsight by Petitioner and its expert, not the teachings of the prior art, to arrive at the claimed inventions. *See TWI Pharms, Inc. v. Merck Serono SA*, IPR2023-00050, Paper 8, 21 (P.T.A.B. Mar. 28, 2023) (denying institution because argument that POSA would have “fine tun[ed]” prior art dosing regimen in light of another reference was “improperly guided by hindsight,” given lack of suggestion to make modification in either reference).

2. The Relied-Upon Prior Art Teaches Away from the Recited Dosing Regimen

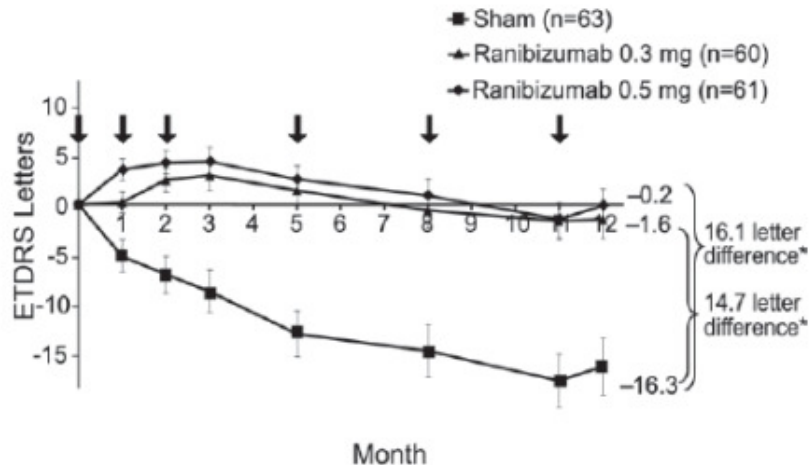
Shams does not disclose five loading doses followed by eight-week dosing. Rather, it teaches away from the claimed dosing regimen by disclosing dosing regimens in which the initial, more frequent doses are administered only *three* times, not five. Ex.1010, 24:14–16 (“The first dose may be administered, for example, one, two or three times, *typically three times* before the less frequent administration dose(s) is (are) administered.” (emphasis added)), 24:24–25 (“In one aspect, the first individual dose is administered at month 0, 1 and 2.”), 24:26–

28 (“In one example, the first individual dose is administered at month 0, 1, and 2”).

In fact, the sole example in Shams is a prophetic description of Genentech’s Phase IIIb PIER study, which involved three monthly loading doses of a different VEGF antagonist—ranibizumab—followed by quarterly dosing. *Id.* at 32–36. Both the initial part of this dosing regimen (which involved three, not five, monthly doses) and the second part (which involved quarterly dosing, not dosing every eight weeks) differ from the requirements of the Challenged Claims. So does the VEGF antagonist used (ranibizumab, which is an antibody fragment, not aflibercept, which is a fusion protein).

Even if one were to incorrectly conclude that Shams teaches towards the recited regimen, a POSA would not have had any motivation to adopt the regimen taught in Shams in the first place. By the priority date of the Challenged Claims, the PIER study and its extended dosing regimen were known to be failures. Thus, to the extent that a POSA was evaluating the generalized disclosures of extended dosing regimens from Shams that Petitioner relies on, she would have been motivated to avoid, not adopt them. Notably, by 2011, the PIER dosing regimen disclosed in Shams was regarded as ineffective, “highly disappointing,” and a “failure.” Ex.2005, ¶¶ 46–59. Patients in the treatment arm gained visual acuity during the first three monthly injections of ranibizumab, but then lost all visual

acuity gains after moving to fixed quarterly dosing. Ex.1004. Those losses are shown in the two upper lines in the chart below:



* $P < .0001$

FIGURE 1. Ranibizumab for neovascular age-related macular degeneration (AMD). Mean change from baseline visual acuity, measured as letters read on the Early Treatment of Diabetic Retinopathy Study (ETDRS) chart, at monthly intervals. At month 12, the 0.3 mg ranibizumab group and the 0.5 mg ranibizumab group differed from the sham group by 14.7 and 16.1 letters, respectively ($P < .0001$). The arrows indicate that ranibizumab or sham injections occurred at day zero, month one, month two, month five, month eight, and month 11.

Id. Thus, it was not merely the case that the PIER regimen was less effective at improving visual acuity as compared to a monthly regimen: following the end of the monthly doses and the transition to the “subsequent, less frequent interval of administration of the therapeutic compound” that Petitioner relies on (Pet. 36) led to vision loss, with ultimately *zero* gains in visual acuity as compared to baseline. By contrast, it was known by 2005, based on the results of Genentech’s Phase 3

ANCHOR and MARINA trials, that *monthly* ranibizumab successfully produced visual acuity gains, with mean gains at the one-year mark as high as +10.7 letters over baseline in one arm. Ex.2005 ¶¶ 32-38. There would have been little motivation to pursue PIER's extended dosing regimen when treatments that could produce visual acuity *gains* were available.

The PIER results were considered so disappointing that Genentech amended the PIER study protocol to allow all patients in the quarterly arms to roll over from extended (quarterly) dosing to receiving monthly dosing for the remainder of the two-year study. Ex.2006, 2; Ex.2007, 2 (“[W]hile quarterly dosing on average provided a 15- to 16-letter improvement over sham injections, the visual acuity of patients receiving quarterly injections of ranibizumab had on average returned to baseline by month 12. The PIER data have led Genentech to recommend that patients receive either monthly injections of ranibizumab, or have their retreatment schedules determined through individualized testing.”). The protocol change reflects an acknowledgment by Genentech that Shams's extended dosing regimen did not work well. *See also* Ex.2004, 1 (acknowledging that that quarterly dosing is “less effective” and “[c]ompared to continued monthly dosing, dosing every 3 months will lead to an approximate 5-letter (1-line) loss of visual acuity benefit, on average, over the following 9 months.”).

The recognized failure of Shams's PIER regimen is referred to in the specification of the '601 patent itself. After citing the U.S. national phase application of Shams, the patent states that "there remains a need in the art for new administration regimens for angiogenic eye disorders, especially those which allow for less frequent dosing while maintaining a high level of efficacy." Ex.1001, 1:64–67. That reflects the fact that Shams did not manage to come up with an effective, non-burdensome extended dosing regimen (let alone the one reflected in the Challenged Claims), and instead reflected a failed attempt to solve the problem that the '601 patent was successful in solving.

Petitioner does not address any of these facts about the Shams extended-dosing regimen. Unlike Petitioner's hindsight-driven assertions, the contemporaneous evidence from the '601 patent and the above-quoted articles reveals that the conclusion that clinicians *actually* drew from the failure of the PIER regimen was to move away from less frequent dosing and away from fixed dosing, not pursue it further. Petitioner is not free to ignore that the art taught away; to the contrary, "[w]hether the prior art teaches away from a reference may be dispositive of a challenge set forth in an *inter partes* review." *Apotex Inc. v. Novartis AG*, IPR2017-00854, 2018 WL 3414289, at *12 (P.T.A.B. July 11, 2018). Petitioner's failure to address this powerful evidence against Petitioner's arguments confirms that Petitioner has not met its burden. *See Cyclobenzaprine*,

676 F.3d at 1081 (noting that “actual reports of failure” carry significant weight in an obviousness inquiry and “evidence of failed attempts by others could be determinative on the issue of obviousness” (internal citations omitted)). It was only the inventors of the Challenged Claims who proceeded in an unexpected and inventive direction to arrive at the new dosing regimen reflected in the claims.

3. The “Routine Adjustments” Methodology Petitioner Advocates Does Not Render the Challenged Claims Obvious

Because neither reference discloses the recited dosing regimen, Petitioner argues that a POSA reading them would be motivated to create a tailor-made dosing regimen for a patient, administering doses as-needed and making “routine adjustments” based on exercising the POSA’s “clinical judgment” during regular visits. Pet. 36. Petitioner speculates that these “routine adjustments” might arrive at the recited dosing regimen of five loading doses followed by fixed eight-week dosing. *Id.* Petitioner’s speculation fails to render the Challenged Claims obvious, for at least two reasons.

First, Petitioner does not show that making these “routine adjustments” to the dosing regimens disclosed in the 2009 Press Release or Shams would, in fact, result in the dosing regimen of the Challenged Claims—five loading doses followed by fixed eight-week dosing. Despite many patients having been treated for angiogenic eye disorders in the wake of the 2009 Press Release and Shams, Petitioner fails to point to disclosure of “routine adjustments” resulting in *even one*

patient receiving five loading doses followed by a dose every eight weeks.³ That is true even if art involving VEGF antagonists other than aflibercept (such as Lucentis or Avastin) are considered, which they should not be. *See* Ex.1008, 5 (noting that VEGF Trap-Eye “may have longer duration of effect in the eye” than other VEGF antagonists).

Second, and more fundamentally, the challenged claims are directed to methods for treating DME and DR using a *fixed*, extended dosing regimen—not based on individualized patient assessments. A fixed approach provides for treatment on a predetermined schedule regardless of whether reaccumulated fluid has been detected, while assessment-based approaches take a fundamentally different approach by making injections conditional on patient characteristics. Ex.2009 1617–18 (1824:22–1825:6), 1618 (1825:12–25); *see also* 643–44 (781:19–782:7), 781 (919:15–23). The ’601 patent’s achievement of the first

³ That is a key distinction between this case and *Biomarin Pharm. Inc. v. Genzyme Therapeutic Prods. Ltd. P’ship*, IPR2013-00534, Paper 81, 8–11, cited by Petitioner. Pet. 36. In that case, the Petitioner cited prior art that “disclose[d] every limitation of” the challenged claims, along with reasons to combine the disclosures. *Biomarin*, IPR2013-00534, Paper 81, at 11.

fixed, extended dosing regimen was a *departure* from prior assessment-based approaches, rather than an obvious variant of them.

A major advantage of a fixed dosing regimen as compared to one based on individualized assessments is that monitoring visits are unnecessary. The 2009 Press Release itself explains that the regular monitoring visits necessary to implement Petitioner’s “routine adjustments” dosing regimen would result in a significant burden as compared to a fixed dosing regimen, like the one reflected in the claims:

“Even with recent advances in the treatment of wet AMD, vision is not improved or stabilized in all patients despite monthly office visits and examinations that are inconvenient for these often elderly patients,” said George D. Yancopoulos, M.D., Ph.D., President of Regeneron Research Laboratories.

Ex.1009, 1; *see also* Ex.1002 ¶ 62 (acknowledging the “significant burden of making monthly visits to [the patient’s] retinal specialist” (quoting Ex.1007)). Indeed, it was “[t]he time and financial burden of monthly injections” that “ha[d] led to the initiation of studies to examine the efficacy of alternative dosing schedules” in the first place. Ex.1008, 2. Petitioner ignores these differences in suggesting that assessment-based approaches render fixed regimens obvious. Thus, even if Petitioner showed that a patient on PRN dosing were coincidentally administered PRN doses on a schedule approximating that recited in the claims

(and Petitioner has made no such showing), such a PRN dosing strategy is fundamentally different than the advantageous fixed, extended dosing regimen recited in the Challenged Claims, and such happenstance would not have motivated the POSA to pursue any particular fixed regimen except with the benefit of hindsight.

B. Petitioner Fails to Show That Elman 2010 in Combination with the 2009 Press Release Would Lead a POSA to the Recited Dosing Regimen (Grounds 3 and 6)

Ground 3 is directed to the same claims as Ground 2 but is based on the 2009 Press Release alone⁴ or in view of Elman 2010, a ranibizumab trial.

Ground 6 is directed at the claims that recite exclusion criteria (claims 17, 25, and 33), and relies on the same two references to address the dosing regimen itself, with the addition of references describing the CATT and PIER studies purportedly to address the exclusion criteria. Both grounds fail because, as with Ground 2, nothing in the combination of the 2009 Press Release or Elman 2010 discloses or renders obvious a dosing regimen consisting of five monthly loading doses followed by eight-week dosing.

1. Petitioner's References Do Not Disclose, and Instead Teach Away from, the Recited Dosing Regimen

⁴ Petitioner's theory that the 2009 Press Release alone renders the Challenged Claims obvious has already been addressed above with respect to Ground 2.

As with Ground 2, Petitioner mixes and matches disclosures from these references, picking some and discarding others. This selection is based not on any articulated rationale, but rather on hindsight—Petitioner selected disclosures it views as being closest to the dosing regimen in the Challenged Claims and argues that it would be obvious for a POSA to modify them as necessary to arrive at the challenged claims. But nothing in the prior art supports Petitioner’s selective combinations, nor does the prior art provide any reason to cobble the references together in the way Petitioner has done, with the benefit of the Challenged Claims in front of it as a hindsight roadmap. Specifically, Petitioner purports to obtain a regimen of five monthly loading doses followed by eight-week dosing as follows:

1. **Five monthly loading doses:** Elman 2010’s disclosure of a ranibizumab trial in which patients were given four fixed doses followed by individualized assessment-based dosing, with no disclosure of subsequent eight-week dosing.
2. **Eight-week dosing:** The 2009 Press Release’s disclosure of a DME trial with four arms, *one* of which involved three (not five) monthly doses followed by eight-week dosing.

Petitioner provides no credible motivation to combine these components to arrive at the regimen recited in the Challenged Claims.

First, Petitioner asserts that “the use of five initial loading doses” is disclosed by Elman 2010. Pet. 42. Not so. In fact, the dosing protocol used in Elman did not involve five fixed monthly loading doses for *any* arm, and Elman 2010 does not disclose that the study included even a single patient who received five (and only five) initial monthly doses of ranibizumab (the drug that was the subject of the study).

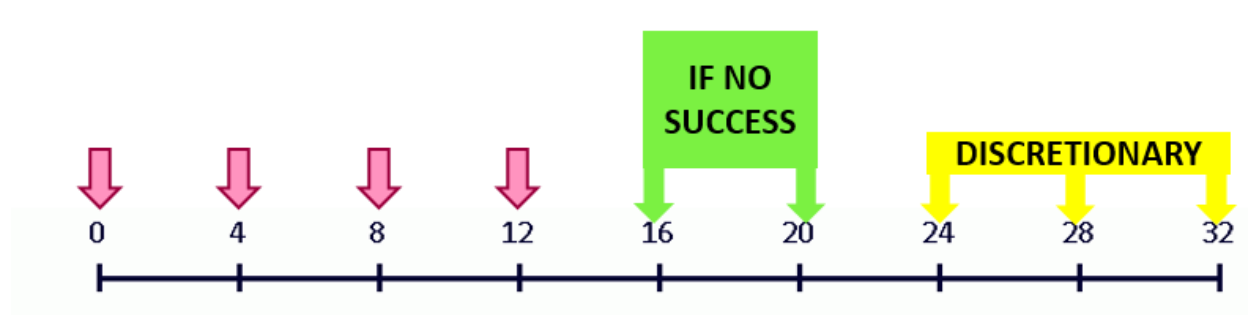
Petitioner relies on one of the arms of study described in Elman 2010, known as “deferred laser,” in which patients received injections of ranibizumab pursuant to a “treatment protocol,” with photocoagulation laser therapy deferred until at or after 24 weeks. *Id.*, 24–25. The protocol for Elman 2010 provided for *four* initial monthly doses for all patients; made it likely that patients would receive at least *six* initial monthly doses; and allowed for patients to receive *even more* monthly doses. Ex.1006, 3. The Elman 2010 protocol provides as follows:

The treatment protocol (summarized in Appendix 1, available at <http://aaojournal.org>) included a baseline treatment followed by intravitreal study drug or sham injection retreatments **every 4 weeks through the 12-week study visit. From the 16-week study visit and thereafter, a retreatment algorithm** for study drug injections and sham injections (Appendices 2 and 3, available at <http://aaojournal.org>) **was designed to require retreatments unless a study visit was deemed a “success”** (defined below and in Table 1, available at <http://aaojournal.org>) at which point retreatment was at

investigator discretion. From the 24-week study visit and thereafter retreatment was at investigator discretion if the study visit was deemed “no improvement” (defined in Table 1, available at <http://aaojournal.org>).

Id. (emphasis added).

Summarized in graphical form, the Elman 2010 protocol generally provided for injections as shown below:



Thus, the claimed dosing regimen and Elman 2010 involve two divergent approaches: The claims recite a dosing regimen that is *fixed*, rather than based on individualized patient assessments, throughout the course of treatment, with a transition to extended (but still fixed) dosing after the *fifth* dose. By contrast, Elman 2010 discloses fixed dosing followed by individualized patient assessments, with the transition to individualized dosing after the *fourth* dose, and a further transition to a different individualized dosing methodology after the *sixth* dose.

Petitioner focuses on Elman 2010’s disclosure that 22% of patients did not receive a fifth dose at the 16-week visit to conclude that 78% of patients *did* receive five initial monthly doses. Pet. 25–26. But in fact, there is no disclosure

that that 78% of patients received just five initial monthly doses, as the Challenged Claims require, nor any disclosure that five would have been a desirable number of doses. In fact, the 78% may include *no* such patients and consist only of patients who received six or more initial monthly doses. Petitioner fails to show the disclosure of any patient who received five initial monthly doses (much less that the POSA would have had reason to pursue such a regimen based on the disclosure of Elman 2010). Thus, the Petition is deficient in showing a motivation to take five initial loading doses from Elman 2010.

Not only is there no disclosure of any patient receiving just five initial monthly doses, as the claims require, but the Elman 2010 protocol makes that scenario unlikely, further undermining any case for a motivation to cherry pick 5 loading doses from Elman 2010 and combine them with the 2Q8 dosing of the 2009 Press Release. As shown above, the criteria for administering a dose at 16 weeks and 20 weeks are *exactly the same*: Patients who didn't meet specified success criteria were likely to receive a dose. At both week 16 and week 20, a patient would only be deemed a "success" if they had "[e]ither visual acuity letter score ≥ 84 (20/20) or OCT central subfield thickness < 250 microns since the last non-sham injection or since baseline for the sham+prompt laser group."

Ex.1006, 25. The claimed dosing regimen, which requires five and only five loading doses, corresponds to a dose at week 16 but not at 20; Elman 2010, on the

other hand, treats both visits the same and spells out a regimen that would result in a patient receiving a dose at *both* visits unless she achieved 20/20 vision or low central subfield thickness. The change in dosing criteria in Elman 2010 comes not after five loading doses, but six. And treatment after the 20-week visit was discretionary, meaning that patients may have received still more monthly doses after the sixth. Thus, to the extent that Elman 2010 teaches any particular number of initial doses, it is six-plus, not five, as taught by the Challenged Claims. Samsung's attempt to read five loading doses into the reference is hindsight-driven.

Second, Elman 2010 does not disclose the subsequent fixed eight-week dosing required by the Challenged Claims. Again, Petitioner does not address Elman 2010's lack of disclosure of this element of the recited dosing regimen at all, and the design of the trial makes it unlikely that a patient who received five initial monthly doses would have subsequently received fixed eight-week doses. The next dose after five initial doses was most likely a sixth initial monthly dose, but to the extent a patient did not receive a sixth initial dose at week 20, that would likely have been because, as explained above, that patient met the study's stringent criteria for "success." But patients that were deemed a "success" would be unlikely to receive further injections at all, because "[a]ccording to the DRCR.net retreatment algorithm used in this study, eyes assigned to ranibizumab that met

‘success’ criteria at the 16-week study visit [*i.e.*, after five doses] were not required to have continued injections unless visual acuity worsened or macular edema returned.” Ex.1006, 11.

Petitioner’s sole attempt to locate any disclosure of or motivation to use a fixed eight-week dosing schedule after the initial doses in Elman is based on the fact that the recited dosing regimen would involve nine doses over the course of 52 weeks, and Elman 2010 discloses that the *median* number of injections that the ranibizumab with deferred laser group received was also nine. Pet. 26.

Petitioner’s attempt to suggest that nine median doses correspond in any way to eight-week dosing fails for numerous reasons.

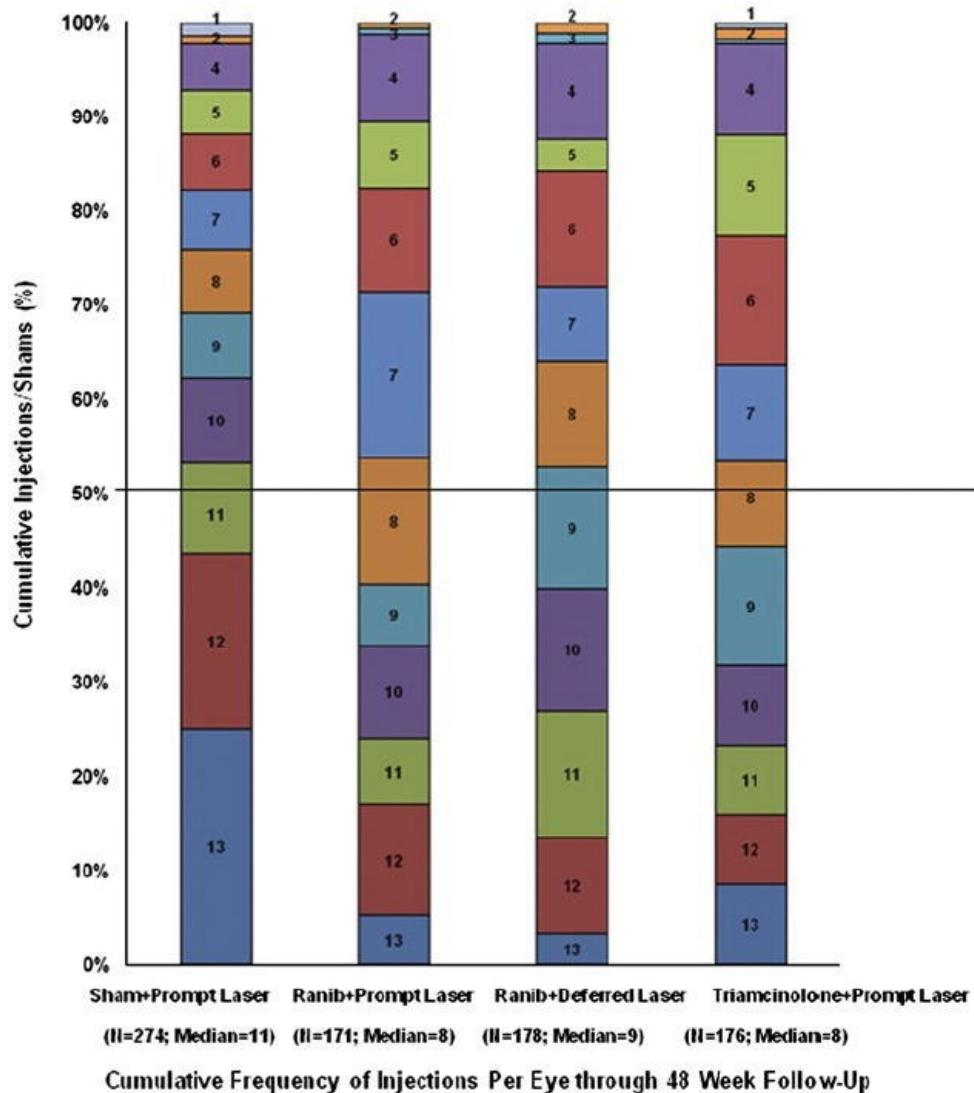
First, as Petitioner concedes, that median number of doses is derived from *all* the patients in the deferred laser arm, including those who did not receive a fifth dose. But Petitioner contends that only the subgroup of patients who received a dose at week 16 is relevant, and the median number of doses *that* subgroup received is unknown. In fact, Elman 2010 makes clear that over a fifth of those patients (22%) did not receive a fifth initial monthly dose and are therefore known not to have received the recited dosing regimen. Ex.1006, 4. Thus, the median reported by Elman 2010 has no connection to the subgroup of patients that Petitioner suggests is relevant—those who received a dose at 16 weeks.

Second, even if Elman 2010 *had*, contrary to fact, disclosed that median applied to the subgroup Petitioner contends is relevant (*i.e.*, those who received a dose at week 16), that median figure says nothing about whether those patients received five initial loading doses. Receiving nine doses over the course of a year is consistent with receiving *more* than five initial monthly doses. For example, a patient who received injections at weeks 0, 4, 8, 12, 16, 20, 28, 32, and 36 would have received six monthly doses and therefore not have received the recited dosing regimen, despite having received nine doses. Thus, there is no connection at all between receiving nine doses and receiving five initial monthly doses, as the claims require.

Third, even if a patient received *exactly five* initial monthly doses (and again, Elman 2010 does not disclose even a single patient doing so), and *even if* that same patient received nine doses over the course of a year, that does not mean that they received any doses on an eight-week schedule. For example, a patient who received injections at weeks 0, 4, 8, 12, 16, 28, 32, 36, and 48 would have both (1) received five initial monthly doses and (2) received nine doses total over the course of a year, but would not have received a single dose that was eight weeks after the previous dose.

Fourth, even though nine doses has no connection to the recited dosing regimen, Petitioner's reliance on it is further misplaced because only a small

number of patients received nine doses over the course of a year. Figure 2 of Elman 2010 shows a breakdown of the number of patients in each arm who received each given number of doses, with the second bar from the right representing the deferred laser arm that Petitioner relies on:



Ex.1006, 28. The figure indicates that only a small fraction of the patients in that arm received nine doses, which is the number that they would have had to receive if they received five initial monthly doses followed by eight-week dosing up to and

including week 48. And, as stated above, receiving nine doses does not mean that they received any doses on an eight-week schedule—the meager number of patients who received nine doses does not even make it likely that any received eight-week dosing *by pure chance*. A POSA reviewing these results would therefore have had no reason to arrive at the recited dosing regimen.

2. Petitioner Fails to Show a Motivation to Combine

Although the 2009 Press Release does disclose an arm with fixed eight-week dosing (after three initial monthly doses), Petitioner does not provide any reason why a POSA would have been motivated to choose *that particular arm* (out of the three others disclosed). Petitioner also fails to provide a reason to change the 2009 Press Release’s disclosure of three initial monthly doses to five based on Elman 2010, given that Elman 2010 not only does not teach five initial doses, but rather teaches towards six or more initial monthly doses. Pet. 43, 44. Nothing in either reference suggests that three loading doses was inadequate: The 2009 Press Release does not disclose any results for the arms it discloses, and Elman 2010 does not contain data on the results (much less any *difference* in results) between using three initial monthly doses and five. Thus, the 2009 Press Release and Elman 2010 do not provide any reason to add doses.

Petitioner argues based on two post-priority date articles⁵ that POSAs would have been motivated to “add” loading doses (presumably to the eight-week dosing arm described in the 2009 Press Release) “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 of neovascular leakage and.... gains in visual acuity....,’” Pet. 43-44 (citations omitted), but both articles make this statement in the context of discussing the benefits of three initial monthly doses, not five, and neither suggests increasing the number of initial monthly doses would have been desirable. Petitioner otherwise provides no reason why a POSA would have modified the eight-week dosing arm described in the 2009 Press Release to involve five, and just five, initial monthly doses. Indeed, a POSA’s motivation would have been the opposite—as common sense would suggest, both the sheer burden of intravitreal injections and the risk of rare but severe adverse events would have militated *against* increasing the number of loading doses. Ex.1007, 1. Petitioner’s argument is at best an argument that adding doses would have been “obvious to try,” but “[w]here the prior art, at best

⁵ The articles post-date the January 2011 priority date claimed on the face of the ’601 patent. Pet. 43-44 (citing Ex.1005, 3 (published June 2011); Ex.1007, 12 (available online October 17, 2012)).

gives only general guidance as to the particular form of the claimed invention or how to achieve it, relying on an obvious-to-try theory to support an obviousness finding is impermissible.” *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1356 (Fed. Cir. 2013) (citation omitted). And here there is not even general guidance in favor of the modification that Petitioner asserts a POSA would have made.

More fundamentally, even if a POSA would have been motivated to add doses to the regimens disclosed in the 2009 Press Release (and there is no reason to believe she would have been), there are innumerable ways to add doses. For example, there is no reason why a POSA would select the specific arm—one of four—that Petitioner relies on as a starting point for modification, given that the 2009 Press Release does not disclose the results for any arm. Nor is there any reason why a POSA would have added two loading doses instead of one, or three, or four, or why they would not have been motivated to make the subsequent dosing discretionary (as it was in Elman 2010 and other arms in the 2009 Press Release) rather than fixed. As explained with respect to Ground 2, “[w]hen a field is ‘unreduced by direction of the prior art,’ and when prior art gives ‘no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful,’ an invention is not obvious to try.” *Unigene Lab’ys, Inc. v. Apotex, Inc.*, 655 F.3d 1352, 1361 (Fed. Cir. 2011) (citations omitted); *see also Ortho-McNeil Pharm., Inc. v. Mylan Lab’ys, Inc.*, 520 F.3d

1358, 1364 (Fed. Cir. 2008) (stating that the number of alternatives must be “easily traversed, small and finite”). In short, Petitioner has not shown that a POSA would have combined the 2009 Press Release and Elman 2010, or that a POSA would have arrived at the dosing regimen of the Challenged Claims even if she had.

VI. THE *FINTIV* FACTORS WEIGH AGAINST INSTITUTION

Discretionary denial is warranted under 35 U.S.C. § 314(a) and *Fintiv* because the validity of claims 11 and 19 of the ’601 patent is being tried in the district court proceeding. *Apple Inc. v. Fintiv, Inc.*, IPR2020-00019, 2020 WL 2126495 (P.T.A.B. Mar. 20, 2020) (precedential); *see generally Regeneron Pharms., Inc. v. Mylan Pharms. Inc.*, 1:22-cv-00061-TSK-JPM (N.D. W. Va.). Following a two-week trial, Patent Owner and Mylan are expected to present closing arguments on August 3, 2023. Ex.2019. After the district court issues its judgment, an appeal is likely, not only on the issues decided at trial, but also on the Court’s earlier construction of the “exclusion criteria” limitations akin to those found in claims 17, 25, and 33 of the ’601 patent. *See* Ex.2014; Ex.2016. The appeal is likely to be expedited due to the statutory framework of the BPCIA. *See* Ex.2020, 20:11-19. Given the advanced stage of the litigation, continuing with this proceeding would result in duplicative efforts and potentially conflicting results between the district court and the Board.

The Board regularly exercises its discretion to deny institution under § 314(a), especially when related litigation has reached an “advanced state” that would render an IPR proceeding an inefficient use of the Board’s and the parties’ resources. *NHK Spring Co. v. Intri-Plex Techs., Inc.*, IPR2018-00752, Paper 8, 20 (P.T.A.B. Sept. 12, 2018) (precedential). In *NHK*, the Board denied institution where the related district court litigation involving “the same prior art and arguments, is nearing its final stages,” with trial set to take place months before any final written decision would issue. *Id.* The Board explained that given the fact that “[a] trial before us on the same asserted prior art will not conclude until” after the district court trial, “[i]nstitution of an *inter partes* review under these circumstances would not be consistent with ‘an objective of the AIA . . . to provide an effective and efficient alternative to district court litigation.’” *Id.* (citation omitted).

Such is the case here. To institute review in these circumstances—where the parties await judgment and only appeal remains—would needlessly waste the resources of the Board and would result in inefficient and disorderly disposition of the parallel validity challenges to the ’601 patent, with the potential for conflicting decisions by the Board and the district court on everything from claim construction to the final merits decision.

Petitioner argues that “Patent Owner could turn around and dismiss [the challenged claims] from the litigation, thereby avoiding any challenge,” but the procedural timing of the district court proceeding forecloses any hypothetical dismissal. Pet. 64. Petitioner’s other worst-case-scenario—that Patent Owner and Mylan settle—is speculative. *Id.* If the Board considered risk of settlement in the *Fintiv* analysis, the Board would never exercise discretion to deny institution based on *Fintiv* when Petitioner was not a party to the parallel proceeding. That is not the case. *Fintiv*, 2020 WL 2126495, at *6 (“Even when a petitioner is unrelated to a defendant, . . . if the issues are the same as, or substantially similar to, those already or about to be litigated, or other circumstances weigh against redoing the work of another tribunal, the Board may, nonetheless, exercise the authority to deny institution.”).

A. Legal Standard for *Fintiv* Discretionary Denial

The Board weighs a set of nonexclusive factors, articulated in *Fintiv*, that balance considerations of system efficiency and fairness when a patent owner raises an argument for discretionary denial due to a parallel proceeding. *Fintiv*, 2020 WL 2126495, *2–3. Here, factors one through three favor denial because (1) the district court can no longer stay the proceedings, (2) Patent Owner already tried the validity of key claims of the ’601 patent, and (3) all substantive deadlines in the district court proceeding have passed. Factor four likewise favors denial

because both proceedings challenge claims 11 and 19, and Petitioner here relies on the same primary prior art reference (2009 Press Release) relied on the district court.

In evaluating these factors, the Board takes “a holistic view of whether efficiency and integrity of the system are best served by denying or instituting review.” *Fintiv*, 2020 WL 2126495, at *2-3 (citing Patent Trial and Appeal Board Consolidated Trial Practice Guide, 58 (Nov. 2019)).

1. *Fintiv* Factors One, Two, Three, Four, and Six Favor Denial

The bench trial concerning validity of some claims of the ’601 patent in the district court proceeding took place from June 12 to June 23, 2023, and post-trial closing argument is mere days away. Ex.2019. Given the advanced stage of the district court proceeding and the overlap of the challenged claims and prior art in both proceedings, five out of six *Fintiv* factors favor denial.

First, *Fintiv* factor one, which considers whether the district court has granted a stay or evidence exists that one may be granted, weighs in favor of denial because the district court has not, and no longer can, stay the proceedings.

Second, as trial on the challenged claims has occurred, *Fintiv* factor two weighs in favor of denial because any Final Written Decision will necessarily be after the trial. “If the court’s trial date is earlier than the projected statutory deadline, the Board generally has weighed this fact in favor of exercising authority

to deny institution under *NHK*.” *Fintiv*, 2020 WL 2126495, at *4. The appeal of the district court’s judgment is expected to proceed expeditiously. *See* Ex.2020, 20:11-19. Because “the claims remain subject to further judicial review during the appeal of the district court’s invalidity determination,” the Board should “determine whether to exercise discretion to deny institution based on the parallel proceeding under *Fintiv*.” *Volvo Penta of the Ams., LLC v. Brunswick Corp.*, IPR2022-01366, Paper 15 at 7-9 (P.T.A.B. May 2, 2023) (Director Review Decision) (ordering the Board to consider *Fintiv* factors where appeal was pending at the time of institution on claims the district court invalidated). If this matter proceeds, there will be clear potential for conflicting opinions and “inefficiency and duplication of efforts.” *Fintiv*, 2020 WL 2126495, at *3. This factor favors denial.

Third, *Fintiv* factor three—“the amount and type of work already completed in the parallel litigation by the court and the parties at the time of the institution decision”—also favors denial. *Fintiv*, 2020 WL 2126495, at *4. Here, Patent Owner and the District Court’s investment in the W.D. Virginia case has been extensive, as nearly all work—including statutory pre-litigation exchanges, claim construction, discovery, expert reports, substantive motions, pre-trial submissions, trial itself, and the bulk of post-trial briefing—has been completed. This factor likewise favors denying institution. *Commscope Techs. LLC v. Dali Wireless, Inc.*,

No. IPR2022-01293, 2023 WL 2604001, at *6 (P.T.A.B. Mar. 9, 2023) (“If, at the time of the institution decision, the district court has issued substantive orders related to the challenged patent, . . . this fact weighs in favor of denial.”).

Fourth, *Fintiv* factor four, which considers overlap between issues raised in the petition and in the parallel proceeding, favors denial even though only a subset of claims at issue here are challenged in the district court proceeding. *See Samsung Elecs. Co. v. Clear Imaging Rsch., LLC*, IPR2020-01399, Paper 13 at 19–24 (P.T.A.B. Feb. 3, 2021) (denying institution where only three of the petition’s 29 challenged claims and a subset of its asserted references were raised in district court); *Fintiv*, 2020 WL 2126495, at *5 (“[I]f the petition includes the same or substantially the same claims, grounds, arguments, and evidence as presented in the parallel proceeding, this fact has favored denial.”).

Regeneron tried two claims, 11 and 19, that are representative of claims 10–12, 18–19, 21, and 26–28 challenged here. These claims are all similar in scope: Independent claims 10 and 18 require dosing every four weeks until week 20. The dependent claims merely add that “every 4 weeks comprises approximately every 28 days or approximately monthly” (11 and 19) and that “after 20 weeks, administering, via intravitreal injection, 2 mg of aflibercept once every 4 weeks” (12 and 21). Claims 10-12 and claims 18-19 and 21 are identical to claims 26-28, except that, where the former two sets require treatment of DR or DME, claims 26-

28 require treatment of “diabetic retinopathy in a patient with diabetic macular edema” (i.e., the same two disorders as the claims tried). Petitioner treats claims 10–12, 18–19, 21, and 26–28 as similar for purposes of their validity over the 2009 Press Release by relying on the exact same disclosures in the 2009 Press Release for each of these claims. Pet. 34-41.⁶

The issues further overlap because of the district court’s claim construction order, on which Regeneron has preserved its right to appeal. *See* Ex.2018; Ex.2016. The court construed the exclusion criteria limitations of the asserted patents, as found in dependent claims 17, 25, and 33.

Finally, Petitioner here relies on the same primary prior art reference (2009 Press Release) as in the parallel district court proceeding for each of grounds 2, 3, and 6. Pet. 2, 10-11. Both Petitioner and Defendants start with the point that the 2009 Press Release disclosed multiple aflibercept dosing regimens for DME including “initial doses spaced 4 weeks/1 month apart, followed by extended dosing intervals, such as 8 weeks/2 months.” Ex.2018, 26; Pet. 34-35 (“The 2009

⁶ Petitioner relies on a different arm of the DA VINCI trial, the monthly dosing arm, for claims 12, 21, and 28 only “[t]o the extent Patent Owner argues that these claims should be read as requiring dosing every 4 weeks (monthly).” Patent Owner does not advocate this construction.

Press Release teaches . . . the use of *three* initial injections of 2 mg that are spaced a month apart, followed by maintenance doses spaced eight weeks apart.”).

Petitioner and Defendants acknowledge that the dosing regimens in the 2009 Press Release start with three monthly loading doses, and both argue that a POSA would, from the teachings of the 2009 Press Release, arrive at a regimen with five loading doses followed by doses every 8 weeks. Ex.2018, 27 (“[A] POSA . . . can readily envision that the claimed 5-dose regimen is one of the existing dosing options.”); Pet. 36 (“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 . . .”).

Finally, the sixth *Fintiv* factor considers other circumstances that affect the Board’s discretion. The merits of the Petition are weak for at least the reasons set forth above. But a full merits analysis is not necessary to evaluate this factor. Even “if the merits of the grounds raised in the petition are a closer call,” this factor “has favored denying institution when other factors favoring denial are present.” *Fintiv*, 2020 WL 2126495, at *6. Because four out of five of the *Fintiv* factors all favor denial, this sixth factor also favors denying institution.

2. *Fintiv* Factor Five Is Neutral

Petitioner is not involved in the parallel proceeding. Nevertheless, “[e]ven when a petitioner is unrelated to a defendant, . . . if the issues are the same as, or substantially similar to, those already or about to be litigated, or other

circumstances weigh against redoing the work of another tribunal, the Board may, nonetheless, exercise the authority to deny institution.” *Fintiv*, 2020 WL 2126495, at *6; *Google LLC v. Personalized Media Commc’ns, LLC*, IPR2020-00724, 2020 WL 6530785, at *3 (P.T.A.B. Nov. 5, 2020) (same). Petitioner has offered no persuasive reason “why addressing the same or substantially the same issues would not be duplicative of the prior case,” as *Fintiv* instructs Petitioner should. *Fintiv*, 2020 WL 2126495, at *6. Thus, the Board should deny institution to avoid duplicating the district court litigation, even though that litigation is against a defendant who is not Petitioner. *See Fitbit, Inc. v. Philips N. Am. LLC*, IPR2020-00828, 2020 WL 6470312, at *7 (P.T.A.B. Nov. 3, 2020) (considering litigation against a defendant who was not the petitioner to weigh against institution).

VII. CONCLUSION

In sum, the Board should deny institution because Petitioner fails to show that the prior art teaches the five-loading-dose regimen required by each of claims 10–12, 17–21, 25–28, and 33. In addition, because representative challenged claims of the ’601 patent are the subject of ongoing court proceedings, the Board should exercise its discretion to deny institution.

IPR2023-00739

Dated: July 28, 2023

Respectfully submitted,

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Certification of Word Count (37 C.F.R. § 42.24)

I hereby certify that this PATENT OWNER’S PRELIMINARY RESPONSE has 10,169 words (as counted by the “Word Count” feature of the Microsoft Word™ word-processing system), exclusive of “a table of contents, a table of authorities, mandatory notices under § 42.8, a certificate of service or word count, or appendix of exhibits or claim listing.”

Dated: July 28, 2023

By /Adam Brausa/
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Certificate of Service (37 C.F.R. § 42.6(e)(4))

I hereby certify that the attached PATENT OWNER'S PRELIMINARY RESPONSE was served as of the below date via email on the Petitioner (by agreement) at the following correspondence address:

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