

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. 11,253,572

Inter Partes Review No. IPR2023-00884

PATENT OWNER'S PRELIMINARY RESPONSE

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2002	EYLEA® Label (rev. Oct. 2014)
2003	Trial Transcript (unsealed portions), <i>Regeneron Pharms., Inc. v. Mylan Pharms. Inc.</i> , No. 1:22-cv-00061-TSK-JPM (N.D.W. Va.)
2004	Press Release, <i>Positive Interim Phase 2 Data Reported for VEGF Trap-Eye in Age-Related Macular Degeneration</i> , Regeneron Pharmaceuticals, Inc. (Mar. 27, 2007)
2005	Email from George Yancopoulos to Murray Goldberg re Top Line sum for PR (Mar. 22, 2007)
2006	Interim Analysis of Phase 2 Study of VEGF Trap in AMD patients (Mar. 22, 2007) (Attachment to Ex.2005)
2007	George D. Yancopoulos, VEGF Trap : Scientific Background, BSP / REGN Kick-Off (Feb. 16, 2007)
2008	Email from Kathleen Lawrence re Decisions & Actions: AMD Ph3 Program Mtg – 4/2/07 (Apr. 2, 2007)
2009	Email from George Yancopoulos to Darlene Jody re Summary of issues for call: AMD P3 Planning with enclosed outline attached (Apr. 4, 2007)
2010	Email from Robert Terifay to George Yancopoulos re VGTeye VIEW 430 presentation (Nov. 19, 2010)
2011	Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration (AMD) - VIEW 1 and VIEW 2 – 1-Year Results (Attachment to Ex.2010)
2012	Regeneron Pharmaceuticals, <i>Phase 1 Study of VEFT Trap in Patients With Diabetic Macular Edema</i> , https://clinicaltrials.gov/study/NCT00320814 (last updated Jun. 10, 2011)
2013	Regeneron, <i>Clinical Study Concept - Ophthalmology-Diabetic Macular Edema-Phase 2-IVT-VGFT-OD-0706</i> (updated May 19, 2008)

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2015	DA VINCI – DME And VEGF Trap-Eye: Investigation of Clinical Impact: One Year Data (Dec. 8, 2010) (attachment to Ex.2024)
2016	Regeneron Pharmaceuticals, <i>DME And VEGF Trap-Eye [Intravitreal Aflibercept Injection (IAI; EYLEA®; BAY86-5321)] INvestigation of Clinical Impact (DA VINCI)</i> , https://clinicaltrials.gov/study/NCT00789477 (last updated Sep. 9, 2014)
2017	Email from Caroline Saxton re Data Review (Feb. 1, 2010)
2018	Regeneron Pharmaceuticals, Inc., <i>VGFT-OD-0706 Week 24 Topline Results</i> (Feb. 1, 2010) (attachment to Ex.2017)
2019	DRAFT – DA VINCI – 6-Month Primary Endpoint (Feb. 1, 2010) (attachment to Ex.2017)
2020	Regeneron Pharmaceuticals, Inc., <i>VEGF Trap-Eye Shows Positive Results in a Phase 2 Study in Patients With Diabetic Macular Edema</i> (Feb. 18, 2010)
2021	Email from Alyson Berliner to Dave Brown re ARVO late breakers (Mar. 1, 2010)
2022	<i>DA VINCI: DME And VEGF Trap-Eye: Investigation of Clinical Impact: Phase 2 study in patients with Diabetic Macular Edema (DME)</i> (Mar. 1, 2010) (Attachment to Ex.2021)
2023	Email from Dave Brown to Alyson Berliner and James Major re ARVO abstract (Mar. 3, 2010)
2024	Email from Caroline Saxton re Slides and tables – DaVinci (Dec. 8, 2010)
2025	U.S. Provisional Patent Application No. 61/434,836 (Jan. 21, 2011)
2026	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)
2027	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 Jun. 5, 2023)

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2029	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)
2030	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)
2031	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)
2032	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)
2033	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)
2034	Transcript of the Status Conference held on Sept. 28, 2022, <i>Regeneron Pharms., Inc. v. Mylan Pharms. Inc.</i> , No. 1:22-cv-00061-TSK-JPM (N.D.W. Va.), ECF No. 90 (filed Nov. 2, 2022)
2035	Email from George Yancopoulos re DME Phase 2 – ALL TABLES (Feb. 2, 2010)
2036	DME Target Product Profile - VEGF Trap-Eye (Sept. 26, 2007)
2037	Clinical Development & Regulatory Affairs Weekly Update (Oct. 29, 2010)
2038	Clinical Development & Regulatory Affairs Weekly Update (Dec. 3, 2010)
2039	Email from George Yancopoulos re DME PLANS & FDA meeting pre-discussion (Jan. 9, 2008)
2040	MEMO re Guidance From Bayer/ REGN Sr. Management Regarding Additional Indications in Ophthalmology from George Yancopoulos to Bayer/REGN Joint Development Group (Mar. 28, 2008)

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2041	Action Items by GD Yancopoulos - Bayer/REGN JSC (Feb. 15, 2008)
2042	Email from Yuhwen Soo to George Yancopoulos re Can you send me that slide you made combining the VA curves for View1 & View2 (Nov. 20, 2010)
2043	Vascular Endothelial Growth Factor (VEGF): Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration (AMD)—VIEW1 + VIEW 2: 1-Year Results (Nov. 20, 2010) (Attachment to Ex.2042)
2044	Email from Michael Aberman to George Yancopoulos and Leonard Schleifer re Press Release (Nov. 19, 2010)
2045	Regeneron, <i>Bayer and Regeneron Report Positive Top-Line Results of Two Phase 3 Studies with VEGF Trap-Eye in Wet Age-related Macular Degeneration</i> (Nov. 19, 2010) (Attachment to Ex.2044)
2046	U.S. Food & Drug Administration, <i>22 Case Studies Where Phase 2 and Phase 3 Trials Had Divergent Results</i> (Jan. 2017)
2047	VEGF Trap-Eye in Wet AMD - CLEAR-IT 2: Summary of One-Year Key Results, Presented at 2008 Retina Society Meeting, Scottsdale, Arizona (Sep. 28, 2008)
2048	Regeneron Pharmaceuticals, Inc., <i>A Double-Masked, Randomized, Controlled Study of the Safety, Tolerability and Biological Effect of Repeated Intravitreal Administration of VEGF Trap-Eye in Patients with Diabetic Macular Edema (DME)</i> (Issued Jan. 28, 2009)
2049	Appendix to Heier et al., <i>Intravitreal Aflibercept (VEGF Trap-Eye) in Wet Age-Related Macular Degeneration</i> , 119 OPTHALMOLOGY 2537 (2012)
2050	<i>Retinal Physician Symposium Covers Broad Range of Topics</i> , Retinal Physician (Sept. 1, 2006), https://www.retinalphysician.com/issues/2006/september2006/retinal-physician-symposium-covers-broad-range-of
2051	Prema Abraham et al., <i>Randomized, Double-Masked, ShamControlled Trial of Ranibizumab for Neovascular Age-Related Macular Degeneration: PIER Study Year 2</i> , 150 AM. J. OPTHALMOLOGY 315 (2010)

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2052	FDA, <i>Step 3: Clinical Research</i> , https://www.fda.gov/patients/drug-development-process/step-3-clinical-research (last accessed Aug. 23, 2023)
2053	Prosecution History of U.S. Patent App. No. 16/159,282 B2
2054	Anant Pai et al., <i>Current concepts in intravitreal drug therapy for diabetic retinopathy</i> , 24 SAUDI J. OPHTHALMOLOGY 143 (June 30, 2010)
2055	David M. Brown et al., <i>Long-term Outcomes of Ranibizumab Therapy for Diabetic Macular Edema: The 36-Month Results from Two phase Ill Trials</i> , 120 OPHTHALMOLOGY 2013 (2013)
2056	Jean-Francois Korobelnik et al., <i>Intravitreal Aflibercept for Diabetic Macular Edema</i> , 121 OPHTHALMOLOGY 2247 (2014)
2057	Quan Dong Nguyen et al., <i>Ranibizumab for Diabetic Macular Edema, Results from 2 Phase Ill Randomized Trials: RISE and RIDE</i> , 119 OPHTHALMOLOGY 789 (2012)
2058	Ursula Schmidt-Erfurth et al., <i>Three-Year Outcomes of Individualized Ranibizumab Treatment in Patients with Diabetic Macular Edema</i> . 121 OPHTHALMOLOGY 1045 (2014)
2059	Default Protective Order

I. INTRODUCTION

This is the second challenge to the claims of U.S. Patent No. 11,253,572 (“the ’572 Patent,” Ex.1001) at this Board. As in the previous challenge by Apotex, where institution was denied,¹ Petitioner argues that the Challenged Claims are invalid based on Regeneron’s own disclosures of certain information regarding its clinical trials. But despite Petitioner using that prior challenge as a roadmap, the present challenge fails for similar reasons.

Like the claims challenged in the previous petition, virtually all the remaining Challenged Claims² require not just a particular dosing regimen of aflibercept, but also require that the patient achieve certain visual acuity results, which the Board previously referred to as “*results limitations*.” The Board previously ruled that these limitations have patentable weight and found that prior art disclosure of the dosing regimens failed to inherently disclose those results. Ex.1004, 34. Petitioner employs three general approaches in its attempt to avoid the Board’s prior decision.

¹ *Apotex Inc. v. Regeneron Pharmaceuticals, Inc.*, IPR2022-01524, Paper 9 (P.T.A.B. Mar. 10, 2023) (“Apotex Institution Denial”).

² All but Claims 15, 24, and 25.

First, Petitioner insists that it is arguing obviousness in Grounds IV-VIII, not anticipation. But the law of inherency is enforced with *greater* strictness in the obviousness context. Where the prior art lacks express disclosure of results, a possibility, or even a probability of the claimed results is insufficient.

Second, in Grounds II-III and V-VIII, Petitioner contends that the prior art expressly discloses the claimed *results limitations*. But the references Petitioner relies on share two fatal features: They are from less than a year before the conceded priority date, and they report on the results of the Patent Owner Regeneron's own clinical trials. Common sense dictates that Regeneron and Dr. Yancopoulos (the company's Chief Scientific Officer and the patent's sole inventor) completed those trials and perfected the invention before the results were reported. That means those references are not prior art, both because the invention was conceived and reduced to practice before the reference was published, and because the relied-upon disclosures were derived from the inventor himself. Petitioner's failure to offer any evidence supporting its assertion that these references are prior art is fatal to the associated grounds.

Third, in Grounds X and XI, Petitioner argues that the *results limitations* lack patentable weight. But the Board already rejected this argument in the Apotex Institution Denial.

Petitioner's Ground IX challenges the sole '572 claim that requires four monthly secondary doses after an initial dose, followed by tertiary doses every eight weeks. The prior art does not teach four monthly secondary doses, and Petitioner does not articulate why a POSA would have modified the prior art to arrive at the recited regimen.

Petitioner's remaining ground, Ground I, relies in part on a reference from 2010 that is not prior art, and in part on the disclosure of a Phase II clinical trial. Even though Petitioner concedes that the preamble of the challenged claims requires administering a VEGF antagonist *for the purpose* of improving a patient's angiogenic eye disorder, it points to no disclosure of such a purpose in the prior art.

Each of these flaws is apparent from the face of the Petition, and therefore, institution should be denied.

II. BACKGROUND

A. EYLEA®

The FDA in 2011 approved aflibercept, under the brand name EYLEA®, for treatment of wet AMD. Ex.2001 ¶ 64. Approval for another angiogenic eye disorder, diabetic macular edema (DME), followed in 2014. *Id.* ¶ 67. Despite debuting five years after other anti-VEGF agents, EYLEA® is now the anti-VEGF therapy most commonly used for both wet AMD and DME. *Id.* ¶¶ 64-67, 69. Its popularity is largely due to the fact that it is able to not just halt progression of

disease, but provide for visual acuity *gains* comparable to other anti-VEGF options—and do so with less frequent dosing. *Id.* ¶¶ 29, 86-89, 93. Unlike Genentech’s Lucentis, whose label requires monthly administration for wet AMD and DME, EYLEA® can be administered every eight weeks. *Id.* ¶¶ 40-41. This eight-week dosing follows an initial “primary” dose and a certain number of “secondary” doses, administered monthly: For wet AMD, the label directs two secondary doses, and for DME, it directs four. Ex.2002 §§ 2.2, 2.4.

1. Development of Eylea® for AMD

Dr. George Yancopoulos, Regeneron’s co-founder, president, and chief scientific officer, came up with the idea to use two secondary doses every four weeks followed by tertiary doses every eight weeks, and he tested the efficacy of this regimen in the Phase III VIEW clinical trials.

The VIEW trials followed Regeneron’s Phase I and II trials, called CLEAR-IT-1 and CLEAR-IT-2, respectively. Ex.1009, 3-4. CLEAR-IT-1 and CLEAR-IT-2 used different dosing regimens than the one the EYLEA label recommends. *See* Ex.2003, 137:22-24.³ For CLEAR-IT-1, each of the 21 subjects received a single injection of 0.05 to 4 mg. Ex.1009, 3. For CLEAR-IT-2, Regeneron tested dose amounts from 0.5 to 4 mg. Ex.1009, 4. In the first

³ Citations to Ex.2003 use the transcript’s original page and line numbers.

12 weeks, subjects were randomized to receive injections either monthly or quarterly. *Id.* Then, all subjects were treated on a PRN (as-needed) basis. *Id.* Regeneron and Dr. Yancopoulos obtained positive interim results from CLEAR-IT-2 in late March 2007. Ex.2004; Ex.2005; Ex.2006.

Around this time, Dr. Yancopoulos came up with the idea to test a dosing regimen of two secondary doses every four weeks followed by doses every eight weeks. *See* Ex.2003, 137:3-6. Dr. Yancopoulos realized that a dose of Genentech's anti-VEGF agent, Lucentis, did not last two months—in the two months after an injection, patients would gain vision and then lose vision before the next injection. Ex.2003, 131:5-23; Ex.2007, 47; Ex.1015, 2. Dr. Yancopoulos hoped that aflibercept could last longer and be dosed every two months. Ex.2003 131:24-132:5, 137:7-21; Ex.2007, 44. This less-frequent dosing would, in Dr. Yancopoulos's words, "halve the treatment burden" and "provide a major advance." Ex.2003 131:24-132:5, 134:11-14, 135:24-136:3, 137:7-21.

Dr. Yancopoulos initially decided to pair this eight-week dosing with three preceding monthly doses. Ex.2003 133:17-20; 137:3-6, 137:15-21; *see* Ex.2008. Regeneron selected 2 mg as the highest dose for the VIEW trials because, as Dr. Yancopoulos recognized, the 4 mg dose provided a limited benefit and could result in additional toxicities during the phase III trial. Ex.2003, 125:22-126:16; 135:7-12; Ex.2009, 2. In April 2007, Regeneron selected the arms for the VIEW

trial design, which included the “2q8” arm, in which subjects received 2 mg aflibercept in two secondary doses followed by tertiary doses every eight weeks. Ex.2003, 133:10-25, 136:19-137:2; *see* Ex.2008.

With Dr. Yancopoulos’s guidance, Regeneron then carried out the VIEW trial. Ex.2003, 150:18-21; *see also* Ex.2003, 1231:10-15, 1231:21-23. Regeneron announced in September 2009 that it had completed enrollment in the VIEW trials, and the trial was completed in September 2010. Ex.1005, 1, Ex.1038, 3. On November 19, 2010, Dr. Yancopoulos received the VIEW results. Ex.2010; Ex.2011, 4-6. Three days later, on November 22, Regeneron published the top-line VIEW results in the November 2010 Press Release. Ex.1007.

2. Development of Eylea® for DME

After starting the VIEW trial, Regeneron began testing the same 2q8 regimen for DME patients in its Phase II DA VINCI trial. Regeneron had completed its Phase I trial, CLEAR-IT DME, in 2007. Ex.1030; Ex.2012. The five subjects in CLEAR-IT-DME each received a single 4 mg injection. Ex.1030, Ex.1009, 3. Regeneron selected five treatment arms for its DA VINCI trial in mid-2008, including a 2q8 arm that matched VIEW. *Compare* Ex.2013 *with* Ex.1006 *and* Ex.1007. DA VINCI included a primary visual acuity endpoint at 24 weeks and a secondary visual acuity endpoint at 52 weeks. Ex.2014, 2; Ex.2003, 1615:17-18; Ex.2015, 3.

The 24-week primary endpoint results in DA VINCI were available within Regeneron by early 2010. Ex.2014, 2; Ex.2016, 6; Ex.2003, 1615:18-19. Dr. Yancopoulos received these results on February 1, 2010. Ex.2017; Ex.2018; Ex.2019, 13-14. On February 18, Regeneron published the top-line 24-week results in a press release. Ex.2020. Regeneron then sought to present these results at the 2010 meeting of the Association for Research in Vision and Ophthalmology (ARVO). It provided an abstract summarizing the 24-week results to Drs. David Brown and James Major who, after making minor edits, submitted it to the 2010 ARVO meeting on March 3. Ex.2021; *compare* Ex.2022 *with* Ex.1010; Ex.2023.

Regeneron completed the DA VINCI trial and then, on December 8, 2010, Dr. Yancopoulos received the one-year results. Ex.2024; Ex.2015. On December 20, Regeneron reported the top-line one-year results in the December 2010 Press Release. Ex.1006.

B. '572 Patent

The '572 Patent discloses and claims eight-week extended dosing regimens for aflibercept and the successes achieved while using it. The patent is directed to therapeutic treatments for angiogenic eye disorders (including wet AMD and DME) to achieve certain results. Ex.1001, 2:13-16, 38, 42-46, 61-67, 3:38-41, 5:30-49. All but three of the remaining Challenged Claims require not only a

particular dosing regimen, but also that the patient achieve certain visual acuity results.⁴

The '572 Patent claims priority on its face to provisional application No. 61/434,836, filed on January 21, 2011, shortly after the one-year results of the VIEW and DA VINCI trials became available to Regeneron. Ex.1001. The provisional application reports both the trial protocol and results for the VIEW and DA VINCI trials. *See* Ex.2025, ¶¶ 58-60 (VIEW), ¶¶ 61-62 (DA VINCI); Ex.1001 at 13:10-27 (VIEW), 14:32-15:12 (DA VINCI).

C. Apotex Petition

In 2022, Apotex Inc. filed a petition against claims 1-14 and 26-30 of the '572 Patent. Ex.1004, 2. The Board denied institution on March 10, 2023, a month and a half before Samsung filed its petition. *Id.*

In that prior petition, Apotex “assert[ed] that the *results limitations* merely state the intended results of the otherwise claimed methods of administering aflibercept and, as such, have no patentable weight.” *Id.* at 15. The Board disagreed. The Board analogized to *Los Angeles Biomedical Research Institute at*

⁴ Claim 25 differs from the other claims by requiring four secondary doses, which the prior art does not disclose or teach. Claims 15 and 24 require a “method of treatment,” which the Petitioner’s prior art does not disclose.

Harbor-UCLA Medical Center v. Eli Lilly & Co., 849 F.3d 1049 (Fed. Cir. 2017) (“*LA Biomed*”), where results limitations carried patentable weight. In *LA Biomed*, the claims “included a limitation in the body of the independent claim to a treatment result of ‘arresting or regressing’ a tissue fibrosis by the administration of the recited dosage.” Ex.1004, 16 (citing *LA Biomed.*, 849 F.3d at 1053-54). In the Apotex Institution Denial, the Board recognized that “because the phrase was drafted as a part of a separate step of the method rather than of the preamble, the ‘arresting or regressing’ language demanded efficacy.” *Id.* at 17 (citing *LA Biomed.*, 849 F.3d at 1060-61). The Board therefore concluded that the *results limitations* of the Challenged Claims in the ’572 Patent “are limitations and must be given patentable weight for the same reasons *arresting or regressing a tissue fibrosis* was a limitation in *Los Angeles Biomed.*” *Id.* at 18.

Apotex also argued that, even if the *results limitations* carried patentable weight, the claims were unpatentable over Dixon and other references disclosing the dosing regimen of the VIEW trials. *Id.* at 25, 27. None of Apotex’s references expressly disclosed visual acuity results from the VIEW trials, but Apotex argued the references inherently disclosed the limitations. *Id.* at 26-27. The Board disagreed. “Inherency,” the Board explained, “may not be established by probabilities or possibilities” and “[t]he mere fact that a certain thing may result from a given set of circumstances is not sufficient.” *Id.* at 34 (quoting *In re*

Oelrich, 666 F.2d 578, 581 (CCPA 1981)). Examining the VIEW trial results reported in the '572 Patent and published after the priority date, the Board found that “although most would, about 4-5% of patients (or, possibly, an even higher number...) would not see the gains in visual acuity required by claims 1 and 26 or the maintenance in visual acuity required by claim 29.” *Id.* at 34. Therefore, the Board found that the claimed visual acuity results were not inherent, because they “may *typically* flow from the claimed method, but not *necessarily*.” *Id.* at 34.

The Board also considered the results of the Phase II CLEAR-IT-2 study. *Id.* at 35-36. But Apotex failed to show that “such phase 2 promising results would *necessarily* be replicated with a less frequent dosing regimen, as claimed.” *Id.* at 36. Thus, the Board concluded that the cited Phase II results were “very weak evidence that the claimed and disclosed regimen would exhibit the claimed *results limitations*.” *Id.* at 36.

D. District Court Litigation

Regeneron is litigating the validity of several challenged claims 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.2026, 62-64, 73, 115-17; Ex.2027. Regeneron filed its complaint on August 2, 2022. Ex.2028.

On April 19, 2023, the court construed multiple limitations in the '572 Patent, including the *results limitations* and exclusion criteria limitation. Ex.2029. Although the court construed the claims after the Board in *Apotex*, the court diverged from the Board and decided that the *results limitations* have no patentable weight. *Id.* 37-39. As required by the scheduling order, Ex.2030, Regeneron narrowed the number of claims for trial after the district court's claim construction order, selecting nine claims of the '572 Patent at that time. Ex.2031.

Simultaneously, Regeneron stipulated to summary judgement of invalidity with respect to claims 1-5, 8-11, 14, and 26-28 of the '572 Patent based on, and solely as a result of, the district court's claim construction, which Regeneron disagrees with. *Id.* The stipulation provides a procedural vehicle to obtain an appealable decision on the construction of those claims. *Id.*; *cf. Portney v. CIBA Vision Corp.*, 401 F. App'x 526, 529 (Fed. Cir. 2010).

A trial on the remaining claims was held in June 2023. Ultimately, Regeneron selected claims 6 and 25 of the '572 Patent for trial, and the defendants challenged the validity of these claims on bases including anticipation and obviousness. Defendants argued that claim 6 was anticipated by or obvious over Dixon, or over Dixon and Hecht. Ex.2032, 23-25. Defendants argued that claim 25 was anticipated by or obvious over the 2009 Press Release. *Id.* at 27-28. The parties presented closing arguments on August 3, 2023, and await the district

court's judgment. Ex.2033. An expedited appeal is likely to follow. *See* Ex.2034, 20:11-19; Ex.2031.

III. PRIORITY DATE

All claims of the '572 Patent are entitled to a priority date no later than January 21, 2011.⁵ Petitioner does not contest this priority date, except as to claim 25. Pet. 14 & n.1. Petitioner asserts that claim 25, which recites the use of four secondary doses to treat DME followed by eight-week dosing, is not entitled to a priority date earlier than July 12, 2013. But the only way in which claim 25's dosing regimen differs from those of the other DME claims is the use of four (rather than one or more) secondary doses, which is expressly disclosed in the January 21, 2011 provisional application. Ex.2025 ¶ 18 (disclosing administering four secondary doses after the initial dose); Ex.1001 4:26-28. The '572 Patent's literal description of all elements of claim 25 is sufficient written description, and so claim 25 is entitled to a priority date of at least as early as January 21, 2011. *See Snitzer v. Etzel*, 465 F.2d 899, 902 (CCPA 1972) (“[T]here would seem to be little doubt that the literal description of a species provides the requisite legal

⁵ Petitioner does not explain why it relies on January 21, 2011, rather than the date of the provisional application filed January 13, 2011, but the Board need not address that issue at this stage.

foundation for claiming that species.”); *see also Ariad Pharmaceuticals, Inc. v. Eli Lilly and Co.*, 598 F.3d 1336, 1352 (Fed. Cir. 2010) (“[T]he specification need not ‘recite the claimed invention *in haec verba*.’”).

Because all claims are entitled to a 2011 priority date, the entire ’572 Patent is subject to the first-to-invent provisions of pre-AIA 35 U.S.C. §§ 102 and 103. *See* MPEP § 2159. As discussed below, however, regardless of whether AIA or pre-AIA standards apply, Petitioner has not shown a reasonable likelihood that any of the challenged claims are unpatentable.

IV. LEVEL OF ORDINARY SKILL IN THE ART

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

V. CLAIM CONSTRUCTION

For purposes of this Preliminary Response only, Patent Owner does not challenge Petitioner’s proposed construction of the preambles, Pet. 17-18, or the exclusion criteria limitation, Pet. 18-20. 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.

A. The *Results Limitations* Have Patentable Weight

As the Board previously determined, the *results limitations* “are limitations and must be given patentable weight for the same reasons *arresting or regressing a tissue fibrosis* was a limitation in *Los Angeles Biomed.*” Ex.1004, 18; *see also* Ex.1004, 14 (noting that claims 16-23, which were not challenged by Apotex, include analogous *results limitations*).

The Board’s prior decision is consistent with precedent holding that “wherein” clauses must be given effect when they “relate back to and clarify what is required by the count,” giving “meaning and purpose to the manipulative steps.” *Griffin v. Bertina*, 285 F.3d 1029, 1033 (Fed. Cir. 2002). They are given effect where they narrow the claims and do not merely “duplicate” other limitations. *LA BioMed*, 849 F.3d at 1061; *Allergan Sales, LLC v. Sandoz, Inc.*, 935 F.3d 1379, 1378-80 (Fed. Cir. 2019) (Prost, C.J., concurring). That is true of the method claims challenged here. The *results limitations* in the Challenged Claims add requirements that may be—but are not necessarily—met upon performance of the dosing steps recited earlier in the claim. Claim 1, for example, requires a certain dosing regimen of aflibercept to “a patient.” But claim 1 further requires that “the patient achieves a gain in visual acuity within 52 weeks following the initial dose.” Ex.1001, 23:1-14. This is a requirement that is not met unless the patient receiving

the doses does, in fact, experience the required gain in visual acuity within the timeframe specified. *Id.*

The results of Regeneron's clinical trials show that the *results limitations* are not always met. Examining the VIEW results, the Board previously found that, "although most would, about 4-5% of patients (or, possibly, an even higher number...) would not see the gains in visual acuity required by claims 1 and 26 or the maintenance in visual acuity required by claim 29." Ex.1004, 34. An even smaller number would achieve the specific visual acuity gains required by claims 3, 8, 10, 17, or 21. The same reasoning applies to claims 16-24, covering methods of treating DME. Claim 16, from which claims 17-24 depend, requires that "the patient achieves a gain in visual acuity within 52 weeks." Ex.1001, 23:65-67. In the DA VINCI trial, three subjects who received the "2q8" dosing regimen (two secondary doses every four weeks followed by doses every eight weeks) failed to achieve a " ≥ 0 letter gain" at week 24. Ex.1031, 4 Fig.3. At week 52, four subjects in this group had a loss of visual acuity compared to baseline. Ex.2014, 5 Figs.3-4. Thus, not all patients will achieve the *results limitations*, and Petitioner does not argue that the *results limitations* "merely state[] the result of the limitations in the claim," as required for them to lack patentable weight. *Lockheed Martin Corp. v. Space Sys./Loral, Inc.*, 324 F.3d 1308, 1319 (Fed. Cir. 2003); *see also Allergan*, 935 F.3d at 1379 (Prost, C.J., concurring) ("Sandoz provides no basis for us to

conclude with any certainty that the safety and efficacy requirements of the ‘wherein’ clauses would always result from two doses of (1) any formulation of the combination at (2) any interval in a 24-hour period.”); *Gilead Scis., Inc. v. United States*, IPR2019-01456, 2020 WL 582217, *12 (P.T.A.B. Feb. 5, 2020) (finding efficacy limitations had patentable weight because they were not “necessarily inherent in administering” claimed drugs).

Petitioner relies on *Bristol-Myers* and *Copaxone* in support of its argument that the *results limitations* lack patentable weight, but both of these cases involved construction of clauses in the preamble. *Bristol-Myers Squibb v. Ben Venue Lab’ys, Inc.*, 246 F.3d 1368, 1371-72 (Fed. Cir. 2001) (“A method for treating a patient suffering from a taxol-sensitive tumor,” “A method for treating a cancer patient to effect regression of a taxol-sensitive tumor” (emphases added)); *In re Copaxone 40 Mg*, No. CV 14-1171-GMS, 2016 WL 873062, at *2 (D. Del. Mar. 7, 2016) (noting that the court was construing “the preamble terms [as] nonlimiting”). Here, however, and as was the case in *LA Biomed*, the *results limitations* are found in the body of the claim. As the Board previously recognized in the *Apotex* Institution Denial, “[w]hile not dispositive, it is significant that the phrase...is drafted as part of a separate step of the method, not as the preamble or introduction to a process carried out by the administration of the drug.” *LA Biomed*, 849 F.3d at 1061.

Petitioner argues that, because the *results limitations* are listed in “wherein” clauses, *LA Biomed* is not analogous. Petitioner relies on the legal standard articulated in *Minton* to imply that wherein clauses face a higher legal standard to be limiting than other language in the body of the claim. They do not. In *Minton*, the Federal Circuit held that “[a] whereby clause in a method claim is not given weight when it simply expresses the intended result of a process step positively recited,” *Minton v. Nat’l Ass’n of Sec. Dealers, Inc.*, 336 F.3d 1373, 1381 (Fed. Cir. 2003). But the court was articulating the standard for whether *any* claim language is limiting, not announcing a heightened standard for “whereby” or “wherein” clauses as Petitioner contends. *Syntex (U.S.A.) LLC v. Apotex, Inc.*, 407 F.3d 1371, 1378 (Fed. Cir. 2005) (applying the “intended result” standard to the phrase “in a stabilizing amount” not in a “wherein” or “whereby” clause); *LA Biomed* 849 F. 3d at 1060 (applying the same standard to “arresting or regressing the [penile fibrosis]” not in a “wherein” or “whereby” clause).

Indeed, the structure of the *results limitations* within the ’572 claims indicates that they have patentable weight. First, the limitations are specific. In cases Petitioner cites, including *Bristol-Myers* and *Minton*, “the language at issue identified a property in only very general terms and appeared in the very same claim that stated the other more concrete requirements.” *L’Oréal USA, Inc. v. Olaplex, Inc.*, 844 F. App’x 308, 324 (Fed. Cir. 2021). These cases stand in

contrast to the '572 claims, which state particular visual acuity results, including in separate dependent claims. *See Allergan*, 935 F.3d at 1379 (Prost, J., concurring) (efficacy limitation entitled to patentable weight where it “d[id] not simply require some general level of therapeutic effectiveness”).

Second, the *results limitations* appear in several dependent claims, and construing them to have no weight would render swaths of claims identical in scope, contrary to the principle of claim differentiation. *Comark Comm'ns, Inc. v. Harris Corp.*, 156 F.3d 1182, 1187 (Fed. Cir. 1998); *Jones v. Hardy*, 727 F.2d 1524, 1528 (Fed. Cir. 1984). For example, claim 3 specifies that the “patient gains at least 7 letters,” while claim 8 requires the patient to gain “at least 8 letters.” Ex.1001, 24. The sole difference between these claims is their respective *results limitations*.

Petitioner attempts to further distinguish *LA Biomed*, it concerned claims specifying a maximum dosage and minimum treatment period, not a complete treatment regimen. Pet. 60. Again, the claims here are analogous to those in *LA Biomed*. The '572 claims specify only a minimum treatment. For example, claim 21 requires only three doses: “a single initial dose,” “one or more secondary doses...administered approximately 4 weeks following the immediately preceding dose” and “one or more tertiary doses...administered approximately 8 weeks

following the immediately preceding dose” and further requires that the patient “gains at least 8 letters...BCVA.”

Patients who received the minimum number of doses would not necessarily meet the *results limitations*. For example, in the DA VINCI trial, average visual acuity gain after 3 doses was lower than the 8 letters required by claim 21. The average did not exceed 8 letters until after the fourth dose. Ex.1031, 4. Because many patients would not achieve the claimed visual acuity upon administration of the minimum dosing regimen, the outcomes are not “necessarily inherent in administering” the claimed treatment regimen. *Gilead*, 2020 WL 582217, at *12.⁶

⁶ The district court overlooked *LA Biomed* and the ‘572 claims’ short minimum treatment duration when it concluded that the *results limitations* are not entitled to patentable weight. Further, the district court took an overly narrow view of how the limitation could limit claim scope. The dispute before the district court focused on what a clinician would do if a patient failed to meet the visual acuity limitations “after the method is performed.” Ex.2029, 37. The law does not require claim language to modify a method claim at a particular time. *See Allergan*, 935 F.3d at 1380 (Prost, C.J., concurring) (assigning patentable weight to safety and efficacy requirements in part because they imply limits on the formulation: “Sandoz cannot point to any place in the specification that suggests these traits are inherently found

So as in *LA Biomed*, they do more than merely “duplicate” the other limitations; instead, they narrow the claims and carry patentable weight. *LA Biomed*, 849 F.3d at 1061.

VI. THE BOARD SHOULD DENY INSTITUTION BECAUSE PETITIONER HAS NO REASONABLE LIKELIHOOD OF SUCCESS ON ANY GROUND

The Petition includes 11 separate grounds, based on 14 different references.

Despite Petitioner’s kitchen sink approach, it fails to show a reasonable likelihood of success on any ground, for the reasons summarized below:

Ground	Claims	Art	Primary Reason Institution Denial Is Appropriate
I	15, 24	2009 Press Release or Dec. 2010 Press Release	Not prior art/no disclosure that VEGF Trap-Eye was administered for the purpose of improving angiogenic eye disorder
II	1-5, 8-11, 16-17, 20-21	Dec. 2010 Press Release	Not prior art
III	26-30	Nov. 2010 Press Release	Not prior art
IV	1-5, 8-11, 26-30	Dixon alone or in view of the 2006 Press Release	Does not disclose <i>results limitations</i>

in all formulations that combine 0.2% w/v brimonidine tartrate and 0.68% w/v timolol maleate.”). And even if it did, Regeneron’s clinical trial results show that a modification—i.e., continuation of the dosing regimen after the minimum number of doses—could help patients meet the *results limitations*.

Ground	Claims	Art	Primary Reason Institution Denial Is Appropriate
V	16-17, 20-21	2009 Press Release alone or in view of 2007 ARVO Abstract and/or Dixon	Does not disclose <i>results limitations</i>
		2009 Press Release in view of 2010 ARVO Abstract	2009 Press Release does not disclose <i>results limitations</i> and 2010 ARVO Abstract is not prior art
VI	6-7, 12-13	Dixon in view of Hecht; Dixon in view of the 2006 Press Release and Hecht	Does not disclose <i>results limitations</i>
		Dec. 2010 Press Release in view of Hecht	Dec. 2010 Press Release is not prior art
VII	18-19, 22-23	Dec. 2010 Press Release in view of Hecht	Dec. 2010 Press Release is not prior art
		2009 Press Release in view of the 2007 ARVO Abstract and Dixon and view of Hecht	Does not disclose <i>results limitations</i>
		2009 Press Release in view of 2010 ARVO Abstract and Hecht	2009 Press Release does not disclose results and 2010 ARVO Abstract is not prior art
VIII	14	Dixon alone or in view of CATT Study and/or PIER Study	Does not disclose <i>results limitations</i>
		Dec. 2010 Press Release alone or in view of CATT Study and/or PIER Study	Dec. 2010 Press Release is not prior art
IX	25	2009 Press Release alone or in view of Shams or Elman 2010	Does not disclose four secondary doses
X	1-5, 8-11, 26-30	Dixon	<i>Results limitations</i> have weight
XI	1-5, 8-11, 16-17, 20-21	2009 Press Release	<i>Results limitations</i> have weight

A. Ground II: The December 2010 Press Release Is Not Prior Art⁷

Ground II concerns Regeneron's December 2010 Press Release, which is dated less than one year before the priority date of the '572 Patent and reports the results of Patent Owner Regeneron's own clinical trials. Pet. 31-32. Petitioner has not demonstrated that the December 2010 Press Release is prior art. It is not, and therefore Ground II fails. As discussed below, Regeneron necessarily conceived of and reduced to practice the invention in the '572 Patent before publicly reporting results of that invention. Further, the December 2010 Press Release reflects the inventor's own work, and is not prior art for this additional reason.

1. The Invention Was Conceived and Reduced to Practice Before December 20, 2010

As discussed in III, *supra*, the first-to-invent provisions of pre-AIA 35 U.S.C. § 102 apply to the '572 Patent. A printed publication is prior art under pre-AIA 35 U.S.C. § 102(a) only if it was publicly accessible "before the invention thereof by the applicant for patent." The December 2010 Press Release was not. Petitioner contends that it reports on Regeneron's own clinical trials that featured

⁷ Patent Owner's Preliminary Response on Ground I follows discussion of Grounds II-XI, because the deficiencies in Ground I are reflected in various of the other Grounds.

every element of claims 1-5, 8-11, 16-17, and 20-21 of the '572 Patent, and it follows that the invention of those claims took place before its December 20, 2010 publication date.

Petitioner relies on the December 2010 Press Release for its disclosure of the results of the completed DA VINCI Phase II DME clinical trial, which Petitioner contends included all aspects of the claimed invention. Ex.1006, 2. But a report of an invention necessarily means the invention itself took place earlier.

More specifically, the 24-week results of the DA VINCI trial were completed and sent to the sole inventor, Dr. Yancopoulos, on February 1, 2010. Ex.2017; Ex.2018, Ex.2019; *see also* Ex.2035 (showing Dr. Yancopoulos's awareness of the results). These results showed 18 subjects had received three initial doses of aflibercept followed by doses every eight weeks, and at 24 weeks attained a gain of 10 or more letters, satisfying the results limitations of claims 1-5, 8-11, 16-17, and 20-21. Ex.2018, 21; Ex.2019, 14; *see also* Ex.1031, 3-4. Conception therefore occurred at least by that point: The protocol and results evidence "a definite and permanent idea of" the 2q8 dosing regimen and *results limitations* in DME patients as a "complete and operative invention." *Townsend v. Smith*, 36 F.2d 292, 295 (CCPA 1929).

By December 8, 2010, weeks before the December 2010 Press Release, the final 52-week results of the DA VINCI trial had also been obtained and reported.

Ex.2024; Ex.2015. In the meantime, the VIEW results had also been obtained, comparing aflibercept with ranibizumab, and together these results established that the less-frequent dosing schedule for aflibercept “worked for its intended purpose” of providing comparable efficacy to Lucentis. *Newkirk v. Lulejian*, 825 F.2d 1581, 1583 (Fed.Cir.1987); Ex.2036. The VIEW results were reported internally, including to Dr. Yancopoulos, by November 19, 2010. Ex.2010; Ex.2011. The claimed inventions were therefore conceived of, and reduced to practice before the December 2010 Press Release was published.⁸

⁸ Though not necessary to show completion of the invention, the continuous running of the clinical trials during this time period also shows diligence: Data was collected in both the DA VINCI and VIEW trials through September 2010, Ex.1038, 3; Ex.2016, 6, after which Regeneron would proceed to “clean the data,” “lock the database,” and “initiat[e] statistical analysis,” Ex.2003, 1615:24-1616:3, and then provide “the output from the statistical analysis is provided to the clinical group,” which would “review the detailed data and typically summarize it in PowerPoint presentation format” for the previously-discussed internal reporting. Ex.2003, 1616:4-7; *see* Ex.2037, 1 (noting timeline of data cleaning activities leading up to database lock for VIEW in mid-November 2010); Ex.2038, 2 (noting

2. The December 2010 Press Release Discloses the Inventor's Own Work

The December 2010 Press Release is not prior art for the separate reason that the results of the DA VINCI trial reported in the December 2010 Press Release reflect Dr. Yancopoulos's own work. "One's own work is not prior art under [pre-AIA] § 102(a) even though it has been disclosed to the public in a manner or form that otherwise would fall under § 102(a)."⁹ *In re Katz*, 687 F.2d 450, 454 (C.C.P.A. 1982). The Board may find a reference is not prior art upon the Patent Owner's "satisfactory showing which would lead to a reasonable conclusion that [the named inventor] is the sole inventor" of what is disclosed in the printed publication. *Id.*

preparation of tables, figures, and listings following DA VINCI database lock on December 1, 2010).

⁹ Even if the first-to-file provisions of AIA § 102 apply, the December 2010 Press Release is not prior art because the reference is dated less than a year before the conceded priority date, January 21, 2011, and was "made by the inventor...or by another who obtained the subject matter disclosed directly or indirectly from the inventor." § 102(b)(1)(A); *see* MPEP 717.01(a)(1) (citing *In re Katz* and noting the similarity in the support required under AIA § 102(b)(1)(A) and to argue a reference is an inventor's own work under the pre-AIA standards).

The aspects of the DA VINCI trial reported in the December 2010 Press Release are Dr. Yancopoulos's own work. *See* Ex.2003 1231:7-15; Ex.2009 (Dr. Yancopoulos explaining Regeneron's "top-down approach" to clinical trial design). Dr. Yancopoulos was the source of the 2q8 dosing regimen. Ex.2003, 137:3-6. He was involved in choosing that dosing regimen and the visual acuity endpoints for the DA VINCI trial, *see* Ex.2039; Ex.2040; Ex.2041. A Regeneron press release reporting the outcomes of the 2q8 arm of DA VINCI is thus not prior art because it simply reports the inventor's own work.

B. Ground III: The November 2010 Press Release Is Not Prior Art

Petitioner's argument that Claims 26-30 (the AMD Results Claims) are anticipated by the November 2010 Press Release fails for the same reasons outlined in VI.A, *supra*, for the December 2010 Press Release.

1. The Invention Was Conceived and Reduced to Practice Before November 22, 2010

The November 2010 Press Release is not prior art under pre-AIA 35 U.S.C § 102(a) because it reports on the inventions of claims 26-30, which were conceived of before its November 22, 2010 publication date and reduced to practice around the same time.

Again, Petitioner does not dispute that the November 2010 Press Release reports the results of Regeneron's own Phase III VIEW trial. Pet. vi, Ex.1007. Regeneron could only publish the results of the VIEW study after it obtained those

results. Indeed, the 52-week results of the VIEW trial were reported internally, including to Dr. Yancopoulos, on November 19, 2010. Ex.2010; Ex.2011; *see also* Ex.2042; Ex.2043 (both showing Dr. Yancopoulos's awareness of the VIEW results before November 22, 2010). These data included the visual acuity results, including maintenance of baseline visual acuity and improvements in visual acuity for subjects in each dosing arm. Ex.2011, 4-6. On both measures, the results were comparable for subjects in the 2q8 arm compared to the ranibizumab arm. *Id.* at 4. That suffices to show the “complete and operative invention” of claims 26-30 before November 22, 2010. *Townsend*, 36 F.2d at 295.

2. The November 2010 Press Release Discloses the Inventor's Own Work

The November 2010 Press Release is also not prior art because the results of the VIEW trial it reports reflect the inventor's own work.¹⁰ *See* Ex.2003, 1231:7-15; Ex.2009. As the inventor, Dr. Yancopoulos was the source of the 2q8 dosing regimen. Ex.2003, 137:3-6. He “played a major role in designing” and carrying out the VIEW trial, including the decision to test the 2q8 regimen in the

¹⁰ The November 2010 Press Release is likewise not prior art under AIA § 102, because the reference is dated less than a year before the conceded priority date, January 21, 2011, and it reflects subject matter “disclosed directly or indirectly from the inventor.” § 102(b)(1)(A); *see* MPEP 717.01(a)(1).

VIEW Trial. Ex.2003, 150:18-21, 1231:10-15; *see* Ex.2008; Ex.2009.

“[U]ltimately it was [Dr. Yancopoulos’s] decision to move forward with the final study design” for VIEW. Ex.2003, 1231:21-23, 1260:6-10. And when the results became available, Dr. Yancopoulos had the opportunity to review the draft press release. Ex.2044; Ex.2045. A Regeneron press release reporting the result of the 2q8 arm of VIEW is therefore a report of the inventor’s own work, and is not prior art.

C. Ground IV: Dixon and the 2006 Press Release Do Not Disclose the Visual Acuity Results

The claims challenged in Ground IV all require (1) treatment of either any angiogenic eye disorder or wet AMD; (2) a dosing regimen that transitions to eight-week dosing after a certain number of monthly secondary doses; and (3) a specified visual acuity gain. Petitioner argues all 14 challenged claims are obvious based on mixing and matching the disclosures of three different clinical trials from two different references, each of which involved a different dosing regimen. Pet. 39-41. As detailed below, the disclosures add up to less than what Apotex advanced in the previous proceeding, and institution should be denied.

The relevant disclosures of the clinical trials Petitioner relies on are summarized below:

Trial	Reference	Regimen	Reported Results
VIEW (Phase III AMD)	Dixon	Eight-week dosing after three monthly doses of 2 mg	None
CLEAR-IT-2 (Phase II AMD)	Dixon	PRN after four monthly doses of 2 mg	Mean gain of 9 letters Some subjects gained 15 letters
Phase I (AMD)	2006 Press Release	One dose of 2 mg or 4 mg	Three of six subjects gained 15+ letters

The only disclosure that involves the dosing regimen recited in the claims challenged in this ground is a *prospective disclosure* of the structure of the Phase III VIEW trials. Ex.1009 (noting that the Phase III study “*will* evaluate the safety and efficacy of intravitreal VEGF Trap-Eye ...” (emphasis added)). Because the trials had not yet occurred when Dixon was published, Dixon (as Petitioner admits) “does not expressly disclose the ‘results limitations’ in independent claims 1, 26, or 29 or their dependents.” Pet. 40. The only results disclosed in any of the relied-upon references involve *different* regimens—*pro re nata* (as needed) dosing after *three* secondary doses (rather than eight-week dosing after *two* secondary doses), or a *single* dose of *either* 2 mg (as the claims require) or 4 mg.

That disclosure falls short of what the Board already found insufficient to show a reasonable likelihood of success in the Apotex Institution Denial. There, the Board considered the results for *the claimed dosing regimen itself* (rather than, as here, different regimens), and concluded that they would, in “most” cases,

produce the required visual acuity gains. Ex.1004, 33-34. But because at least “4-5% of patients” would not experience those gains, the Board denied institution. *Id.* at 34. Here, Petitioner points to *no* results from the claimed dosing regimen at all, much less results that would fill the gap identified in the Apotex Institution Denial.

Moreover, the Apotex Institution Denial addressed—and found wanting—the very same Phase II results that Petitioner relies on here. Apotex, like Petitioner here, Pet. 42-45, attempted to rely on the results from CLEAR-IT-2 as evidence that patients who received the dosing regimen recited in the ’572 claims would meet the recited visual acuity results. The Board rejected the argument, noting that CLEAR-IT-2 “did not apply the claimed dosing regimen for the drug,” *id.* at 35, and concluded:

We find that effectiveness of aflibercept administered at a different dosing regimen than that claimed to be very weak evidence that the claimed and disclosed regimen would exhibit the claimed *results limitations*. There is simply no evidence identified to persuasively support that such phase 2 promising results would necessarily be replicated with a less frequent dosing regimen, as claimed.

Id. at 36.

In addition, as discussed further below, the Phase II results on which Petitioner relies suffer from the same problem that the Apotex Institution Denial

identified in the *Phase III* results: the results produced by the dosing regimen varied based on the patient, with 71% failing to gain more than 15 letters by 52 weeks. Ex.1009, 1576. Thus, achieving the *results limitations* was a matter of chance, not certainty. Even if the CLEAR-IT-2 methodology were modified to use the same regimen as the claims and that new trial were run, the patient-by-patient variation in results can at most provide a *possibility* that the *results limitations* would be met, which, as the Apotex Institution Denial observed, is not enough. Ex.1004, 34 (holding that evidence showing “that the claimed *results limitations* may *typically* flow from the claimed method, but not *necessarily*” was not enough); *Gilead*, 2020 WL 582217, at *17 (fact that “it is possible (even if ‘unlikely’)” for patient to receive drug and not meet efficacy limitation “undermines inherency, which ‘may not be established by probabilities or possibilities’” (quoting *Bettcher Indus., Inc. v. Bunzl USA, Inc.*, 661 F.3d 629, 639 (Fed. Cir. 2011))). Phase III clinical trials regularly fail even when the Phase II results show promise. Ex.2046.¹¹

¹¹ For similar reasons, Petitioner’s insistence that only “a patient,” not all patients, need to achieve the claimed visual acuity gain is unavailing. “Inherency...may not be established by probabilities or possibilities.” *PAR Pharm., Inc. v. TWI Pharms., Inc.*, 773 F.3d 1186, 1195 (Fed. Cir. 2014). If it is, at best, probable (but

The same point applies with greater force to the results from an even more dissimilar regimen Petitioner relies on—the Phase I trials involving a *single* dose administered to a mere six subjects. Pet. 41 (discussing Ex.1027, 2006 Press Release). As an initial matter, Petitioner misdescribes the Phase I trial by claiming “that a single 2 mg dose in AMD patients produced a ‘mean improvement in BCVA [] 13.5 letters, with three of six subjects gaining 15 or more letters’ at six weeks. Ex.1027, 2.” Pet. 41. In fact, the 2006 Press Release states that these results were associated with “the two highest dose groups (2 mg and 4 mg),” not just those who received “a single 2 mg dose” as Petitioner claims. Ex.1027, 2. The 2006 Press Release does not disclose how many of the subjects who achieved this result received a 2 mg dose and how many received 4 mg—a dose twice as large as in the claimed regimen. The actual disclosures of the 2006 Press Release makes clear they are not comparable to the claimed regimen.

Additionally, as with the Phase II results, subjects experienced divergent responses, underlining that visual acuity results do not follow mechanistically from a given dosing regimen: Only three of six subjects gained 15 or more letters, and the mean improvement in visual acuity (13.5 letters) is consistent with one or more

not certain) that a single patient will achieve a visual acuity gain, the same is true as to whether at least one of a *group* of patients will achieve the gain.

subjects experiencing no visual acuity gains at all.¹² Finally, Petitioner fails to show that the Phase I results involved aflibercept at all—the 2006 Press Release identifies the drug administered as only “VEGF Trap,” *id.* at 1, and that term denoted a family of anti-VEGF proteins, *see* Ex.1035, 1, 3.

Petitioner contends that it should succeed where Apotex failed because Petitioner argues obviousness while Apotex argued anticipation. Pet. 4. But it is well-established that the inherency standard is more exacting, not less, when it comes to obviousness. Indeed, the Federal Circuit has “explained that the use of inherency, a doctrine originally rooted in anticipation, must be carefully circumscribed in the context of obviousness.” *PAR Pharm., Inc. v. TWI Pharms., Inc.*, 773 F.3d 1186, 1195-96 (Fed. Cir. 2014). Thus, a “[a] party must...meet a high standard in order to rely on inherency to establish the existence of a claim limitation in the prior art in an obviousness analysis.” *Id.*

Though Petitioner shies away from characterizing its argument as one requiring inherency, there is no dispute that the prior art does not expressly disclose that the claimed dosing regimen produces the claimed results. That leaves inherency as the correct legal label for Petitioner’s arguments that the *results*

¹² For example, if the six patients in the trial gained 19, 19, 19, 14, 10, and 0 letters, respectively, that would be compatible with the reported results.

limitations are disclosed. *See Foundation Medicine, Inc. v. Guardant Health, Inc.*, IPR2019-00636, Paper 10, 13 (P.T.A.B. Aug. 20, 2019) (“Petitioner admits that [the prior art reference] does not expressly teach [the relevant limitation]. Thus, although not stated as such, Petitioner argues [the prior art reference] inherently teaches the limitation.” (citation omitted)). It would certainly make no sense to hold Petitioner to a lesser standard than Apotex (for example, by not requiring it to show that the claimed regimen *necessarily* produced the claimed results) simply based on Petitioner eschewing the “inherency” label. *See In re Best*, 562 F.2d 1252, 1255 (C.C.P.A. 1977) (“Whether the rejection is based on ‘inherency’ under 35 U.S.C. § 102, [or] on ‘prima facie obviousness’ under 35 U.S.C. § 103...the burden of proof is the same” and requires looking to whether the prior art “necessarily or inherently possess[es] the characteristics of [the] claimed product”).

Each of the Petitioner’s challenges in this Ground suffers from the defects identified above:

Claim 1. Claim 1 requires that “the patient achieves a gain in visual acuity within 52 weeks following the initial dose.” Petitioner relies on (and misstates) the results of the Phase I trial, but for the reasons above, that trial does not show the *claimed* regimen would *necessarily* have produced a gain in visual acuity within 52 weeks. Pet. 41. Petitioner also relies on a secondary endpoint of the VIEW 1

Phase III study being a gain of 15 letters of vision at week 52, but does not point to evidence suggesting that all (or even any) of the subjects enrolled in the trial achieved that result. And Petitioner's insistence that the relevant question is whether "*a patient*" rather than "every patient" would achieve the claimed visual acuity gain amounts to a tacit concession that achieving the visual acuity gain is a matter of probability, not certainty—precluding inherency. *PAR Pharm.*, 773 F.3d at 1195-96.

Claim 2. Claim 2 recites the visual acuity gain being expressed in terms of ETDRS score, and the arguments regarding claim 1 apply equally.

Claims 3-4 and 8-10. Claims 3-4 and 8-10 additionally require that "the patient gains at least [7, 8, or 9] letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score" within 52 weeks or 24 weeks. Petitioner relies on the results from the Phase I trial—in particular half the subjects achieving a visual acuity gain of 15 letters or more (and half not achieving it). Pet. 42. But as noted above, that trial involved potentially a different dose, and it produced a diversity of outcomes.

Petitioner also relies on the Phase II trial. Pet. 42-43. As noted above, that trial also involved a different dosing regimen, which the Board found to be "very weak evidence that the claimed and disclosed regimen would exhibit the claimed *results limitations*." Ex.1004, 36. And in any event, CLEAR-IT-2 also showed

that the dosing regimens in that trial (which differed from the claimed dosing regimen) produced a diversity of outcomes, as Petitioner acknowledges.

Pet. 42-43.¹³ Petitioner attempts to argue that CLEAR-IT-2 is probative evidence of the results of the different, claimed dosing regimen by arguing that the *average* number of doses subjects in the PRN dosing arm received was smaller than the total number called for by the claimed dosing regimen. But CLEAR-IT-2 itself demonstrates that the *total number of doses* over the course of a year is not the only factor that affects visual acuity: it showed that differences in the number of monthly secondary doses and the time between them also produced differences in visual acuity outcomes. Ex.2047, 17. Indeed, Dixon itself recognized that it was unclear whether VEGF Trap-Eye would be effective with eight-week dosing and concluded that the most effective dosing regimen was not yet established.

Ex.1009, 5.

Claims 5 and 11. Claims 5 and 11 depend from claims 3 and 10 respectively and additionally recite that “only two secondary doses are administered to the patient.” The deficiencies identified with respect to claims 3 and 10 apply here.

¹³ In addition, Petitioner relies on the 52-week results from CLEAR-IT-2, which cannot be probative of gains within 24 weeks, as required by Claims 4 and 9.

Claims 26-28. Claim 26 recites the same dosing regimen as claims 1 and 15, but further recites that the claimed method is “as effective in achieving a gain in visual acuity” as monthly administration of 0.5 of ranibizumab in AMD patients “at 52 weeks.” Dependent claim 27 specifies only two secondary doses are given, and claim 28 recites that the gain is measured using ETDRS. Petitioner again relies on the Phase II CLEAR-IT-2 results, Pet. 44-45, which the Board found to be “very weak evidence” that the visual acuity results are met, Ex.1004, 36, and repeats its contention that it should not be required to show that the visual acuity results necessarily followed from the claimed dosing regimen.

Petitioner also argues in passing that “a POSA would have found it obvious to modify the Dixon dosing regimen to include additional initial doses,” and states that “[m]odifying the dosing regimen to provide four initial doses, for instance, would bring Dixon further closer to the Phase II regimen, but would provide five additional doses during the remaining 52 week period, rather than only the 1.6 mean doses given in the Phase II trial.” Pet. 45 (citing Ex.1017, 23-24). It is unclear what Petitioner means, nor does Ex.1017, the only cited support, shed any light on Petitioner’s argument. Ex.1017 is a Genentech patent application to Shams, which discloses the regimen for the ranibizumab PIER trial. Ex1017. It does not say anything about four initial doses, much less what effect that would have had on visual acuity. Petitioner also does not provide any reason why a

POSA would have been motivated to *increase* the number of initial doses, given the obvious motivation to *reduce* the number of injections into a patient's eye.

And even if a POSA had modified the PIER dosing regimen as Petitioner suggests, it is unclear why the results of a hypothetical modified regimen (for which results do not exist) would be probative of the dosing regimen recited in claims 26-28.

Claims 29-30. Claim 29 recites the same dosing regimen as claims 1, 15, and 26 but further recites that the claimed method is “as effective in maintaining visual acuity” as monthly administration of 0.5 of ranibizumab in AMD patients “at 52 weeks.” Dependent claim 30 further specifies that such maintenance “means loss of less than 15 letters” BCVA as measured by ETDRS. Petitioner’s arguments duplicate those given for claims 1, 15, and 26, above, and fail for the same reasons. Pet. 45-46.

D. Ground V

Ground V, like Ground IV, involves claims that require specific visual acuity results—the difference is that they do so in the context of DME. As with Ground IV, Petitioner stitches together disclosures of Phase I, II, and III trials, each with a different dosing regimen, and its arguments fail for similar reasons:

Trial	Reference	Regimen	Reported Results
VIEW (Phase III AMD)	2009 Press Release	Eight-week dosing after three monthly doses of 2 mg	None

DA VINCI (Phase II DME)	2009 Press Release	Eight-week dosing after three monthly doses of 2 mg	None
Phase I (DME)	2007 ARVO Abstract/Dixon	One dose of 4 mg	Four of five subjects had improvements four weeks post-injection
DA VINCI (Phase II DME)	2010 ARVO Abstract	Eight-week dosing after three monthly doses of 2 mg	Mean change for VEGF Trap-Eye arms ranged from 8.5-11.4 letters at 24 weeks

1. The 2009 Press Release, Dixon, and 2007 ARVO Abstract Do Not Disclose the Visual Acuity Results

Petitioner primarily relies on disclosures of the dosing regimen of the VIEW and DA VINCI trials. Pet. 47-48. In both cases, the 2009 Press Release that Petitioner relies upon does not disclose the results of those trials. *Id.* Petitioner instead relies on the fact that the VIEW 1 trial included as a secondary endpoint the “proportion of patients who gained at least 15 letters of vision at week 52” and that the DA VINCI trial included as an efficacy endpoint “mean improvement in visual acuity at six months.” *Id.*

Petitioner’s reliance on the 2009 Press Release is rife with problems. As an initial matter, the VIEW 1 trial was a trial for wet AMD (not DME) patients and the claims challenged in Ground 5 are directed towards treating the latter condition. More fundamentally, the presence of an endpoint does not dictate that patients would necessarily meet it. As discussed above in VI.C, Petitioner’s obviousness arguments fail if Petitioner cannot establish that the results limitations

flow necessarily from the claimed regimen. Ex.1004, 33-34; *PAR Pharm.*, 773 F.3d at 1195-96.

Petitioner attempts to patch these deficiencies in the 2009 Press Release with a disclosure of a *Phase I* trial in DME patients that involved a single 4 mg dose administered to just six subjects. Pet. 41 (citing Ex.1009, 1575; Ex.1030); Ex.1031, 1 (noting that “the number of subjects is small”). In other words, the subjects received a dose more than twice as large as that called for by the claims. What’s more, one of the five subjects experienced *no visual acuity gains at all*. *Id.* Thus, the Phase I results show that visual acuity gains do not necessarily follow from the claimed regimen, precluding any argument that those results are inherent in the claimed regimen. *PAR Pharm.*, 773 F.3d at 1195-96.

2. The 2010 ARVO Abstract Is Not Prior Art

Like the December 2010 Press Release, the 2010 ARVO Abstract was published less than one year before the ’572 Patent’s priority date and discloses certain top-line results from the DA VINCI trial. For similar reasons, the 2010 ARVO Abstract is not prior art.

First, Petitioner relies on the 2010 ARVO Abstract for its disclosure of the interim results of a *Regeneron* clinical trial that Petitioner contends included all

elements of claims 16-17, and 20-21.¹⁴ If so, then as discussed in Section VI.A.1, the invention was necessarily completed before the 2010 ARVO Abstract reported on it. Thus, the Abstract is not prior art under pre-AIA § 102(a).

Second, the ARVO abstract is not prior art because the results of the DA VINCI trial it reports reflect Dr. Yancopoulos's own work. As discussed in VI.A.2, *supra*, Regeneron's reports of the visual acuity outcomes from the 2q8 arm of DA VINCI were necessarily disclosures of Dr. Yancopoulos's own work. Regeneron itself drafted the abstract and provided it to Drs. Major and Brown to submit to the ARVO conference. Ex.2021; *compare* Ex.2022 with Ex.1010.¹⁵

¹⁴ Patent Owner submits that the use of the words "method of treating" in the preamble of the challenged claims requires efficacy comparable to the standard of care. However, the Board need not reach this issue because either the 2010 ARVO Abstract does not disclose effective treatment and thus does not anticipate, or alternatively, if the challenged claims include no such requirement (as Petitioner argues), then it follows that the claimed inventions were completed before the 2010 references published.

¹⁵ Again, even if the first-to-file provisions of AIA § 102 apply, the 2010 ARVO Abstract is not prior art under § 102(b)(1)(A). *See also* MPEP 717.01(a)(1).

E. Ground VI

1. Dixon and the 2006 Press Release Do Not Disclose the Visual Acuity Results

As discussed above in VI.C, Dixon and the 2006 Press Release neither expressly nor inherently disclose the claimed visual acuity results.

2. The December 2010 Press Release Is Not Prior Art

The December 2010 Press Release is not prior art to claims 6-7 and 12-13 because the claimed inventions were earlier conceived and reduced to practice. As detailed above in VI.A.1, the December 2010 Press Release simply reports the results of Regeneron's own DA VINCI trials. The VEGF-Trap Eye formulation used in the DA VINCI trial was an isotonic solution containing a non-ionic surfactant, polysorbate 20. Ex.2048, 88. The inventor, Dr. Yancopoulos, made the

Additionally, the 2010 ARVO abstract is not prior art under the AIA because it was not Regeneron's first public disclosure of the subject matter. *See* § 102(b)(1)(A). Regeneron disclosed the subject matter of the 2010 ARVO abstract in its February 18, 2010 Press Release. The Press Release discloses the same subject matter for which Petitioner relies on the 2010 ARVO Abstract: that at 24 weeks, the mean visual acuity gain in each VEGF-Trap Eye arm of the DA VINCI trial ranged from +8.5 to +11.4 letters. Pet. 49 (citing Ex.1010, 1); Ex.2020, 1.

final decision to proceed with this solution of aflibercept at the time Regeneron was developing the VIEW trial protocol. Ex.2003, 141:14-19. Thus, as discussed in VI.A.1, the claimed inventions—including the formulation requirements of claims 6-7 and 12-13—were conceived and reduced to practice no later than December 8, 2010, when the DA VINCI results were internally reported. Because that predates the December 20, 2010 publication date of the December 2010 Press Release, it is not prior art.

As discussed above in VI.A.2, the December 2010 Press Release also discloses the inventor's own work and is thus not prior art.

F. Ground VII

1. The 2009 Press Release, Dixon, and 2007 ARVO Abstract Do Not Disclose the Visual Acuity Results

As discussed above in VII.D.1, the 2009 Press Release, Dixon, and the 2007 ARVO Abstract neither expressly nor inherently disclose the claimed visual acuity results.

2. The 2010 ARVO Abstract Is Not Prior Art

For the reasons discussed above in VI.D.2 and VI.E.2, the 2010 ARVO Abstract is not prior art to claims 18-19 and 22-23.

3. The December 2010 Press Release Is Not Prior Art

For the reasons discussed above in VI.A and VI.E.2, the December 2010 Press Release is not prior art to claims 18-19 and 22-23.

G. Ground VIII

1. Dixon Does Not Disclose the Visual Acuity Results

As discussed above in VI.C, Dixon neither expressly nor inherently discloses the claimed visual acuity results.

2. The December 2010 Press Release Is Not Prior Art

The December 2010 Press Release is not prior art to claim 14. The DA VINCI trial excluded potential participants with “ocular inflammation” and “infectious blepharitis, keratitis, scleritis, or conjunctivitis.” Ex.1031, 2. The inventor, Dr. Yancopoulos, also approved the claimed exclusion criteria as part of the VIEW trial design. Ex.2049, 3; Ex.2003, 1231:21-23. Thus, as discussed in VI.A.1, claim 14 was conceived and reduced to practice no later than December 8, 2010, when the DA VINCI results were internally reported. Because that predates the December 20, 2010 publication date of the December 2010 Press Release, it is not prior art.

As discussed above in VI.A.2, the December 2010 Press Release discloses the inventor’s own work and is thus not prior art.

H. Ground IX: The 2009 Press Release, Shams, and Elman 2010 Do Not Disclose Four Secondary Doses

Claim 25 depends from claim 15 and specifies that “four secondary doses are administered to the patient,” meaning the dosing regimen consists of five initial monthly doses, followed by an eight-week maintenance dosing. Petitioner argues

that this regimen is obvious in light of the 2009 Press Release, Shams, and Elman 2010, but these references do not disclose the recited dosing regimen, and Petitioner fails to articulate why a POSA would have modified them to arrive at the recited regimen.

First, the 2009 Press Release is a prospective disclosure of Regeneron's DA VINCI clinical 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 and then promptly modify it to match the recited dosing regimen, based on Petitioner's assertion that the Press Release teaches a POSA that more secondary doses are beneficial. But the 2009 Press Release contains no such teaching, nor does it disclose any results of the DA VINCI trial that would motivate Petitioner's proposed modification. Indeed, the motivation would be to *reduce* the number of doses administered into a patient's eye, not increase it, or perhaps to make no changes at all.

Second, Shams does not help Petitioner. It discusses the general concept of more-frequent followed by less-frequent dosing, which would not be enough to motivate a POSA to use exactly four monthly secondary doses followed by doses every eight weeks, as claimed. 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). 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 two secondary doses followed by quarterly dosing, administered to subjects with choroidal neovascularization secondary to AMD). Ex.1017, 32-36. 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 '572 Patent as a failure. Ex.2050, 2 ("[T]he 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."); Ex.1021, 5 fig.1, 7; Ex.2051, 2.

Third, Elman 2010 does not move the needle. Elman 2010 describes a clinical trial protocol that provided for *three* fixed secondary doses for all subjects. Ex.1018, 3, 25. Thereafter, subjects could receive monthly doses based on an assessment, rather than on a fixed regimen. *Id.* 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 challenged claims recite fixed dosing throughout, with a transition from monthly to eight-week dosing after four secondary doses.

Thus, Petitioner fails to show that Claim 25, which (unlike the prior art) requires a dosing schedule of four monthly secondary doses followed by eight-week dosing, is obvious.

I. Ground X: The *Results Limitations* Have Patentable Weight

The Board previously held that the *results limitations* carry patentable weight. Yet, as Ground 10, Petitioner argues that the *results limitations* have no patentable weight and that Dixon anticipates claims 1-5, 8-11, and 26-30 by disclosing all other limitations of these claims. Pet. 60-61. Petitioner is wrong on the construction of the *results* limitations, as discussed in V.A, and thus has no reasonable likelihood of success on Ground 10.

J. Ground XI: The *Results Limitations* Have Patentable Weight

Petitioner relies on the same claim construction argument for Ground 11, and then argues that the 2009 Press Release anticipates claims 1-5, 8-11, 16-17, and 20-21 by disclosing all other limitations of these claims. Pet. 61. Again, Petitioner is wrong on the construction of the *results limitations*, as discussed in V.A, and thus has no reasonable likelihood of success on Ground 11.

K. Ground I: The 2009 Press Release Does Not Disclose that the VEGF Antagonist Was Administered for the Purpose of Treating an Angiogenic Eye Disorder

Ground I argues that claims 15 and 24 are anticipated by the December 2010 Press Release and the 2009 Press Release. Even if it disclosed every claim limitation, the December 2010 Press Release would not anticipate because it is not prior art for the reasons given in Section VI.A, above.

The 2009 Press Release also does not anticipate claims 15 and 24. That is because Petitioner concedes that the preamble of the challenged claims is limiting, and agrees that it at minimum requires “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.” Pet. 18 (alterations and emphasis in original, citations omitted).

Petitioner does not explain how the 2009 Press Release discloses administering a VEGF antagonist “for the purpose of improving or providing a beneficial effect on their angiogenic eye disorder.” See Pet. 28-30. Petitioner relies on the 2009 Press Release’s disclosure of a *Phase II* trial for DME, known as DA VINCI, and cites to paragraph 143 of the declaration of Dr. Chaum to support its argument that the administration of the drug in that trial satisfies the preamble. Pet. 30 (citing Ex.1002 ¶¶ 143-144). Dr. Chaum asserts without citation that the purpose of the Phase II trial was to “*confirm* safety and efficacy as well as positive

results reported in prior trials for the treatment of DME.” Ex.1002 ¶ 143

(emphasis added). The 2009 Press Release does not contain any disclosure that supports Dr. Chaum’s naked opinion about the purpose of the Phase II trial.

Moreover, the FDA has explained that Phase II trials typically “aren’t large enough to show whether the drug will be beneficial” and “[i]nstead, Phase 2 studies provide researchers with additional safety data.” Ex.2052. While Phase II trials may be used to *explore* efficacy, it does not follow that administration of the drug is done with the *purpose* of improving or providing a beneficial effect on an angiogenic eye disorder, as Petitioner concedes is required by the preamble.

Because anticipation requires that *every element* of the claims be present in a single prior art reference, the 2009 Press Release does not anticipate claims 15 and 24.

VII. THE BOARD SHOULD DENY INSTITUTION UNDER *FINTIV* BECAUSE THE SAME CLAIMS AND ART ARE AT ISSUE IN DISTRICT COURT

Discretionary denial is warranted under 35 U.S.C. § 314(a) and the *Fintiv* factors because of the late stage of litigation over the ’572 Patent’s validity. *Apple Inc. v. Fintiv, Inc.*, IPR2020-00019, 2020 WL 2126495 (P.T.A.B. Mar. 20, 2020) (precedential). Contrary to Petitioner’s speculation, Pet. 68, Regeneron selected both AMD and DME claims to assert at trial, and Defendants relied on the same references as Petitioner—Dixon, Hecht, and the 2009 Press Release—to argue invalidity. Post-trial briefing is complete, and the parties await the district court’s

judgment. An expedited appeal is likely, not only on the claims that were tried (6 and 25), but also on the court’s earlier construction of the *results limitations*. See Ex.2034, 20:11-19; Ex.2029; Ex.2031. The Board should deny institution, as it regularly does 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. Intrix-Plex Techs., Inc.*, IPR2018-00752, Paper 8, 20 (P.T.A.B. Sept. 12, 2018) (precedential).

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

Factor one—“whether the court granted a stay or evidence exists that one may be granted if a proceeding is instituted”—weighs in favor of denial because the district court has not stayed the proceedings and instead is on the verge of issuing a post-trial decision.

Factor two—“proximity of the court’s trial date to the Board’s projected statutory deadline for a final written decision”—also favors denial. “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. And even if the district court issues its decision before the Board’s deadline to institute, *Fintiv* denial is appropriate because “the claims remain subject to further judicial review during the appeal of the district court’s invalidity determination.” *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 after district court had invalidated the challenged claims).

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. Patent Owner’s and the District Court’s investment in the litigation has been extensive, as nearly all work, including claim construction and trial itself, is complete. *Commscope Techs. LLC v. Dali Wireless, Inc.*, IPR2022-01293, 2023 WL 2604001, at *6 (P.T.A.B. Mar. 9, 2023).

Factor four—“overlap between issues raised in the petition and in the parallel proceeding”—also favors denial. Like Petitioner, Defendants challenge the ’572 claims based on Regeneron’s DA VINCI and VIEW trials, relying on two of Petitioner’s primary references: Dixon and the 2009 Press Release.

Against claim 6, both Defendants and Petitioner rely on “Dixon’s disclosure of a 2 mg aflibercept intravitreal dose, given in a regimen of three monthly doses, followed by an 8-week interval,” i.e., the dosing regimen of Regeneron’s Phase III VIEW trial. Ex.2032, 22; *e.g.*, Pet. 39. Petitioner and Defendants also rely on identical disclosures for the limitation “wherein the aflibercept is formulated as an isotonic solution.” Both rely on Dixon’s disclosure that VEGF Trap-EYE is formulated with “buffers” and is “suitable for the comfortable, non-irritating, direct

injection into the eye.” Pet. 49; Ex.2032, 23. And both rely on Hecht’s disclosures that “[o]phthalmic solutions are formulated to be sterile, isotonic, and buffered for stability and comfort,” and that “[g]iven a choice, isotonicity always is desirable and particularly is important in intraocular solutions.” Pet. 50; Ex.2032, 24.

Against claim 25, both Petitioner and Defendants start with the point that the 2009 Press Release discloses 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.2032, 26; Pet. 53. Petitioner and Defendants acknowledge that the dosing regimens in the 2009 Press Release use two secondary doses, and both argue that a POSA would, from the teachings of the 2009 Press Release, arrive at a regimen with four secondary doses followed by doses every eight weeks. Ex.2032, 27 (“[A] POSA...can readily envision that the claimed 5-dose regimen is one of the existing dosing options.”); Pet. 36.

The overlap in issues does not end with the claims tried. Regeneron accepted summary judgment of invalidity of several claims of the ’572 Patent as a procedural vehicle to obtain appellate review of the district court’s decision construing the *results limitations*. Ex.2031. Nearly every claim of the ’572 Patent (except claim 25) includes an express visual acuity limitation, the construction of which remains a live issue in litigation. Contrary to Petitioner’s argument, Pet. 68, *Fintiv* denial is appropriate even though only a subset of the challenged claims

were tried. *See Samsung Electronics. Co. v. Clear Imaging Research., LLC*, IPR2020-01399, Paper 13 at 20-22 (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.

Instituting this IPR would create a potential for conflicting decisions because of the overlapping issues. Even if the Federal Circuit issued its decision before the deadline for the Board’s final written decision, district court proceedings could stretch longer in the event of a remand.

Finally, factor six—“other circumstances that impact the Board’s exercise of discretion, including the merits”—favors denial. The merits of the Petition are weak and do not warrant institution 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.

B. *Fintiv* Factor Five Does Not Outweigh the Other *Fintiv* Factors

Petitioner is not involved in the parallel proceeding. But “[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 Comms., 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).

VIII. THE BOARD SHOULD DENY INSTITUTION UNDER 35 U.S.C. § 325(D) BECAUSE THE EXAMINER AND BOARD REJECTED THE SAME ART AND ARGUMENTS

In addition to denying institution because Petitioner has failed to show a reasonable likelihood of demonstrating the asserted grounds render the ’572 claims invalid, the Board should also deny institution because the Patent Office has considered the art and arguments that are the basis for those grounds. Petitioner relies on art that both the Examiner and the Board have considered and on

arguments the Board rejected in the Apotex Institution Denial. Thus, discretionary denial is warranted.

In applying § 325(d), the Board uses a two-part test: “(1) whether the same or substantially the same art previously was presented to the Office or whether the same or substantially the same arguments previously were presented to the Office; and (2) if either condition of [the] first part of the framework is satisfied, whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims.” *Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH*, IPR2019-01469, 2020 WL 740292, at *3-4 (P.T.A.B. Feb. 13, 2020) (precedential) (citing *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, 2017 WL 6405100 (P.T.A.B. Dec. 15, 2017) (precedential as to § III.C.5, first paragraph)).

A. The Board Considered and Rejected the Art and Arguments

Much of the Petition relies on the same art and/or arguments that the Board considered and rejected in its March 2023 decision denying institution of Apotex’s IPR petition.

The Board determined that Apotex “ha[d] not established a reasonable likelihood that it would prevail in showing that” claims 1-14 and 26-30 were unpatentable over Dixon alone or in combination with Hecht. Ex.1004, 37-39. The Board’s denial of institution is enough to satisfy *Advanced Bionics* part I for

Petitioner's Grounds that rely on Dixon as a primary reference (Grounds IV, X as well as Petitioner's combination for Ground VI and VIII that rely on Dixon as a primary reference, Pet. 12-13). *See Palo Alto Networks, Inc. v. Centripetal Networks, Inc.*, IPR2021-01520, 2022 WL 945569, at *9 (P.T.A.B. Mar. 22, 2022) (relying for part 1 on the fact that “the Office confirmed the patentability of claims 1-20 over Sourcefire’ after the Board denied institution” of a prior IPR petition).

Even though Petitioner relies on a variety of references not found in the *Apotex* petition, *Advanced Bionics* part 1 is also satisfied because the Board considered and rejected “substantially the same arguments” Petitioner relies on. *Advanced Bionics*, 2020 WL 740292, at *3. Namely, both (1) that the ’572 Patent’s *results limitations* carry no patentable weight, and (2) if they do, the claims are unpatentable over prospective disclosures of clinical trials using the same protocols alone or with the results of earlier clinical trials using different dosing regimens.

The Board considered and rejected Apotex’s argument that “the visual acuity limitations [of the ’572 Patent] merely state the intended results of the otherwise methods of administering aflibercept and, as such, have no patentable weight.” Ex.1004 at 15-18; *see also* Ex.1004, 14 (noting that claims 16-23 include analogous visual acuity requirements although the Apotex petition did not

challenge those claims). Petitioner's Grounds X and XI rely on the same argument. Pet. 60-61; *see* VI.I-VI.J, *supra*.

The Board also considered and rejected Apotex's argument that the claims are unpatentable over prospective disclosures of clinical trials using the same protocols. Ex.1004, 25-37. The references did not expressly disclose the visual acuity results, and the Board reasoned that the limitations were also not inherently disclosed because fewer than all patients who received the disclosed dosing regimen would achieve the recited visual acuity results. *Id.* at 34. The Board further considered and rejected the argument that the lack of results in the prospective clinical trial disclosures could be overcome with the "promising" results of earlier-phase clinical trials using different dosing regimens. *Id.* at 35-36. The Board found efficacy under a different dosing regimen to be "very weak evidence that the claimed and disclosed regimen would exhibit the claimed *results limitations*." *Id.* at 36.

Petitioner's Grounds IV and V rely on substantially the same arguments the Board rejected, as do Petitioner's Grounds VI-VIII to the extent they refer back to Grounds IV and V. Pet. 49, 51. As discussed above, although Petitioner's grounds purport not to rely on inherency, Petitioner cannot escape the application of inherency law to its arguments by omitting the word "inherent." *See* VI.C, *supra*. And although Petitioner's Ground V relies on Regeneron's DME trials, which

were not the subject of Apotex's petition, the reasoning is substantially the same: Petitioner relies on express disclosures of the disease and dosing regimen, then argues that a POSA would expect the *results limitations* based both on the endpoints to be measured and the results of earlier studies. *Compare* Pet. 39-41 with Pet. 46-48 (citing Pet. 29-30); *see Husky Injection Molding Sys., Ltd. v. Plastipak Packaging, Inc.*, IPR2020-00431, Paper 23 at 13-18 (P.T.A.B. July 28, 2020) (finding the first part of the *Advanced Bionics* test satisfied based on the examiner making "substantially the same arguments" that the petitioner raised, because although neither the references nor the claims were identical, both the examiner and the petition relied on similar "result-effective variable" reasoning for how a POSA would arrive at a height limitation from prior art that did not satisfy the limitation).

B. The Examiner Allowed the '572 Patent After Considering the Asserted Art

Regeneron submitted, and the Examiner marked as considered, each of Petitioner's primary references: the December 2010 Press Release, Ex.1014, 1261; the November 2010 Press Release, *id.* 1261; the 2009 Press Release, *id.* 1260; and Dixon, *id.* 1251. But the Examiner's awareness of Petitioner's references is apparent from the examination of an application in the '572 Patent's priority chain, U.S. App. No. 16/159,282. The same Examiner examined both applications. Ex.1014, 1239; Ex.2053, 99. In connection with the prosecution of the

'282 application, a third party submitted a complete copy of Dixon, *id.* at 128-29 (electronic acknowledgement of receipt showing all eight pages were submitted), along with a claim chart mapping Dixon's disclosures to some of the then-pending claims, *id.* at 117-18. The submission also included the Regeneron 2009 Press Release, along with a claim chart mapping the press release disclosures to the rest of the then-pending claims. *Id.* 119-21. The Examiner stated that he considered the third-party submission and rejected each then-pending claim as anticipated by either Dixon or the 2009 Press Release. *Id.* 198-202. Thereafter, Regeneron disclosed, and the Examiner considered, the third-party submission during the prosecution of the '572 application. Ex.1014, 1250.

Most of Petitioner's secondary references were before the Examiner too: the 2006 Press Release, Ex.1014, 1258; the 2007 ARVO Abstract, *id.* 1252; the 2010 ARVO Abstract, *id.* 1256; Shams, *id.* 1249; and the PIER Study, *id.* 1261.¹⁶

¹⁶ Secondary references not specifically named in an IDS were mentioned elsewhere in the art that Regeneron did submit, or they are cumulative of other references submitted. Dixon mentioned the CATT study, Ex.1009, 2, and Petitioner relies on CATT for disclosures cumulative of PIER, Pet. 25, 52. Several disclosed references cite Elman 2010 or mention the same trial. Ex.2054, 6 (cited at Ex.1014, 1257); Ex.2055, 1, 9 (cited at Ex.1014, 1250); Ex.2056, 1, 7 (cited at

The Examiner's attention would be particularly drawn to Regeneron's own clinical trials mentioned in Dixon and the 2009 Press Release. For example, Dixon discloses positive results from Regeneron's clinical trial. Ex.1009, 3. If the Examiner thought the Phase I results might have any relevance despite their different dosing regimen, the Examiner could easily have looked to the 2006 Press Release for additional detail. The same is true of the DME trials—the 2009 Press Release discusses the same Phase II trial discussed in the 2010 ARVO abstract, *compare* Ex.1005, 1, *with* Ex.1010, and Dixon discloses the same Phase I trial discussed in the 2007 ARVO Abstract, *compare* Ex.1009, 3 *with* Ex.1030, 1. Petitioner's assertion that "the Examiner did not consider any combination of the art and arguments presented here," Pet. 64, is thus mere speculation undercut by the connections between the references and by the fact that Regeneron disclosed the secondary references.

Ex.1014, 1256); Ex.2057, 1-2, 11 (cited at Ex.1014, 1257); Ex.2058, 2, 9 (cited at Ex.1014, 1262). Although Hecht was not cited to Examiner, Petitioner relies on it only as a secondary reference for dependent claims. As such, it does not change the analysis. *Microsoft Corp. v. IPA Techs. Inc.*, IPR2019-00839, 2019 WL 5860714, at *6 (P.T.A.B Nov. 8, 2019).

C. No Material Error

Neither the Examiner nor the Board erred in their consideration of Petitioner's asserted art. As discussed in VI, *supra*, each reference is either not prior art or fails to disclose the visual acuity limitations. The lack of material error is further evidenced by the consistency between the Examiner allowing the '572 Patent after considering the asserted references and the Board denying institution of Apotex's petition.

In its discussion of § 325(d), Petitioner does not allege any material error in the Board's consideration and rejection of the art and arguments presented in Apotex's petition. Pet. 64-65. To the extent Petitioner alleges that the Board materially erred in its application of *LA Biomed*, see Pet. 58-60, Patent Owner explains in V.A, *supra*, why Petitioner is wrong. Even if "reasonable minds can disagree regarding the purported treatment of" *LA Biomed*, "it cannot be said that the Office erred in a manner material to patentability." *Advanced Bionics*, 2020 WL 740292, at *3.

The Examiner did not materially err either. The Apotex Institution Denial confirms that the claims are not unpatentable over Dixon, and more generally that the *results limitations* are not unpatentable over references disclosing only dosing regimens or references disclosing visual acuity outcomes for different dosing

regimens. The Board's decision shows the Examiner did not materially err in failing to reject the claims based on these references.

Petitioner alleges that “the Examiner issued obviousness-type double patenting rejections but after a terminal disclaimer, failed to make an obviousness rejection over, for instance, the 2009 Press Release that also disclosed the identical dosing regimen to the reference patents.” Pet. 64-65. But when the full picture of the Examiner's and Board's consideration of the asserted references is considered, it becomes apparent that this was not a material error on the Examiner's part. The Examiner relied on both Dixon and the 2009 Press Release to reject the claims of the '282 application. Ex.2053, 198-202. Rejections to applications in the same family can form the basis for discretionary denial under § 325(d). *See Becton, Dickinson*, 2017 WL 6405100, at *7 (denying institution under 35 U.S.C. § 325(d) based on prior art combination relied on to reject the parent application). The Examiner's familiarity with Dixon and the 2009 Press Release show it was unlikely the Examiner merely overlooked these references in the context of the '572 Patent.

Dated: August 25, 2023

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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 14,000 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: August 25, 2023

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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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