

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SAMSUNG BIOEPIS CO., LTD., CELLTRION INC,
and BIOCON BIOLOGICS INC.
Petitioner,

v.

REGENERON PHARMACEUTICALS, INC.
Patent Owner.

U.S. Patent No. 11,253,572

Inter Partes Review No. IPR2023-00884¹

PATENT OWNER'S RESPONSE

¹ IPR2024-00260 and IPR2024-00298 have been joined with IPR2023-00884.

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TABLE OF ABBREVIATIONS

Petition (Paper 2)	“Pet.”
Decision Granting Institution (Paper 13)	“DI”
2009 Press Release (Exhibit 1005)	“2009 PR”
December 2010 Press Release (Exhibit 1006)	“December 2010 PR”
November 2010 Press Release (Exhibit 1007)	“November 2010 PR”
2010 ARVO Abstract (Exhibit 1010)	“2010 ARVO”
2006 Press Release (Exhibit 1027)	“2006 PR”
2007 ARVO Abstract (Exhibit 1030)	“2007 ARVO”
Person of ordinary skill in the art	“POSA”
Wet age-related macular degeneration	“wAMD”
Diabetic macular edema	“DME”

I. INTRODUCTION

The challenged patent relates to Regeneron’s inventive methods for treating angiogenic eye disorders and preventing blindness. The claimed methods involve injecting patients suffering from angiogenic eye disorders with fixed numbers of monthly “loading doses” of aflibercept (also at times called “VEGF Trap-Eye” or “Eylea®”) and then extending the dosing interval to every-two-month “maintenance doses.” This regimen halves the number of ongoing injections needed to treat wAMD and DME.

In early 2011, Regeneron filed a provisional patent application disclosing the new regimen and related clinical trial results. That application matured into the ’572 patent, which claims both that regimen and achieving certain visual acuity outcomes (the “*result limitations*”). Samsung now seeks to cancel all of those claims and has taken a kitchen-sink approach to doing so, spreading its challenge across more than 12 references and 11 grounds, and across more than 32 anticipation and obviousness theories. Despite the Board’s invitation for Samsung to drop unnecessary or irrelevant grounds (*see* DI at 15), Samsung has not done so.

The Board should reject Samsung’s challenge for at least four reasons:

First, many of Samsung’s references are not prior art, which is fatal to some or all of Samsung’s arguments for Grounds II-III and V-VIII. ARVO 2010, the November 2010 PR, and the December 2010 PR published less than a year before

the '572 patent's priority date, and they report results of Regeneron's own clinical trials. Regeneron and Dr. Yancopoulos perfected the claimed inventions before the results were reported. Thus, each invention was reduced to practice before the references were published, and the relied-upon disclosures were derived from the inventor. In its DI, the Panel noted the need for evidence so proving; Regeneron provides that evidence here.

Second, with respect to Grounds IV-VIII, Samsung has not shown that the *results limitations* are obvious over partial results from different trials. The partial data in Samsung's references derive from different dosing regimens than claimed, and they in no way give the POSA a reasonable expectation of success of achieving the *results limitations*, much less show the claimed regimens always yield those results. Samsung's arguments to the contrary are conclusory and unpersuasive, particularly for the challenged claims with *results limitations at 52* weeks, which Samsung barely addresses.

Third, Ground IX fails because Samsung has not shown that it would have been obvious to increase the number of monthly loading doses from three to five. To the contrary, doctors were motivated to decrease the number of injections to reduce the treatment burden on patients, not to increase them.

Fourth, Samsung’s alternative argument in Grounds X and XI, that the *results limitations* lack patentable weight, also fails. As the Board has now held twice, the *results limitations* constrain what methods practice the claims.

II. BACKGROUND

A. EYLEA®

In 2011, the FDA approved aflibercept, under the brand name Eylea®, for treatment of wAMD. (Ex.2001, ¶¶64.) Approval for another angiogenic eye disorder, 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 wAMD and DME. (*Id.*, ¶¶64-67, 69.) Its popularity is largely due to a dosing regimen that allows for less frequent maintenance dosing compared to other anti-VEGF options while halting disease progression and yielding visual acuity gains. (*Id.*, ¶¶29, 86-89, 93.) Unlike Genentech’s Lucentis®, whose label requires monthly administration for wAMD and DME, Eylea® can be administered on a fixed, every-eight-week schedule. (*Id.*, ¶¶40-41.) This “q8” maintenance dosing follows an initial “primary” dose and a number of monthly “secondary” doses. (Ex.2002, §§ 2.2, 2.4.)

1. Development of Eylea® for AMD

Dr. George Yancopoulos, Regeneron’s co-founder, President, and Chief Scientific Officer, had the idea to use one initial dose, followed by two secondary doses every four weeks, and then followed by tertiary doses every eight weeks.

Dr. Yancopoulos directed Phase III VIEW clinical trials to test the efficacy of this regimen. (Ex.2063, ¶¶16-25, 28; Ex.2064, ¶¶21-22.)

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 investigatory dosing regimens significantly different from what the Eylea® label would eventually recommend. (*Compare* Ex.1009, 3-4 *with* Ex.2002 *and* Ex.2003, 137:22-24.)² For CLEAR-IT-1, each of 21 subjects received a single injection of 0.05 to 4mg. (Ex.1027.) For CLEAR-IT-2, Regeneron tested dose amounts from 0.5 to 4mg. (Ex.1009, 4.) In the first 12 weeks, subjects received 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.2063, ¶19; Ex.2064, ¶17; Exs.2004-2006.)

By March 2007, Dr. Yancopoulos had the idea to test a dosing regimen of three loading doses administered every four weeks (an initial dose and two secondary doses) followed by doses every eight weeks (the “q8” dosing regimen). (Ex.2063, ¶¶16-22; Ex.2064, ¶21.) With the knowledge that Lucentis® did not last two months—in the two months after an injection, patients would gain and then lose vision before the next injection, (Ex.2063, ¶18; Ex.2003, 131:5-23, 137:7-21;

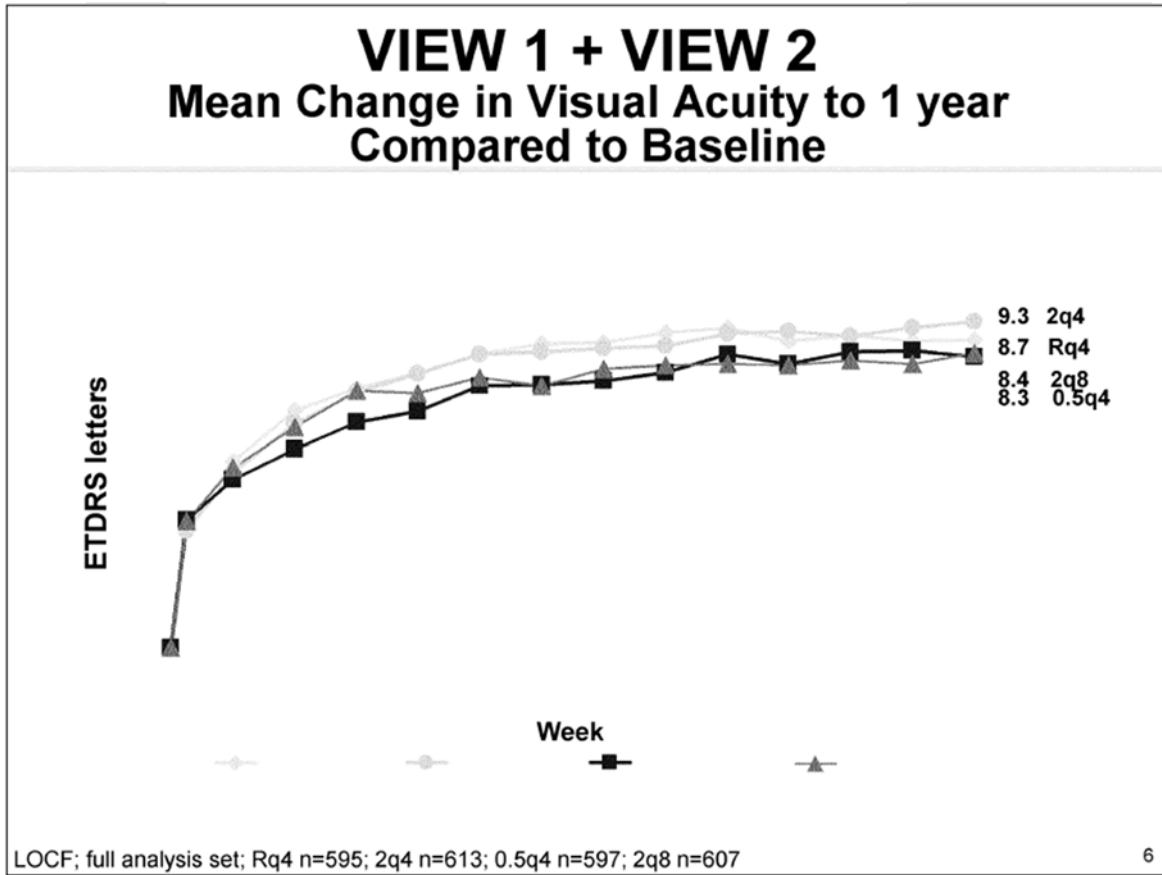
² Citations to Ex.2003 use the transcript's original page and line numbers.

Ex.2007, 46-47)—he hoped that aflibercept could achieve lasting gains when dosed every two months, (Ex.2063, ¶25; Ex.2003, 131:24-132:5.). This less-frequent dosing would, in Dr. Yancopoulos’s words, “halve the treatment burden” and “provide a major advance.” (Ex.2003, 132:2-4.)

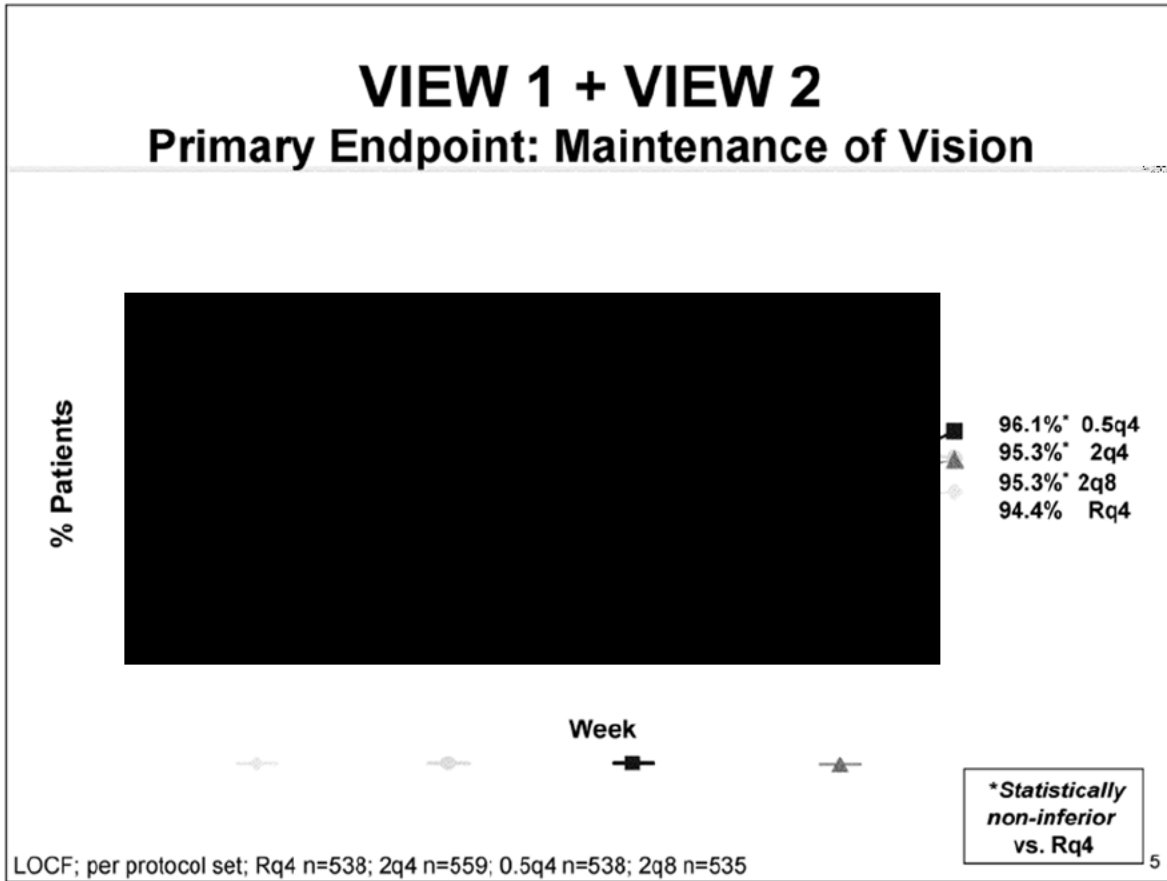
Dr. Yancopoulos initially decided to pair this eight-week dosing with three monthly loading doses. (Ex.2063, ¶¶20-23; *compare* Exs.2073-2074 with Exs.2070-2072.) He decided that the highest dose tested in the VIEW trials would be 2mg because the benefits of using a 4mg dose were not clear, and there was also concern of an increased risk of toxicities at a higher dose. (Ex.2063, ¶24; Ex.2009; Ex.2075, 1.) He also made the final decision to proceed with the VIEW trial design, which included his q8 dosing regimen, monthly dosing of 0.5mg and 2mg of aflibercept, and a comparator arm of monthly Lucentis®. (Ex.2063, ¶28; Ex.2064, ¶¶21-23; Ex.2076, 2.)

Executing on Dr. Yancopoulos’s idea, Regeneron and its commercial partner Bayer carried out the VIEW trials. (Ex.2063, ¶30; Ex.2064, ¶24; Ex.1005.) Regeneron announced in September 2009 that it had completed enrollment of the VIEW trials, and the last patient completed 52 weeks of treatment in September 2010. (Ex.1005; Ex.1038, 3.) On November 19 and 20, 2010, Dr. Yancopoulos received the VIEW results and recognized that his q8 dosing regimen had worked. (Ex.2063, ¶¶32-34; Ex.2010; Ex.2011, 4-6.) The results included the following

charts, which show the 2q8 regimen both improved vision compared to baseline and was non-inferior to monthly 0.5mg Lucentis ® (ranibizumab):



(Ex.2043, 6.)



(Ex.2043, 5.)

Confidential

4

VIEW 1 & 2

Results Summary

	Ranibizumab 0.5 mg monthly	VEGF Trap-Eye 0.5 mg monthly	VEGF Trap-Eye 2 mg monthly	VEGF Trap-Eye 2 mg every 2 months
Maintenance of vision (% patients losing <15 letters) at week 52 versus baseline				
VIEW 1	94.4%	95.9%*	95.1%*	95.1%*
VIEW 2	94.4%	96.3%*	95.6%*	95.6%*
Mean improvement in vision** (letters) at 52 weeks versus baseline (p-value versus ranibizumab 0.5 mg monthly)				
VIEW 1	8.1	6.9 (NS)	10.9 (p<0.01)	7.9 (NS)
VIEW 2	9.4	9.7 (NS)	7.6 (NS)	8.9 (NS)

*Visual acuity score was measured using the Early Treatment Diabetic Retinopathy Study (ETDRS) eye chart

* Statistically non-inferior based on a non-inferiority margin of 10%, using confidence interval approach (95.1% and 95% for VIEW 1 and VIEW 2, respectively)

*** Test for superiority

NS=non-significant

(Ex.2011, 4.)

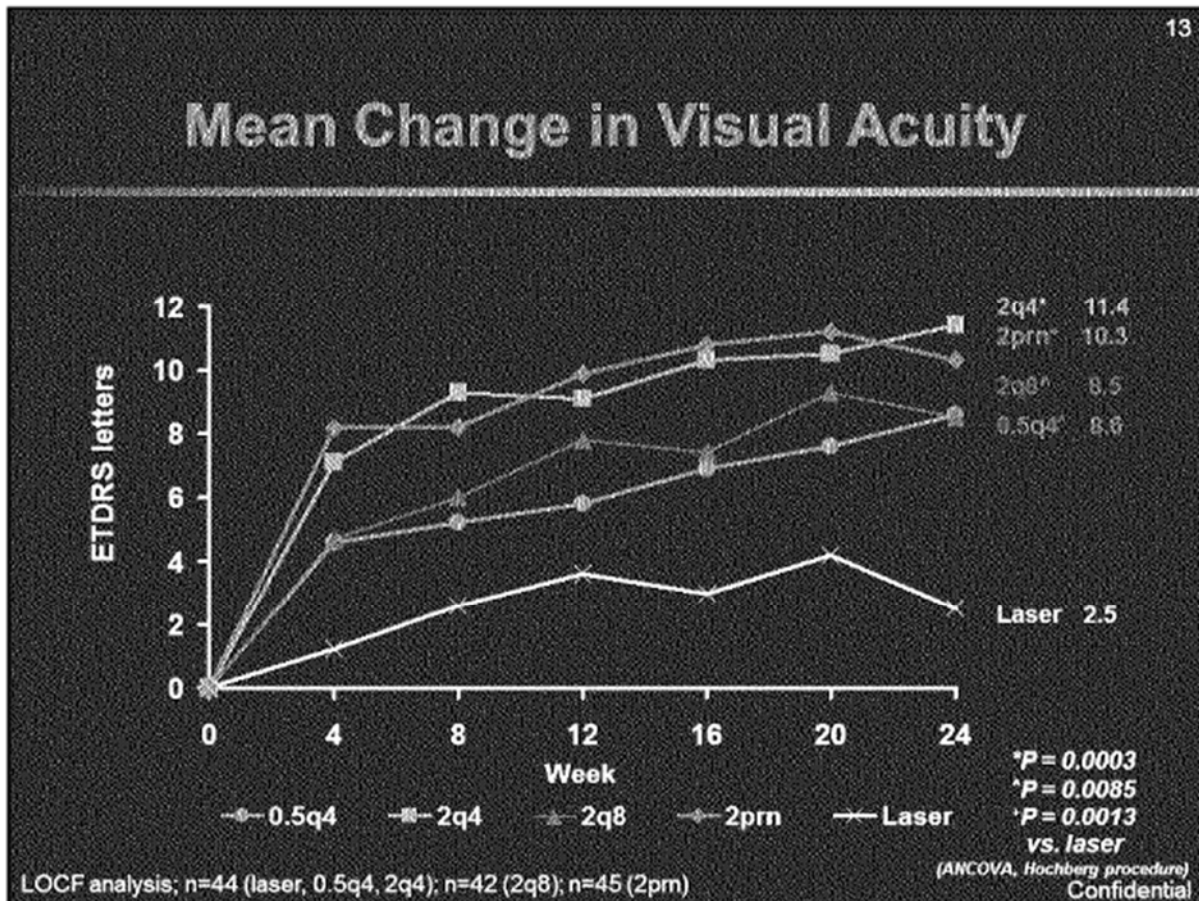
On November 22, 2010, Regeneron published the top-line VIEW results in the November 2010 PR. (Ex.2063, ¶35; Ex.1007).

2. Development of Eylea® for DME

After starting the VIEW trial, Regeneron began testing the same q8 dosing regimen for DME patients in its Phase II DA VINCI trial. (Ex.2063, ¶¶36-38; Ex.2064, ¶¶29-31.) By mid-2008, Regeneron had selected five treatment arms for its DA VINCI trial, including a q8 arm as in 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.2015, 3.)

The 24-week results in DA VINCI became available within Regeneron by early 2010. (Ex.2063, ¶40; Exs.2017-2019.) Dr. Yancopoulos received these results on February 1, 2010, at which time he recognized that his 2q8 regimen yielded an improvement of 9 or more letters in some patients with DME as compared to baseline at 24 weeks:

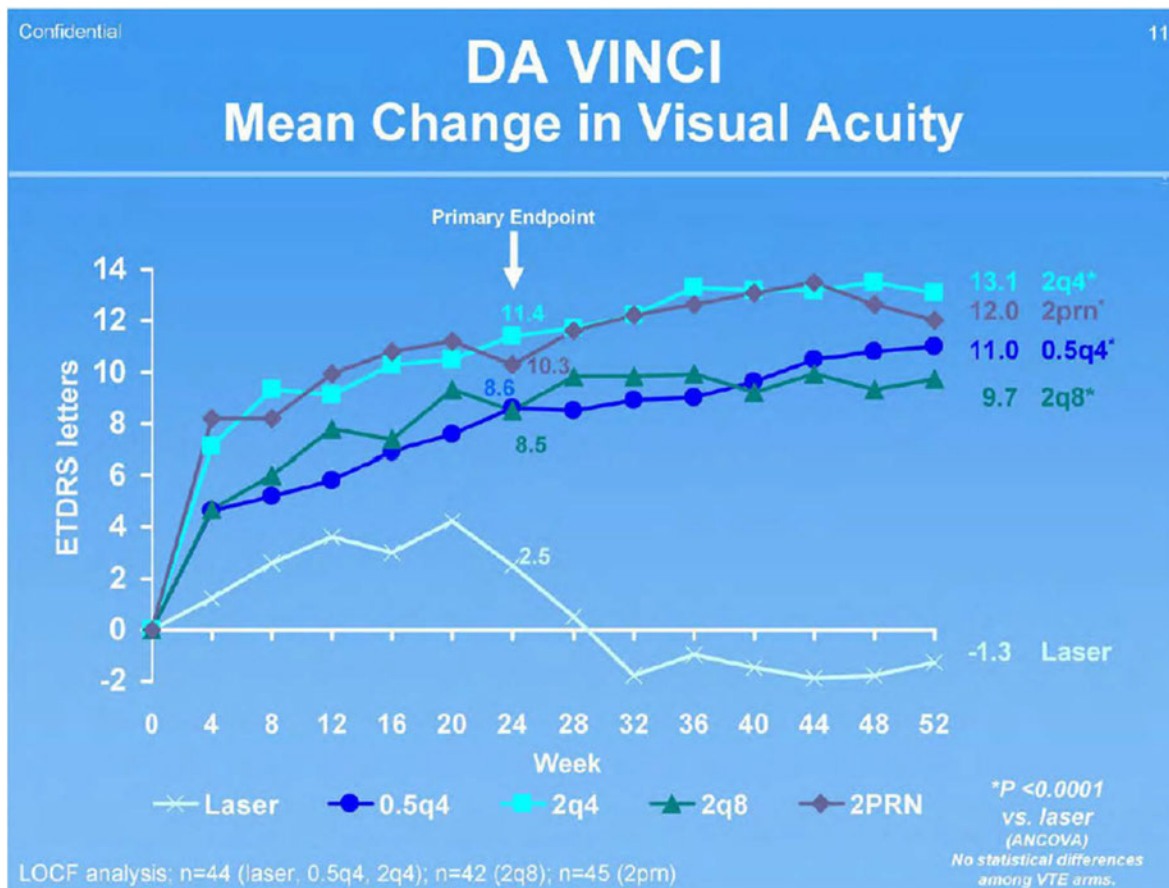


(Ex.2019, 13; Ex.2063, ¶¶40-41; Exs.2017-2019.)

On February 18, 2010, Regeneron published the top-line 24-week DA VINCI results in a press release. (Ex.2020.) Regeneron then presented these results at the 2010 meeting of the Association for Research in Vision and Ophthalmology (ARVO). (Ex.2064, ¶¶41-42; Ex.2066, ¶40.) It provided an abstract summarizing the 24-week results to Drs. David Brown and James Major, who submitted it to the 2010 ARVO meeting. (Ex.2066, ¶¶42-45; Ex.2021; *compare* Ex.2022 with Ex.1010.)

Regeneron began planning its Phase III DME trial after receiving the 24-week DA VINCI results. By October 2010, Regeneron planned to test the q8 regimen that it had used in the DA VINCI trial, (Ex.2003, 162:7-9, 1616:19-25), but it awaited the DA VINCI 52-week data to “provide additional guidance on the number of loading doses.” (*Id.*, 162:10-163:3.)

Regeneron completed the DA VINCI trial and, on December 8, 2010, Dr. Yancopoulos received the one-year results. (Ex.2063, ¶¶45-46; Ex.2015; Ex.2024.) The results confirmed that the 24-week visual acuity gains could be sustained over time using the 2q8 regimen:



(Ex.2063, ¶46; Ex.2015, 11.)

On December 20, 2010, Regeneron reported the top-line one-year DA VINCI results in the December 2010 PR. (Ex.2063, ¶47; Ex.1006.) Then, after reviewing the 52-week data, Dr. Yancopoulos made the decision to test five loading doses, one “initial” dose and four “secondary doses,” followed by q8 dosing in the Phase III DME trial. (Ex.2003, 1622:15-1623:14, 1234:8-1235:4, 167:25-168:22.)

3. Eylea®'s Commercial Success

Following FDA approval, Eylea® was an immediate success. By 2012, Eylea®'s share of sales across all indications was [REDACTED]. (Ex.2067, ¶20, [C-6].) By 2021, that figure had [REDACTED]. (*Id.*) Today, Eylea® has the highest market share among anti-VEGF products for the treatment of both DME and wAMD. (Ex.2067, ¶¶22, 24, [C-7, C-9].) It also ranks as the top preference for a majority of physicians compared to other anti-VEGF treatments. (Ex.2067, ¶30, [E-1].) That is due in large part to its q8 dosing regimen, which is effective with fewer painful injections into the eye than other treatments. (Ex.2067, ¶¶38-39, [E-3]; [E-4]; Ex.2143, 46; Ex.2144, 94.)

B. '572 Patent

The '572 Patent discloses and claims eight-week extended dosing regimens for aflibercept and the successes achieved while using it. It addresses a “need in the art for new administration regimens for angiogenic eye disorders, especially those which allow for less frequent dosing while maintaining a high level of efficacy.” (Ex.1001, 2:6-9.) All but three claims require not only a particular dosing regimen, but also achieving certain visual acuity results.

The '572 Patent claims priority to provisional application No. 61/432,245, filed on January 13, 2011, shortly after Regeneron received the critical one-year results of the VIEW and DA VINCI trials. (Ex.1001.) The provisional application

reports both the trial protocols and results for the VIEW and DA VINCI trials.

(See Ex.2145, ¶¶58-60 (VIEW), ¶¶61-62 (DA VINCI); Ex.1001, 13:10-27

(VIEW), 14:32-15:12 (DA VINCI).)

III. PRIORITY DATE

Consistent with the Board’s DI, all claims of the ’572 Patent are entitled to a priority date no later than January 13, 2011. (DI, 30-34.) Samsung challenges that date for only one claim, contending that Regeneron did not disclose claim 25’s subject matter—four secondary doses—before July 12, 2013. But Regeneron’s January 13, 2011 provisional discloses exactly that: “In other embodiments, two or more (e.g., 2, 3, 4, 5, 6, 7, 8, or more) secondary doses are administered to the patient.” (Ex.2145 ¶18; Ex.1001, 4:26-28.) So does Regeneron’s January 21, 2011 provisional. (Ex.2025, ¶18.) And if that were not enough—it is—both provisionals point the reader to the lower end of that disclosed range. (Ex.2145, ¶5 (“about three doses”); Ex.2025, ¶5 (same).) Claim 25 thus has a January 2011 priority date. (DI, 33.) 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 foundation for claiming that species.”); *Ariad Pharms., Inc. v. Eli Lilly and Co.*, 598 F.3d 1336, 1352 (Fed. Cir. 2010).

Samsung’s Petition identifies no reason why the foregoing disclosures are insufficient. In Samsung’s two-paragraph argument (Pet. 14) it merely cross

references nine paragraphs of its expert Dr. Chaum’s testimony (Ex.1002, ¶¶91-103). But that opinion deserves no weight. Dr. Chaum conducted no analysis of the priority dates of the claims. (Ex.2090, 325:9-12.) When asked how he reached his opinion, Dr. Chaum testified that July 12, 2013 was just “the date that I have been asked to assume.” (*Id.*, 324:11-12.) In a related proceeding involving similar claims, Dr. Chaum admitted he “did not know the requirements” for what disclosure is required to obtain a patent (Ex.2062, 40:13-22), and that he had not reviewed any provisional applications in reaching his opinion regarding the priority date. (*Id.*, 154:4-22.)

The ’572 Patent thus has a priority date of January 13, 2011, and is subject to the first-to-invent provisions of pre-AIA 35 U.S.C. §§ 102 and 103. *See* MPEP § 2159.³

IV. LEVEL OF ORDINARY SKILL IN THE ART

For purposes of this IPR, Regeneron does not contest Samsung’s proposed definition of a person of ordinary skill. (Pet. 14-15.)

³ Even if AIA standards were applicable, Samsung has not shown that any of the challenged claims are unpatentable.

V. CLAIM CONSTRUCTION

A. The *Results Limitations* Have Patentable Weight (all claims)

As the Board has now found twice, the *results limitations* have patentable weight because they constrain the claims. (DI, 21-30; Ex.1004, 18.) Specifically, they “inform the reader about the purpose of the methods (or ‘the essence of the invention’), which, for most claims, is to gain or maintain visual acuity, and also illuminate the dosage administration steps in a material way, *i.e.*, so that one may know collectively how many secondary or tertiary doses are sufficient.” (DI, 27.)

The Board thus should again follow *LA Biomed v. Eli Lilly* and confirm patentable weight. 849 F.3d 1049, 1061 (Fed. Cir. 2017). There, an efficacy limitation had patentable weight because it narrowed the claims covering a variable dosing regimen to instances where that regimen worked. *Id.* at 1061. Here too, the *results limitations* require achieving listed gains in visual acuity and that the number of secondary and tertiary doses administered be sufficient to yield those gains. (See DI, 25, 27.) “[T]he *results limitations* ... must be given patentable weight for the same reasons as ... in *Los Angeles Biomed*.” (DI, 30.)

Samsung’s arguments to the contrary should again be rejected. As an initial matter, Samsung is wrong to treat the *results limitations* as lesser because they appear in “wherein” clauses—“wherein” limitations can and do have patentable weight where, as here, they give meaning and purpose to the manipulative steps of

the claims. (DI, 27). *In re Kubin* is not to the contrary; it is simply a case about an application where one particular “wherein” limitation was, according to the specification, not a requirement. 561 F.3d 1351, 1357 (Fed. Cir. 2009). As the Board noted, “[t]he active steps of every independent claim of the ’572 patent are styled as ‘wherein’ clauses,” and not even Samsung advocates for ignoring those steps. (DI, 27.) Moreover, ignoring the *results limitations* would improperly collapse the distinctions between dependent claims. (Ex.1001 (*compare* claims 3 and 8 with claim 2, where only difference in scope is the *results limitations*)); *Comark Comm’ns, Inc. v. Harris Corp.*, 156 F.3d 1182, 1187 (Fed. Cir. 1998) (presumption of claim differentiation).

The Board also should reject Samsung’s second affirmative argument, which analogizes to some cases where claim limitations directed to intended or inherent results were found to lack patentable weight. (Pet. 57-60.) As the Board previously found, the *results limitations* “are not mere intended results that inherently occur.” (DI, 28; *see also* Ex.1004, 34.) In a 52-week clinical trial involving AMD, for example, the claimed, 2q8 regimen yielded *no* benefits to visual acuity in at least 4-5% of patients. (Ex.1001, 13:7-28.) A shorter clinical trial involving DME was similar. (Ex.1031, 4 (~7% of 2q8 group gained no letters).) Thus, *Syntex*, *Bristol-Myers*, *Copaxone*, *Kubin*, *Lockheed Martin*, and

Minton—all cases involving limitations covering intended results or inherent outcomes—are inapposite.

Samsung’s reliance on the *Mylan* claim construction order is also misplaced. (Pet. 19.) That order “overlooked [the] critical fact[]” that the claimed, 2q8 regimen is “variable and necessarily informed” by the *results limitations*, and the authorities on which it rests are therefore “factually distinguishable.” (DI, 29; Ex.1063, 37-39.) As the Board previously recognized, it “is not bound” by the *Mylan* court’s construction, and it should not follow it here. (DI, 28.)

B. “A method of treating”⁴ (all claims)

Each independent claim requires “[a] method of treating” an “angiogenic eye disorder,” “diabetic macular edema,” or “age[-]related macular degeneration.” (Ex.1001, (claims 1, 15, 26, 29).) As at institution, the Board should find that this term requires at least an intent to treat the recited diseases. (DI, 20.) The parties agree on this construction, and it matches the Board’s treatment of similar terms in related patents. (Pet. 17-18; *see* Ex.1011, 19; Ex.1013, 9-10.)

⁴ Solely for the purposes of this Response, Regeneron applies Samsung and the Board’s claim construction throughout this Response.

C. “approximately 4 weeks following the immediately preceding dose . . . approximately 8 weeks following the immediately preceding dose” (claims 1, 15 26, 29)

The customary meanings of these terms require dosing aflibercept at predetermined, fixed intervals. (Ex.2065, ¶¶64-74.) These terms expressly require dosing at intervals of “approximately 4 weeks” and “approximately 8 weeks.” (Ex.1001, (claims 1, 15, 26, 29); Ex.2065, ¶67.) And they make no mention of individualized, variable dosing schedules decided during (not before) treatment.

The specification confirms their meaning. (Ex.2065, ¶¶65-66, 68-73.) At column 16, lines 23-26, the specification describes the claimed, 2q8 dosing regimen. As Samsung’s expert testified in a related proceeding, that passage refers to a dosing schedule determined *before* treatment has begun. (Ex.2062, 220:4-221:7.) The specification contrasts such a fixed, predetermined dosing regimen with individualized, “as needed”/*pro ne rata* (PRN) maintenance dosing schedules. (E.g., Ex.1001, 16:5-17, 16:28-34; Ex.2062, 216:17-217:4; Ex.2065.) PRN dosing allows for “multiple dosing regimens,” none of which are predetermined. (Ex.2062, 277:5-11.)

Elsewhere, the distinction between predetermined, fixed dosing and PRN dosing is made explicit, and a PRN strategy is described as an *alternative* to dosing every eight weeks:

[E]ach tertiary dose may be administered to the patient 8 weeks after the immediately preceding dose. *Alternatively*, the frequency at

which the secondary and/or tertiary doses are administered to a patient can vary over the course of the treatment regimen. ... The frequency of administration may also be adjusted during the course of treatment by a physician depending on the needs of the individual patient....

(Ex. 1001, 4:39-56 (emphasis added).) Example 5 describes a trial in which one group received “every 8 weeks dosing (2Q8)” and the other group received, in contrast, “as needed dosing with very strict repeat dosing criteria (PRN).” (*Id.*, 14:44-49.) And, similarly, Example 7 refers to predetermined, fixed dosing schedules using “[x] weeks” language and distinguishes them from individualized/PRN strategies, which it describes with phrases like, “as assessed by a physician” or “pro re nata (PRN).” (Ex.1001, 16:7-22; Ex.2065, ¶72.)

The claims of related patents also show that the challenged claims do not cover individualized/PRN dosing. (Ex.2065, ¶74.) U.S. Patent No. 11,730,794, which shares the ’572 Patent’s specification, claims dosing regimens “administered on an as needed or pro re nata (PRN) basis.” (*See* Ex.2146, (claims 1, 18, 35); Ex.2065, ¶74.) And as discussed above, PRN dosing is described as an *alternative* option to dosing on an “[x] weeks” schedule, not something encompassed by it. Regeneron knew how to claim PRN dosing and did not do so here.

The extrinsic evidence further confirms that the POSA would have understood the claims require fixed, predetermined dosing. Samsung’s expert testified that the Eylea® label, which describes the claimed dosing regimen, calls

for “fixed dosing.” (Ex.1002, ¶61; Ex.1059, 1.) He testified that “fixed dosing regimen” means “that it’s prespecified in some regimen as opposed to being given based upon the patient’s response.” (Ex.2062, 141:4-9.) Regeneron’s expert testified to the same. (Ex.2065, ¶65.)

VI. PETITIONER HAS NOT PROVEN THE CHALLENGED CLAIMS UNPATENTABLE

At institution, the Board noted that Samsung argues “potentially many more than the eleven numbered grounds ... suggest[ing] a questionable ambiguity in the Petition.” (DI, 14.) The Board therefore cabined the Petition to the art and combinations “express[ly] list[ed]” under each enumerated ground. (*Id.*, 15; Pet. 11-13.) As set forth below, those grounds do not show unpatentability.⁵

A. Ground II: The December 2010 PR Is Not Prior Art

Samsung relies on the December 2010 PR for its disclosure of the dosing regimen for and results of the DA VINCI DME clinical trial, which it contends anticipates claims 1-5, 8-11, 16-17, and 20-21. But Regeneron’s December 2010 PR is not prior art. It is dated less than one year before the priority date of the ’572 Patent and Dr. Yancopoulos reduced to practice the claimed inventions before its

⁵ Given the volume of references, grounds, and combinations asserted by Samsung, Regeneron has focused its arguments on the parties’ core disputes. For that reason, it does not present substantive argument regarding Ground I.

publication date on December 20, 2010; the press release merely reflects Dr. Yancopoulos's work.

1. Dr. Yancopoulos Reduced to Practice the Claimed Inventions Before December 20, 2010

A Patent Owner may disqualify a reference as prior art under pre-AIA 35 U.S.C. § 102(a) by proving “reduction to practice prior to the effective date of the reference.” 37 C.F.R. § 1.131(b). “Inventor testimony may serve as evidence of reduction to practice, but it must be corroborated.” *Medtronic, Inc. v. Teleflex Innovations S.À.R.L.*, 68 F.4th 1298, 1306 (Fed. Cir. 2023) (citation omitted).⁶ It is not necessary to corroborate every aspect of reduction to practice; the evidence need only support the inventor's account under a “rule of reason.” *E.I. du Pont de Nemours & Co. v. Unifrax I LLC*, 921 F.3d 1060, 1077 (Fed. Cir. 2019). The evidence must show the applicant (1) constructed an embodiment or performed a process that met all the limitations of the claim and (2) determined that the invention would work for its intended purpose. *See id.* at 1075. The evidence here shows that Dr. Yancopoulos satisfied these requirements for claims 1-24 before the December 20, 2010 publication of the December 2010 PR.

⁶ All internal quotation marks and citations are omitted unless otherwise indicated.

a. Dr. Yancopoulos performed a process covered by claims 1-24 before December 20, 2010

An inventor need not “be the one to reduce the invention to practice so long as the reduction to practice was done on his behalf.” *In re DeBaun*, 687 F.2d 459, 463 (C.C.P.A. 1982). Here, Dr. Yancopoulos chose to test his 2q8 dosing regimen in Regeneron’s DA VINCI trial, to measure visual acuity gains from baseline in that arm against those achieved using conventional therapies, and ultimately to proceed with the DA VINCI trial design. (Ex.2063, ¶37; Ex.2064, ¶¶29-32.) Only thereafter did clinical investigators and Regeneron personnel test the claimed dosing regimen in patients with DME in DA VINCI on his behalf and under his direction. (Ex.2063, ¶42; Ex.2064, ¶¶33-34; Ex.2066, ¶¶35-37, 47.) The DA VINCI trial practiced every element of claims 1-24.⁷

2q8 dosing (claims 1-24). The DA VINCI trial tested the 2q8 dosing regimen—a 2mg dose “initial dose,” 2mg “secondary doses” at weeks 4 and 8, and “tertiary doses” every 8 weeks thereafter—in patients with DME, an angiogenic eye disorder. (*See* Ex.2063, ¶39; Ex.2015, 4; Ex.2024.)

Two secondary doses (claims 5, 11, 24). The DA VINCI trial tested two, 2mg “secondary doses” at weeks 4 and 8. (*Id.*)

⁷ *See supra* Note 4.

Formulation (claims 6-7, 12-13, 18-19, 22-23). Each dose of aflibercept used in DA VINCI was administered intravitreally and formulated [REDACTED]

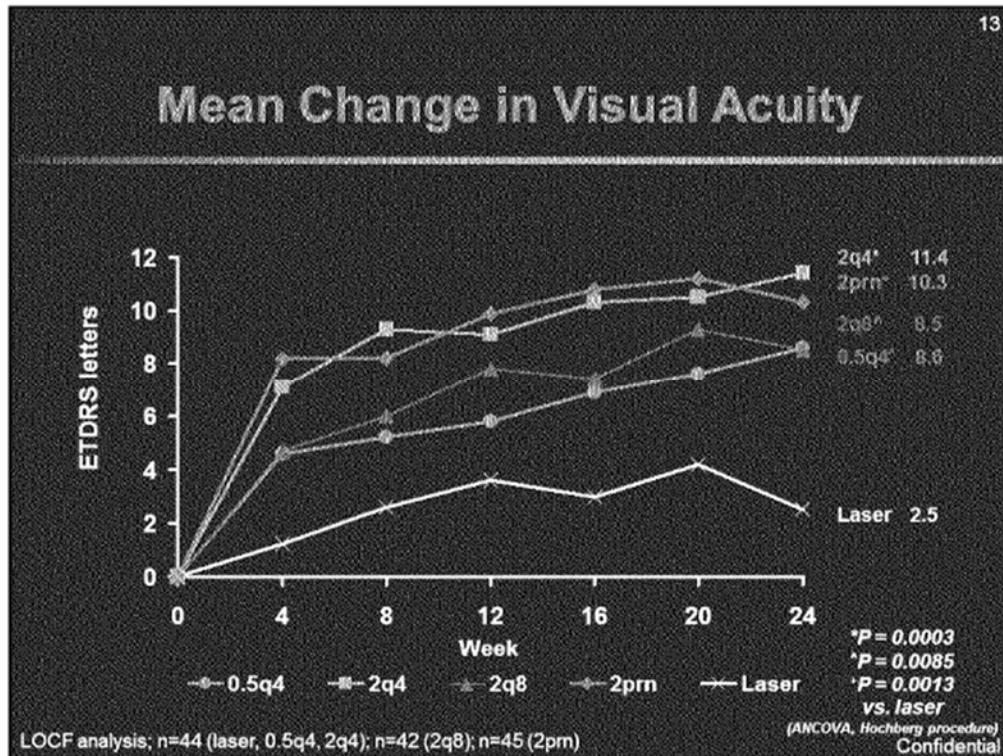
[REDACTED]

[REDACTED]

[REDACTED] The foregoing formulation is an isotonic solution, and [REDACTED] is a non-ionic surfactant. (Ex.2065, ¶34.)

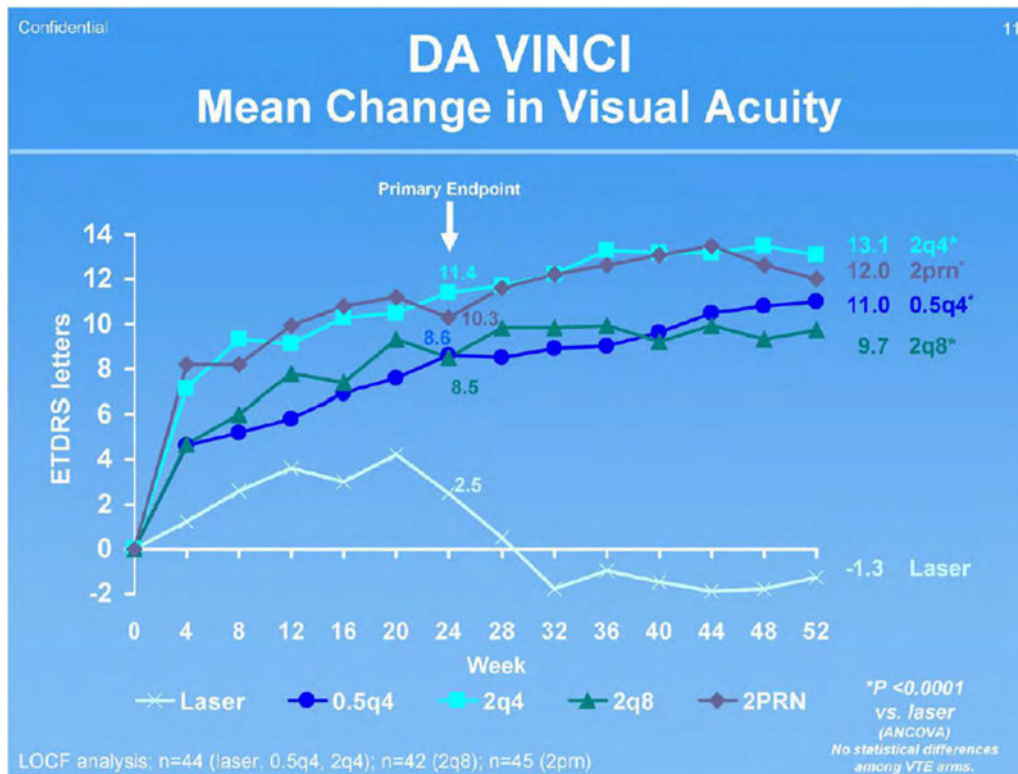
Exclusion criteria (claim 14). The DA VINCI trial excluded “people with ‘ocular inflammation (including trace or above) in the study eye’ and ‘evidence at examination of infectious blepharitis, keratitis, scleritis, or conjunctivitis in either eye or current treatment for serious systemic infection.’” (Ex.2063, ¶38; Ex.2048, 37-38.)

Gains within 52 weeks (claims 1-3, 5-8, 10-19, 21-24). These claims require gains in visual acuity, including gains in visual acuity of up to 9 ETDRS letters. The DA VINCI trial’s 24-week results (collected, processed, and reported to Dr. Yancopoulos by February 2, 2010) showed a mean, statistically significant gain in visual acuity among subjects dosed with the claimed regimen of 8.5 ETDRS letters:



(Ex.2019, 13; Ex.2063, ¶¶40-41; Exs.2017-2019.) Because ETDRS letters are measured in whole-letters, a mean, 8.5 letter gain meant that some patients achieved gains of at least 9 letters. (Ex.2065, ¶182.)

The DA VINCI trial's 52-week results (collected, processed, and reported to Dr. Yancopoulos by December 8, 2010) also showed the same gains as the 24-week results, and additionally showed gains at 52 weeks of more than 9 letters:



(Ex.2063, ¶¶45-46; Ex.2064, ¶37; Ex.2015, 11; Ex.2024.) Subjects achieved the mean 9.7 letter gain measured at 52 weeks “within” those 52 weeks.

Gains within 24 weeks (claims 4, 9, 20). Claims 4, 9, and 20 require gains of 7, 8, and 9 ETDRS letters within 24 weeks. As discussed above, the DA VINCI trial measured gains of 9 ETDRS letters at 24 weeks.

b. Dr. Yancopoulos determined the invention worked for its intended purpose before December 20, 2010

An invention’s “intended purpose” is a question of law. *Teleflex*, 68 F.4th at 1304. The “‘intended purpose’ need not be stated in claim limitations that define the claim scope,” and can be stated in a preamble or specification. *Barry v. Medtronic, Inc.*, 914 F.3d 1310, 1324-25 (Fed. Cir. 2019).

Here, the specification of the '572 patent indicates that the purpose of the invention is to provide improved dosing regimens of aflibercept for angiogenic eye disorders, including wAMD and DME, that allow for less frequent dosing. *See* Ex.1001, title and brief summary section; *Teleflex*, 68 F.4th at 1304 (patent specification and title supported a finding of a broad intended purpose).

Dr. Yancopoulos determined that the dosing regimens recited in claims 1-24 worked for that purpose by at least three dates. First, by at least February 2, 2010, Dr. Yancopoulos received summaries of the 24-week DA VINCI results. (Ex.2063, ¶40; Ex.2064, ¶35; Exs.2017-2019; Ex.2035 (showing Dr. Yancopoulos's awareness of the results).) From those results, Dr. Yancopoulos recognized and appreciated that his 2q8 dosing regimen worked for DME as evidenced by the visual acuity gains of "9 or more letters in some DME patients as compared to baseline." (Ex.2063, ¶41.)

Second, and as explained below, by at least November 20, 2010, Dr. Yancopoulos received summaries of the VIEW trials for AMD, which tested the methods recited in claims 1-3, 5-8 and 10-14, among others. (*Infra* § VI.B.1.) By that date, Dr. Yancopoulos had recognized and appreciated that the VIEW results showed that the 2q8 dosing regimen was an improved dosing regimen for patients with AMD. Thus, Dr. Yancopoulos had reduced at least claims 1-3, 5-8 and 10-14 to practice by at least November 20, 2010 for that additional reason.

Third, by at least December 8, 2010, Dr. Yancopoulos recognized and appreciated from the 52-week DA VINCI results that the 2q8 dosing regimen was an improved dosing regimen for DME. (Ex.2063, ¶¶45-46; Ex.2064, ¶37.) Specifically, Dr. Yancopoulos recognized and appreciated that those results indicated “that the 24-week visual acuity gains [in DME] could be sustained over time using the 2q8 dosing regimen, as evidenced by the mean change in visual acuity at 24-weeks (8.5 letters) versus at 52 weeks (9.7 letters).” (Ex.2063, ¶46.)

* * *

All claims challenged in Ground II therefore were reduced to practice before the December 20, 2010 publication date of the December 2010 PR. That reference thus is not prior art against those claims.

2. The December 2010 PR Discloses Dr. Yancopoulos’s Work

Disclosure of “one’s own work is not prior art under [preAIA] § 102(a)” so long as the disclosure occurred less than one year before a patent’s critical date. *In re Katz*, 687 F.2d 450, 454 (C.C.P.A. 1982). The December 2010 PR published on December 20, 2010, which is within one year of the ’572 Patent’s January 11, 2011 critical date. Thus, all that remains is for the Board to determine whether it was “by another.” It was not.

Dr. Yancopoulos conceived of everything in the December 2010 PR on which Samsung relies, namely DA VINCI’s 2q8 dosing regimen and results

measured in ETDRS letters.⁸ First, he conceived of the 2q8 dosing regimen tested in DA VINCI. (Ex.2063, ¶¶16-25, 36-38.) He testified:

In my role as Chief Scientific Officer of Regeneron, I conceived of the idea to test a VEGF Trap-Eye dosing regimen of 2 mg every 4 weeks for the first three injections, followed by 2 mg every 8 weeks, for the treatment of angiogenic eye disorders, including AMD and DME.

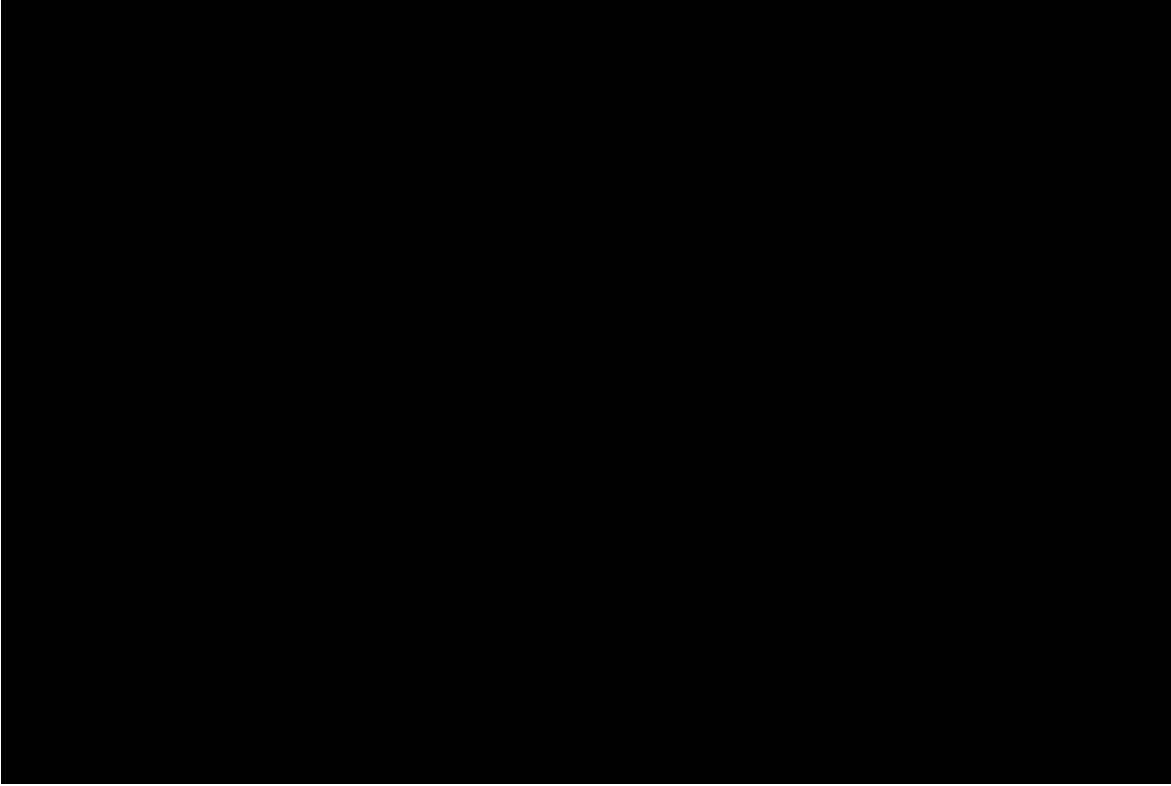
(Ex.2063, ¶16; *see* Ex.2003, 137:3-6 (“I was the initiator and driver” of the 2q8 strategy).) Contemporaneous documents confirm that testimony. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

⁸ Dr. Yancopoulos’ role in VIEW also corroborates his conception of the relevant information in the December 2010 PR. (*Infra* § VI.B.2.)



(Ex.2073, 9 (highlighted); Ex.2091, ¶14; Ex.2092, 20; *see* Ex.2063, ¶¶21-22.)

Second, it was Dr. Yancopoulos’s decision to test his 2q8 dosing regimen in DA VINCI, his decision to assess gains via ETDRS letter scores, and thus his work that yielded the disclosed results. (Ex.2063, ¶¶25, 37; Ex.2064, ¶¶29-37; *see* Ex.2009 (Regeneron had a “top-down approach” to trial design).)

Third, Bayer, which the Board mentioned at institution, did not contribute to conception of the claimed inventions. (DI, 49; *see* Ex.2063, ¶¶12-26.) Dr.

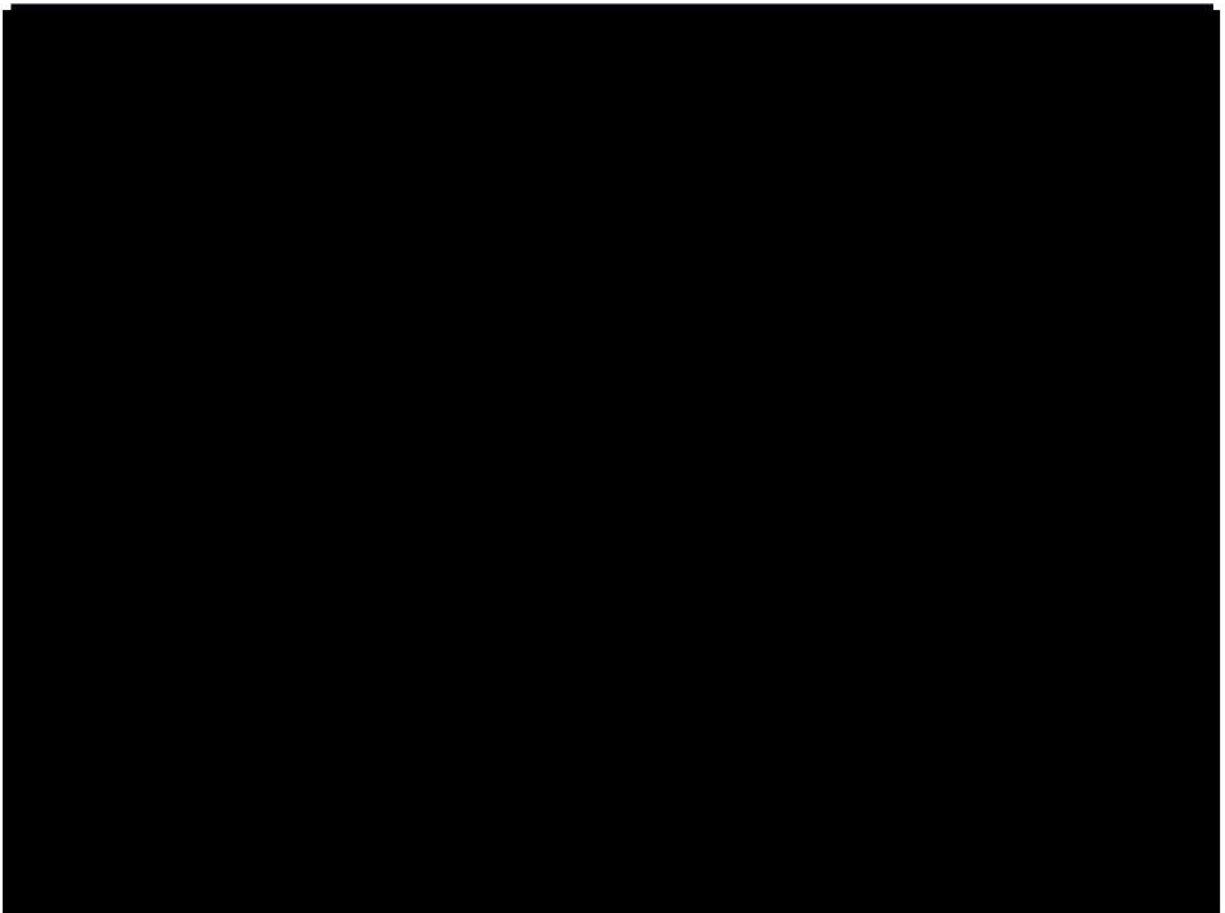
Yancopoulos explained:

Regeneron’s primary reason for collaborating with Bayer was to ensure that we had the resources needed to commercialize a drug and compete against more established companies like Genentech

...



(Ex.2063, ¶¶13, 15.) Karen Chu, then Regeneron's Director of Therapeutic Area Project Management, corroborated that testimony. (Ex.2064, ¶¶8-21.) So does this contemporaneous PowerPoint slide from December 2006:



(Ex.2069, 2 (boxed red).)

Because the relevant parts of the December 2010 PR are Dr. Yancopoulos's work alone, and because its publication date is less than 1 year before the '572 Patent's priority date, it is not prior art under Pre-AIA §§102(a) or (b).⁹

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

Samsung relies on the November 2010 PR for its disclosure of the dosing regimen for and results of the VIEW AMD clinical trials. But like the December 2010 PR, the November 2010 PR is not prior art. It is dated less than a year before the priority date of the '572 patent, Dr. Yancopoulos reduced to practice the challenged claims before the November 22, 2010 publication date of the November 2010 PR, and the press release discloses Dr. Yancopoulos's own work.

1. Dr. Yancopoulos Reduced to Practice Claims 1-3, 5-8, 10-14, and 26-30 Before November 22, 2010

The same legal standard outlined in Section VI.A.1, *supra*, governs here.

⁹ The December 2010 PR is likewise not prior art under AIA § 102, because the reference is dated less than a year before January 2011, and it reflects subject matter “disclosed directly or indirectly from the inventor.” § 102(b)(1)(A); *see* MPEP 717.01(a)(1).

a. Dr. Yancopoulos performed a process covered by claims 1-3, 5-8, 10-14, and 26-30 before November 22, 2010

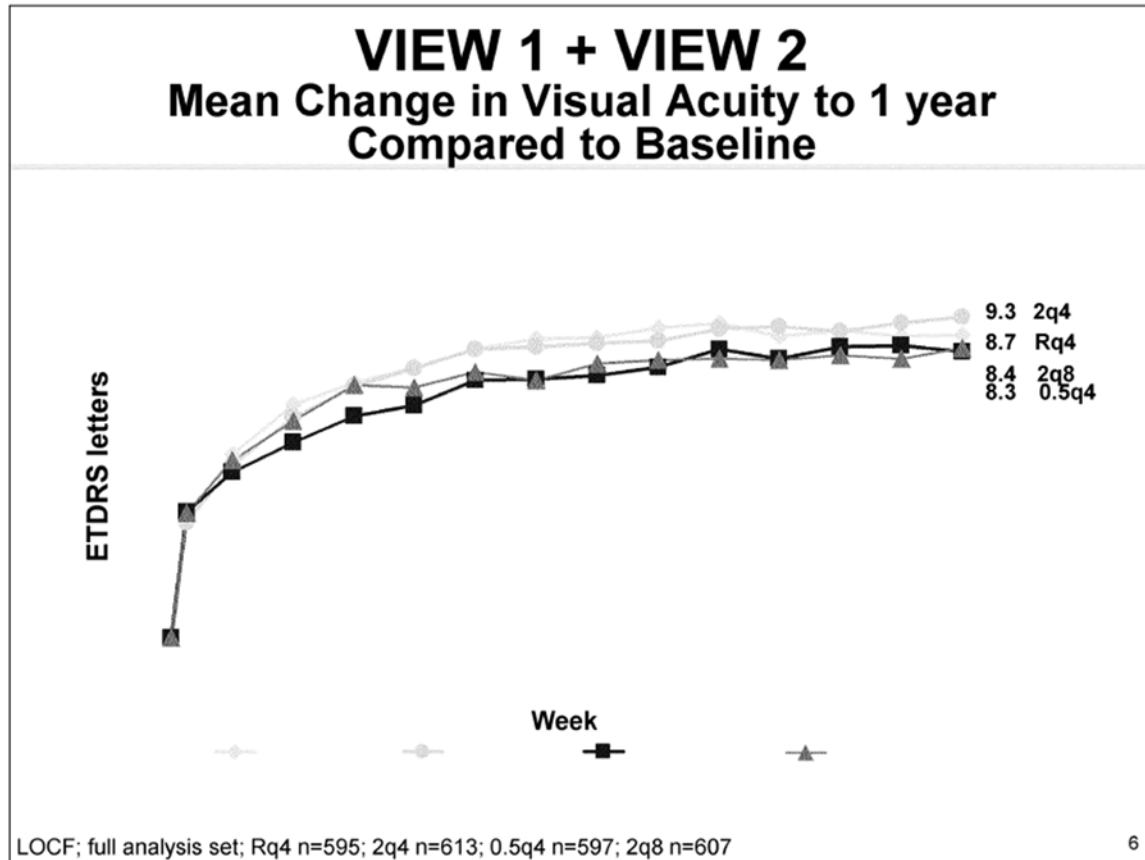
Dr. Yancopoulos chose to test his 2q8 dosing regimen in Regeneron's VIEW trials to measure visual acuity gains compared to ranibizumab, and he ultimately chose to proceed with the VIEW trials design. (Ex.2063, ¶¶25-29.) It was only thereafter that clinical investigators and Regeneron and Bayer personnel tested the claimed dosing regimen in patients with wAMD on his behalf and under his direction, which resulted in patients achieving the claimed *results limitations*. (Ex.2063, ¶¶30-34; Ex.2064, ¶¶24-26.) The VIEW trials practiced every element of claims 1-3, 5-8, 10-14, and 26-30. (See Ex.2076.)

2q8 dosing (claims 1-3, 5-8, 10-14, and 26-30). The VIEW trials tested the 2q8 dosing regimen in subjects with wAMD. (Ex.2063, ¶28; Ex.2064, ¶¶21-23; Ex.1029; Ex.2011. 2; Ex.2076, 38-39.)

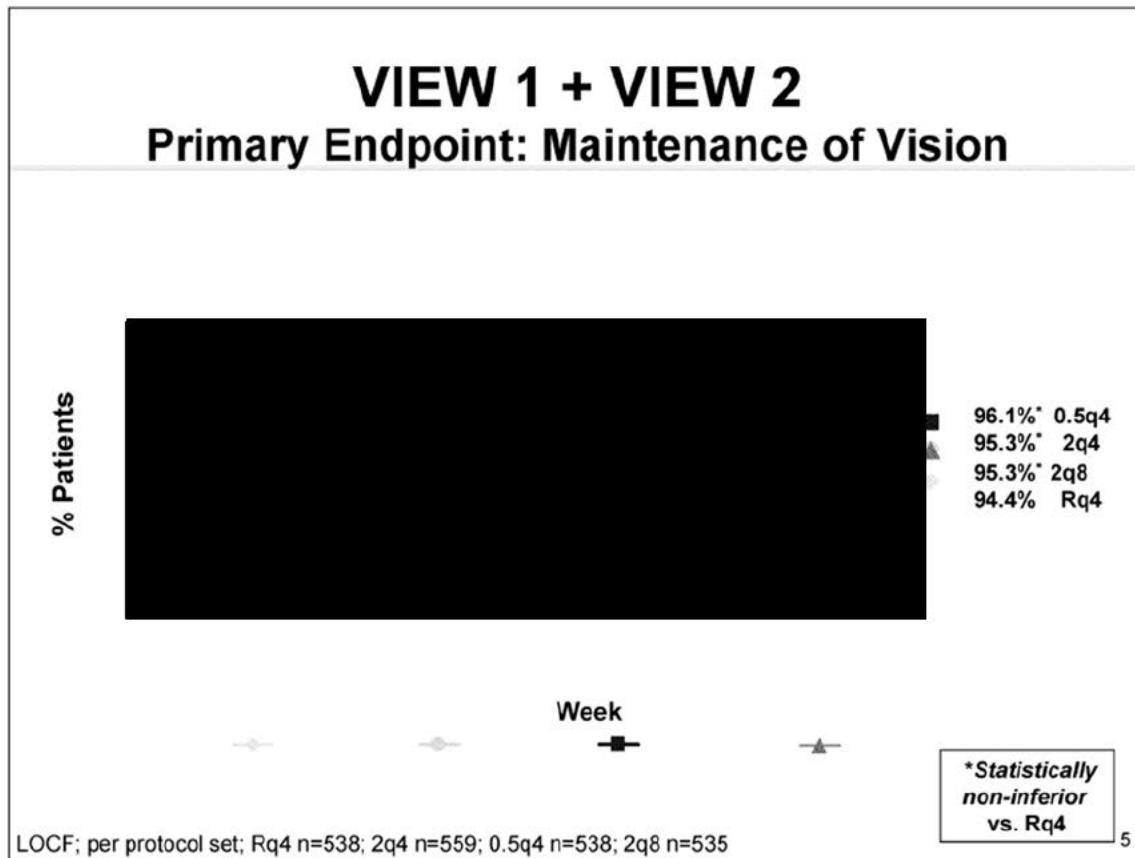
Two secondary doses (claims 5, 11, 27). The VIEW trials tested two, 2mg "secondary doses" at weeks 4 and 8. (Ex.2076,38-39.)

Benefits at 52 weeks (claims 26-30). These claims require, at 52 weeks, gains in visual acuity equivalent to monthly 0.5mg ranibizumab (roughly 8.1-9.4 ETDRS letters) or maintenance of visual acuity equivalent to monthly 0.5mg ranibizumab (loss of less than 15 ETDRS letters). The VIEW trials' 52-week results (collected, processed, and reported to Dr. Yancopoulos by at least

November 20, 2010) showed a mean gain in visual acuity among subjects dosed with the claimed regimen of 8.4 ETDRS letters and maintenance equivalent to ranibizumab:



(Ex.2043, 6.)



(Ex.2043, 5.)

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VIEW 1 & 2

Results Summary

	Ranibizumab 0.5 mg monthly	VEGF Trap-Eye 0.5 mg monthly	VEGF Trap-Eye 2 mg monthly	VEGF Trap-Eye 2 mg every 2 months
Maintenance of vision (% patients losing <15 letters) at week 52 versus baseline				
VIEW 1	94.4%	95.9%*	95.1%*	95.1%*
VIEW 2	94.4%	96.3%*	95.6%*	95.6%*
Mean improvement in vision** (letters) at 52 weeks versus baseline (p-value versus ranibizumab 0.5 mg monthly)				
VIEW 1	8.1	6.9 (NS)	10.9 (p<0.01)	7.9 (NS)
VIEW 2	9.4	9.7 (NS)	7.6 (NS)	8.9 (NS)

*Visual acuity score was measured using the Early Treatment Diabetic Retinopathy Study (ETDRS) eye chart

* Statistically non-inferior based on a non-inferiority margin of 10%, using confidence interval approach (95.1% and 95% for VIEW 1 and VIEW 2, respectively)

*** Test for superiority

NS=non-significant

(Ex.2011, 4.)

Gains within 52 weeks (claims 1-3, 5-8, 10-14). These claims require gains in visual acuity, including of up to 9 ETDRS letters. As shown by the above, combined 52-week results, subjects in the VIEW trials achieved a mean 8.4 ETDRS letter gain. Because ETDRS letters are measured in whole-letters, a mean 8.4 letter gain meant some patients achieved gains of at least 9 letters. (Ex.2065, ¶183.) Subjects achieved gains measured at 52 weeks, which is also “within” 52 weeks.

Formulation (claims 6-7, 12-13). [REDACTED]

[REDACTED].
(Ex.2063, ¶28; Ex.2076, 94.)

Exclusion criteria (claim 14). The VIEW trials excluded people with “[a]ctive ocular inflammation,” or an “[a]ctive ocular or periocular infection.”

(Ex.2063, ¶30; Ex.2076, 43.)

b. Dr. Yancopoulos determined the invention worked for its intended purpose before November 22, 2010

Dr. Yancopoulos determined the dosing regimens recited in claims 26-30 were improved dosing regimens for wAMD by at least November 20, 2010, the dates by which he had received summaries of the visual acuity results from the VIEW trials. (Ex.2063, ¶¶34-35; Ex.2010; Ex.2011; Exs.2042-2043 (showing Dr. Yancopoulos’s awareness of the VIEW results before November 22, 2010).) Upon reviewing the results, Dr. Yancopoulos recognized and appreciated that the 2q8 dosing regimen “achieved a gain in visual acuity of 7.9 and 8.9 letters in VIEW 1 and 2, respectively, [and] that over 90% of patients lost fewer than 15 letters (i.e., “maintenance of visual acuity”) at 52 weeks,” and therefore that the 2q8 dosing regimen worked for its intended purpose. (Ex.2063, ¶34; Ex.2064, ¶27.)

* * *

The November 2010 PR is not prior art to claims 26-30 because Dr. Yancopoulos reduced to practice an embodiment within those claims' scope by at least November 20, 2010, which is before the November 2010 PR published.

2. The November 2010 PR Discloses Dr. Yancopoulos's Own Work

Samsung relies on the November 2010 PR for the disclosure of the 2q8 dosing regimen tested for AMD in the VIEW trials and the resulting visual acuity gains of 7.9 and 8.9 letters at 52 weeks versus baseline. But those portions of the November 2010 PR were conceived by Dr. Yancopoulos, the sole inventor of the '572 Patent, and therefore are his "own work." (*See* Ex.2064, ¶¶21-28.)

As explained in Section VI.A.2, *supra*, Dr. Yancopoulos conceived of testing a 2q8 dosing regimen of aflibercept "for the treatment of angiogenic eye disorders, including AMD and DME." (Ex.2063, ¶16.) He also "played the leading role in designing" and carrying out the VIEW trials: he chose the study design, including the 2q8 comparator arm, and he also chose the study protocol, including the primary endpoints. (Ex.2063, ¶¶27-31; Ex.2003, 1231:10-23; Ex.2009.) As Karen Chu testified, "[u]ltimately, Dr. Yancopoulos made the final decision regarding which study design and protocol to use in the VIEW trials which... included the [2q8 dosing regimen]." (Ex.2064, ¶¶21-23.)

Here, too, Bayer did not contribute to conception of the claimed inventions. (*See* Ex.2063, ¶¶7-25.) [REDACTED]

[REDACTED] (Ex.2069, 2; *supra* §IV.A.2.)

Bayer did execute the VIEW 2 trial abroad, but that trial “employed the same study design as VIEW 1,” which was from Dr. Yancopoulos. (Ex.2064, ¶24; Ex.1029.)

Thus, Bayer’s work does not affect inventorship. *See DeBaun*, 687 F.2d at 463.

Because the relevant parts of the November 2010 PR are Dr. Yancopoulos’s work alone, and because its publication date is less than 1 year before the ’572 Patent’s priority date, it is not prior art under Pre-AIA §§ 102(a) or (b).¹⁰

C. Ground IV

The claims challenged in Ground 4 require that the 2q8 dosing regimen causes gains in, or benefits to, visual acuity. Samsung concedes that its lead reference “does not expressly disclose” such results. (Pet. 40.) Instead, it alleges obviousness over descriptions of three clinical trials, all with different protocols:

¹⁰ Again, even if the first-to-file provisions of AIA § 102 apply, the November 2010 PR is not prior art under § 102(b)(1)(A). *See also* MPEP 717.01(a)(1).

Trial	Art	Regimen¹¹	Results
VIEW (Phase III AMD)	Dixon	Eight-week dosing after three monthly doses of 2mg	None
CLEAR-IT-2 (Phase II AMD)	Dixon	PRN after four monthly doses of 2 mg	Mean gain of 9 letters and some subjects gained 15 letters at 52 weeks
Phase I (AMD)	2006 PR	One dose of 2 mg or 4 mg	Three of six subjects gained 15+ letters at 6 weeks

The Board should reject Samsung's arguments because Samsung has not proved that the claimed results were obvious under any legal standard, much less under the strict test for an inherent obviousness argument, which is the appropriate label for Samsung's arguments.

1. The Claimed Results Were Not Obvious

a. Claim 1

Samsung argues that the 2006 PR, the 2009 PR, and Dixon show that the POSA would have reasonably expected that Dixon's Phase III trial would lead to a gain in visual acuity for at least some patients within 52 weeks. (Pet. 40-41.) The Board should reject Samsung's argument because none of those references reliably indicate the outcome of the planned Phase III trials. (Ex.2065, ¶¶75-97.)

2006 PR. Samsung represents that the 2006 PR teaches "a single 2 mg dose in AMD patients produced a 'mean improvement in BCVA [] 13.5 letters ...' at six

¹¹ The studies summarized in Dixon and the 2006 PR also included other dosing arms. This chart summarizes only the dosing arms on which Samsung relies.

weeks” (Pet. 41; *see also* Ex.1002, ¶168), and the Board relied on that representation in its DI (DI, 54-56.) But as Samsung’s expert conceded, the 2006 PR says no such thing:

Q. [The 2006 PR] doesn’t actually say what the gains were for just the patients who received 2 milligrams, right?

A. It does not.

(Ex.2090, 401:15-18; *see also id.*, 400:23-401:2 (Dr. Chaum characterizing written opinion about the 2006 PR’s disclosure: “I would say its incomplete”).)

What the 2006 PR teaches actually is limited. It states that six patients dosed with *either* 2mg *or* 4mg achieved a *mean* improvement of 13.5 letters, with three of those patients gaining 15 or more letters. (Ex.1027, 2.) In other words, it discloses that between one and five patients received a 2mg dose, and it never says how many achieved a visual acuity gain. (*Id.*; Ex.2090, 401:7-402:20.) Nor does it identify the magnitude of any such gain. (Ex.1027, 2.) In fact, because 5% of the 20 subjects (1 person, or the minimum possible size of 2mg dosage group) saw

no “stabilization or improvement in visual acuity,” the 2006 PR does not even disclose whether any subject dosed with 2mg achieved any benefit.¹² (*Id.*)

Yet even had the 2006 PR disclosed results for the 2mg dose group, the POSA would not have known whether the VEGF inhibitor *caused* the improvement. (Ex.2065, ¶¶84-85.) The Phase I study had a minute sample size, and it was well-known that some patients recover from wAMD without intervention. (*Id.*) Moreover, Phase I trials test safety and dosage, not efficacy. (Ex.2065, ¶79.) The POSA would have known that most drugs in clinical trials fail, and they also would have known of recent failures to develop drugs against angiogenic eye disorders, specifically. (*Id.*, ¶¶79-81.) Because Eylea® is now successful, it is easy to assume that people always believed it would succeed—but that is hindsight. In short, “a POSA would not rely on promising Phase I results as a reasonable predictor of treatment success at Phase II or Phase III.” *Novartis Pharms. Corp. v. West-Ward Pharms. Int’l Ltd.*, 287 F. Supp. 3d 505, 514-519 (D. Del. 2017), *aff’d* 923 F.3d 1051 (Fed. Cir. 2019); (*see* Ex.2065, ¶78 (“results from Phase I and II trials ... do not predict the outcome of a Phase III trial”).)

¹² A mean gain of 13.5 letters with three subjects gaining more than 15 letters matches two subjects gaining 14 letters, three gaining 23, and one losing 16.

2009 PR. Samsung points to the 2009 PR for the proposition that the “VIEW 1 study for AMD” tested whether patients gained “at least 15 letters of vision at week 52.” (Pet. 41.) The Board should reject that argument for two reasons. First, Samsung did not list it “under the numbered obviousness ground,” and, consistent with its DI, the Board should not consider it. (DI, 15; Pet. 12.) Second, an endpoint is not a result, and no POSA would have reasonably believed it predicted efficacy. (DI, 58; Ex.2065, ¶86.) *See Sanofi v. Watson Labs., Inc.*, 875 F.3d 636, 642, 647-50 (Fed. Cir. 2017) (affirming that known expectation that clinical trial would succeed did not show reasonable expectation of success).

Dixon. Dixon partially describes methodology and results from the Phase II CLEAR-IT-2 trial. Dixon never says how many of its 157 subjects received 2mg monthly doses. (Ex.1009, 4.) Nor does it say how many reinjections each subject received. (*Id.*) At most, it recites an “average” PRN dosage rate of 1.6 injections plus four monthly doses, (*id.*), which reveals neither how many injections were required for a gain in visual acuity nor when each dose was given. (Ex.2065, ¶87; Ex.1002, ¶177 (Samsung’s expert: “a POSA would understand that an individual patient ... *may not achieve the mean gain as reported*”) (emphasis added); Ex.2090, 376:16-382:5) And far from establishing that q8 dosing would work, Dixon reports that most of the Phase II subjects needed further injections where one criterion for injections included “a *loss* of ≥ 5 ETDRS letters,” (Ex. 1009, 4).

Finally, the POSA also would not have drawn conclusions about efficacy from Dixon’s limited disclosures because, even had Dixon recited fulsome, promising Phase II trial data, the POSA would have known that Phase III trials regularly fail. (Ex.2046; Ex.2065, ¶¶78-79.) As just one example, Bevasiranib—a drug also targeting wAMD—“showed encouraging Phase I and II data, but the Phase III trial was halted ... for projected failure to meet the primary endpoint.” (Ex.1009, 2; Ex.2065, ¶¶80-81.) All this is, no doubt, why Dixon’s authors *declined to predict* whether the planned q8 dosing regimen would work. (See Ex.1009, 5 (“*If effective at 8 week intervals*”) (emphasis added).) As this panel already found, the partial Phase II results recited in Dixon are “very weak evidence that the claimed and disclosed regimen would exhibit the claimed *results limitations*.” (Ex.1004, 36.)

Because none of Samsung’s arguments for reasonable success have merit, the Board should confirm patentability of claim 1 over this ground.

b. Claims 2, 3, 8, 10

Claims 2, 3, 8 and 10 depend from claim 1 and also require that the 2q8 dosing regimen improves visual acuity. (Ex.1001.) The deficiencies in Samsung’s arguments noted above apply equally to these claims. (*Supra* § VI.C.1.a.; *see also* Ex.2065, ¶88.)

c. Claims 4, 9

Claims 4 and 9 further require gains of 7 and 8 letters BCVA “within 24 weeks” of the initial dose. (Ex.1001.) The 2006 PR indicates nothing about aflibercept’s efficacy. (*Supra* §VI.C.1.a.) Dixon, meanwhile, does not report within-24-week results and therefore conveys no information about efficacy for that time period. (Ex.2065, ¶89.) The Board should confirm the patentability of claims 4 and 9 for this reason, as well as those recited for claim 1. (*Supra* §VI.C.1.a.)

d. Claims 5, 11, 27

Claims 5, 11, and 27 further require that “only two secondary doses are administered to the patient.” (Ex.1001.) The 2006 PR conveys nothing about the viability of this scheme because, again, it indicates nothing about aflibercept’s efficacy. (*Supra* §VI.C.1.a.) And Dixon’s Phase II results involved three secondary doses—not two. (Ex.1009, 4.) The POSA thus could not have anticipated from Dixon’s teachings whether fewer loading doses could yield the same benefits, and Samsung never even tries to explain why they would. (Pet. 42-43; Ex.2065, ¶90.) That is fatal to Samsung’s argument because, again, it cannot fill in the blank on reply. 84 FR 64280, 73 (barring new reply arguments). The Board should confirm the patentability of claims 5 and 11 for these reasons, as well as those recited for claims 1 and 26-28. (*Supra* §VI.C.1.a; *infra* §VI.C.1.e.)

e. Claims 26-30

Samsung's scant arguments are particularly deficient with respect to these claims. Claims 26-30 recite the same dosing regimen as claims 1 and 15, but add that the claimed method is "as effective in [achieving a gain in/maintaining] visual acuity" as monthly administration of 0.5mg of ranibizumab in AMD patients or "at 52 weeks." (Ex.1001.) Dependent claim 27 requires that two secondary doses are given. As the Board noted, claims 26-30's "*at the 52 week mark*" requirement separates them from the other challenged claims. (DI, 58 (original italics)).

As an initial matter, the Board should reject Samsung's arguments for obviousness because Samsung did not state them with particularity. 35 U.S.C. § 312(a)(3). As the Board observed, "there is some ambiguity" regarding Samsung's arguments, (DI 59), and, since Samsung failed to state its case in the Petition, it is now too late to fill the gap, 84 FR 64280, 73; *In re Magnum Oil Tools Int'l., Ltd.*, 829 F.3d 1364 at 1381 (Fed. Cir. 2016).

The Board also should reject Samsung's arguments on the merits. Regarding Samsung's lead argument, neither the 2006 PR nor Dixon supplies a reasonable expectation of achieving the claimed results *at 52 weeks*. (Pet. 43-45; Ex.2065, ¶¶91-93, 95-97.) The 2006 PR only reports efficacy for some subjects at *six weeks*, not 52 weeks, a striking difference. (Ex.1027, 2.) Dixon, meanwhile, involved PRN dosing *customized* to each patient; it says nothing about whether a

predetermined regimen would be effective. (Ex.1009, 3.) Even Dixon’s authors declined to speculate about efficacy versus monthly ranibizumab. (Ex.1009, 5 (“[a] direct comparison of the efficacy ... *will be possible* with the completion of two Phase III trials”).) And for claims 26-28, specifically, far from motivating the POSA to administer additional doses, (DI, 58-59), Dixon reports giving additional doses only under certain conditions, none of which related to achieving a roughly 9-letter gain, (Ex.1009, 4.) Finally, the 2006 PR and Dixon also do not render obvious these claims for the same reasons as claim 1. (*Supra* §VI.C.1.a.)

The Board also should reject Samsung’s alternative, cursory argument about modifying Dixon’s Phase III regimen. (Pet. 45.) Samsung never justifies adding more monthly loading doses at *the beginning* of a 52-week treatment to achieve a roughly 9-letter-gain at *the end* of that treatment. Nor, other than a vague statement that “such a modification was routine,” does it give any reason why the POSA would have *increased* the number of loading doses given the desirability of *reducing* the number of injections into patients’ eyes. (Ex.2065, ¶94.) Exhibit 1017, which Samsung cites for support, is no help. That is a Genentech patent application regarding a different drug: it says nothing about aflibercept, four initial doses, or the 2q8 regimen’s effect, and it is not even listed under this ground (and so should not be considered). (Ex.1017; DI, 15; Pet. 12.) Samsung’s expert testimony, meanwhile, just parrots the Petition and is worth little. (Ex.1002, ¶182.)

Xerox Corp. v. Bytemark, Inc., IPR2022-00624, Paper 9 (P.T.A.B Aug. 23, 2022) (precedential).¹³

2. Ground IV Is a Disguised Inherency Argument That Fails

In the preceding section, Regeneron explained why Samsung's arguments fail under the analytical framework that the Board applied at institution. (*Supra* §VI.C.1.; DI, 56-57.) As set forth the below, Samsung's arguments also fail for other reasons. Samsung's contention that certain results necessarily flow from prior art that *does not* disclose the claimed results is an inherency argument (if a disguised one), and Samsung has not met the rigorous test used for an inherency.

a. Inherency Law Applies

At institution, the Board concluded that Samsung had not argued inherency and therefore did not need to show that the prior art method would *always* produce the claimed result. (DI, 56.) The Board then cited *Hewlett-Packard Co. v. Mustek Systems, Inc.* and *Unwired Planet, LLC v. Google Inc.* to support instituting review. (DI, 57-58 (citing 340 F.3d 1314 (Fed. Cir. 2003), 841 F.3d 995 (Fed. Cir. 2016).) Those cases (never cited by Samsung) involved different issues than Samsung's argument and cannot save this ground.

¹³ Samsung incorporates by reference its arguments for Claim 25 and Regeneron does the same. (*Infra* §VI.H.)

Mustek and *Unwired* are not cases where a claimed result limitation was missing in the prior art and obviousness was nevertheless established. In *Mustek*, the claimed results were expressly disclosed in the prior art—a public use. Fact witnesses had testified that the claimed methods had been publicly performed using a prior art scanner. *Id.* at 1326-27. The prior art scanner had also been used to produce results that were not invalidating, but that did not detract from the fact that it had been used in public prior to the priority date to produce the results claimed in the patent. Thus, even though the scanner had modes that did not meet the claims, the Federal Circuit “rejected the patentee’s argument against invalidity premised on the fact that the scanner would not practice the claimed method if a default setting were changed.” *ParkerVision, Inc. v. Qualcomm Inc.*, 903 F.3d 1354, 1363 (Fed. Cir. 2018) (summarizing *Mustek*). Similarly, in *Unwired Planet*, the claims required prioritizing locations so that farther locations were returned over nearer locations; the prior-art alphabetization scheme produced that result. 841 F.3d at 1002. That the challenger could come up with ways in which alphabetical listing might, by happenstance, not produce the claimed result did not defeat obviousness. *Id.* Again, the results were not missing from the prior art, as is the case here. Here, by contrast, the claimed results are *not* disclosed in the prior art and, for any given patient, there is *no guarantee* the claimed regimen will produce them. The POSA would not have known the claimed results here were

even achievable with the disclosed regimens, whereas the *Mustek* POSA knew that results *had been achieved, and achieved by running the scanner in its default mode*.

Because *Mustek* and *Unwired Planet* are inapposite, and because Samsung's arguments assume that certain doses necessarily yield the claimed results without pointing to any actual disclosure of the claimed result in the prior art, the only remaining legal standard available to fill this gap is inherency. That Samsung framed its argument without mentioning inherency does not matter: in *Foundation Medicine, Inc. v. Guardant Health, Inc.*, the Board confronted similar arguments and—correctly—recognized that they sounded in inherency. There, a petitioner argued that a results limitation, “a [certain] ligation yield,” was obvious and, as here, conceded that no reference disclosed it. IPR2019-00636, Paper 10 at *12-13 (P.T.A.B. Aug. 20, 2019). The Board wrote, “although not stated as such, [the] Petitioner [had] argue[d] [the reference] inherently teaches the limitation” and therefore applied the an inherency standard. *Id.* at *13. And later, when the petitioner complained, the Board confirmed that it had not “misapprehended or overlooked Petitioner’s argument.” *Id.*, Paper 14 at *3 (Dec. 20, 2019).

The same logic applies here. Although it did not use the label “inherency,” Samsung has made an inherency argument. For the 2006 PR, it argues that POSA would have expected the claimed gains within 52 weeks because a 2mg dose

produces those gains. (Pet. 41.) For Dixon, it argues that more doses would yield certain results by 52 weeks because fewer doses did so. (Pet. 42-46.) As in *Foundation Medicine*, the Board should apply the legal standard required by Samsung’s arguments, not the gloss Samsung gave them in its petition.

b. Neither Dixon nor the 2006 PR Inherently Teach the Claimed Results

The inherency doctrine sets additional, exacting requirements atop what Samsung already must prove for obviousness. “[T]o rely on inherency to establish the existence of a claim limitation in the prior art in an obviousness analysis, the limitation at issue necessarily must be present, or the natural result of the combination of elements explicitly disclosed....” *PAR Pharm., Inc. v. TWI Pharms., Inc.*, 773 F.3d 1186, 1195-96 (Fed. Cir. 2014). “Occasional results are not inherent.” *MEHL/Biophile Int’l Corp. v. Milgraum*, 192 F.3d 1362, 1365 (Fed. Cir. 1999). And the doctrine is *harder*, not easier, to satisfy where, as here, the challenge is based on obviousness (as compared to the anticipation challenge in IPR2022-01524). Even if a limitation is necessarily present, inherency in the context of obviousness also requires a further showing that it is “unexpected,” as “that which is unknown cannot be obvious.” *Honeywell Int’l Inc. v. Mexichem Amanco Holding S.A.*, 865 F.3d 1348, 1354-55 (Fed. Cir. 2017). In short, “the use of inherency, a doctrine originally rooted in anticipation, must be carefully circumscribed in the context of obviousness.” *PAR Pharm.*, 773 F.3d at 1195.

(i) Samsung Has Not Shown 2q8 Dosing Necessarily Yields the Claimed Results

Neither the 2006 PR nor Dixon teach that claimed regimen necessarily yields the claimed results. As explained above, the 2006 PR says nothing about the efficacy of 2mg aflibercept. (*Supra* §VI.C.1.a.) Dixon, meanwhile, just recites average—not guaranteed—outcomes from an unclaimed dosing regimen. (*Id.*) And even if either reference taught efficacy “within 52 weeks,” they certainly teach nothing about efficacy “at 52 weeks,” as required by claims 26-30. (*Supra* §VI.C.1.e.) The 2006 PR tested efficacy at 6 weeks, and Dixon’s *customized* PRN dosing conveys nothing about the efficacy of a *predetermined* regimen as claimed. (Ex.1027, 1; Ex.1009, 3.) Samsung has not carried its burden on inherency. *See Gilead Sciences, Inc. v. United States*, 2020 WL 582217 *17 (P.T.A.B. Feb. 5, 2020) (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’”) (cleaned up).

The Board’s recent decision in *Mylan Pharm. Inc. v. Regeneron Pharm., Inc.* regarding Patent No. 10,888,601, does not change matters. IPR2022-01226, Paper 101 (P.T.A.B. Jan. 9, 2024). *Mylan* held that Dixon inherently anticipated some claims covering 2q8 dosing in view of results reported in the ’601 patent. *Id.* at *88-89. Regeneron disagrees with the *Mylan* decision’s use of the ’601 patent to show inherent anticipation for many reasons. Its finding of inherency, conflicts

with governing law. *E.g.*, *PAR Pharm.*, 773 F.3d at 1195. The decision also erred by relying on data from an unclaimed, dosing regimen (six monthly loading doses followed by PRN dosing), which by definition cannot show that a different method necessarily results in anything. But there are still other reasons, set forth below, why *Mylan*'s logic should not be applied here.

First, “the inventor’s own path itself never leads to a conclusion of obviousness; that is hindsight.” *Millenium Pharms., Inc. v. Sandoz Inc.*, 862 F.3d 1356, 1367 (Fed. Cir. 2017) (cleaned up). The *Mylan* decision thus ought not have used the patent specification to support its inherency analysis. But more importantly, Samsung did not make any such argument here, and the Board ought not do so on its own. The Board is not “free to adopt arguments on behalf of petitioners that could have been, but were not, raised by the petitioner....” *In re Magnum Oil*, 829 F.3d at 1381 (Fed. Cir. 2016). Nor, having omitted this argument from its sprawling petition, can Samsung raise it on reply. 84 FR 64280, 73.

Second, the *Mylan* decision dealt with inherency in the context of anticipation; here, the elevated obviousness standard controls. Among other differences, the latter standard requires a finding that the results were expected, which the *Mylan* decision did not make. *See Honeywell*, 865 F.3d at 1355-56

(Board erred “in dismissing properties of the claimed invention as merely inherent, without further consideration as to unpredictability and unexpectedness....”)

Third, the *Mylan* decision necessarily did not address differences between the claims at issue here and those at issue in that proceeding. The *Mylan* decision made no findings about the *results limitations*’ temporal constraints—“within 24 weeks,” “within 52 weeks,” and “at 52 weeks.” Nor did it address this panel’s construction of the same. (DI, 27.) The Board should not follow *Mylan*.

(ii) Samsung Has Not Shown the POSA Would Have Expected the Claimed Results

For the reasons set forth above, Samsung also has not proven the second, necessary element of inherency: that the POSA would have expected the 2q8 dosing regimen to yield the claimed results. (*Supra* §VI.C.1.)

* * *

The Board should confirm patentability because Samsung has not shown inherency and, even if that standard does not apply, also has not met its burden on the overarching question of obviousness.

D. Ground V

Ground V, like Ground IV, involves claims that require specific results—the difference is that they do so in the context of DME. Because no reference teaches those results, however, Samsung again argues obviousness premised on particular

regimens necessarily producing certain outcomes. And, as before, it points to cherry-picked dosing arms from a hodgepodge of clinical trials for support:

Trial	Reference	Regimen	Reported Results
VIEW (Phase III AMD)	2009 PR	Eight-week dosing after three monthly doses of 2 mg	None
DA VINCI (Phase II DME)	2009 PR	Eight-week dosing after three monthly doses of 2 mg	None
Phase I (DME)	2007 ARVO /Dixon	One dose of 4 mg	Four of five subjects had improvements four weeks post-injection
DA VINCI (Phase II DME)	2010 ARVO	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

The Board should reject Samsung's arguments because its first three references convey nothing about efficacy at the claimed dosage and the fourth is not prior art.

1. Samsung Has Not Shown Obviousness Over the 2009 PR, Dixon, and 2007 ARVO

Of the 2009 PR, Dixon, and 2007 ARVO, only the 2009 PR refers to dosing DME patients at the claimed, 2mg dosage. (Ex.1005, 1.) Because the 2009 PR reports no results, however, Samsung argues that the POSA would have expected the trials to succeed based on the 2009 PR's teaching of "secondary endpoint[s]." (Pet. 47-48.) Samsung is wrong. Secondary endpoints are goals, not results, and no POSA would have believed that they predicted a result. (Ex.2065, ¶100.) *See Sanofi*, 875 F.3d at 642, 647-50.

The other two references do not fill this gap. (Pet. 48 (citing Exs.1009, 1030).) According to Dixon and 2007 ARVO, the Phase I study involved five patients, had no control, and used a 4mg dose of aflibercept, which is double the claimed 2mg dose. (Ex.1009, 3; Ex.1030, 1.) No POSA would have drawn conclusions about the efficacy of a 2mg dose of aflibercept in DME patients from those disclosures. (Ex.2065, ¶¶98-102.)

2. 2010 ARVO Is Not Prior Art

2010 ARVO is not prior art for the same reasons that the December 2010 PR is not prior art: an embodiment within the scope of claims 1-24 was reduced to practice by February 2, 2010, the 24-week preliminary DA VINCI results reported in 2010 ARVO are Dr. Yancopoulos's own work, and 2010 ARVO published less than one year before the '572 Patent's priority date. (*Supra* §VI.A.)

That 2010 ARVO does not credit Dr. Yancopoulos as an author makes no difference. "Authorship of an article by itself does not raise a presumption of inventorship with respect to the subject matter disclosed in the article." *In re Katz*, 687 F.2d at 455. Instead, to determine whether a reference with multiple authors qualifies as "by another," the Board must: "(1) determine what portions of the reference patent were relied on as prior art to anticipate the claim limitations at issue, (2) evaluate the degree to which those portions were conceived 'by another,' and (3) decide whether that other person's contribution is significant enough, when

measured against the full anticipating disclosure, to render him a joint inventor of the applied portions of the reference patent.” *Duncan Parking Techs., Inc. v. IPS Grp., Inc.*, 914 F.3d 1347, 1358 (Fed. Cir. 2019). Under that standard, Dr. Yancopoulos remains the sole and correct inventor.

The Relied-Upon Portions. Samsung relies on the dosing regimens and intervals of VEGF Trap-Eye (VTE) tested in DA VINCI of “0.5 mg q4wks, 2 mg q4wks, 2 mg q8wks, 2 mg prn laser photocoagulation” and the interim 24-week results, specifically, that “the mean change in BCVA for each VTE arm ranged from +8.5 to +11.4 letters” and that “[n]o significant difference was noted among the VTE arms” disclosed in 2010 ARVO. (Pet. 28, 49.)

Degree to Which Portions Were Conceived “By Another.” None of the relied upon portions of 2010 ARVO were conceived “by another.” (*See* Ex.2064, ¶¶29-36, 38-42.) The DA VINCI results recited in that document mirror the summarized 24-week DA VINCI results that Dr. Yancopoulos received on February 1, 2010, and those recited in a February 18, 2010, Regeneron Press Release.¹⁴ (Ex.2063, ¶¶40-44; *compare* Ex.1010 with Ex.2018, 5, 11, 19-22, 33

¹⁴ The 24-week results of DA VINCI published in the February 18, 2010 press release represent Dr. Yancopoulos’s own work for the same reasons described in Section VI.A.2, *supra*, with respect to the December 2010 PR.

and Ex.2020.) And once again, the results of the DA VINCI trial are Dr. Yancopoulos’s work. (*Supra* §VI.A.2.)

The persons listed on 2010 ARVO as authors—Drs. Major and Brown, and the rest of the DA VINCI clinical investigators—did not contribute to conception. Ex.2063, ¶¶43-44; Ex.2064, ¶42.) Instead, they executed DA VINCI on Dr. Yancopoulos’s behalf. (Ex.2066, ¶¶36-37, 46-47; Ex.2063, ¶42.) Dr. Brown testified to these facts:

I did not play a role in developing the DA VINCI clinical trial protocol. Neither I nor, to my knowledge, the other clinical investigators chose to test VEGF Trap-Eye in DME, chose the dosing regimen for the VEGF Trap-Eye arms, or chose the visual acuity endpoints.

(Ex.2066, ¶37.) The clinical investigators’ work on Dr. Yancopoulos’s behalf did not transform them into inventors. *See DeBaun*, 687 F.2d at 463.

Significance of Others’ Contributions. Because the listed authors made no contribution to conception, they cannot have made significant contributions. In fact, the listed authors did not even write 2010 ARVO—Dr. Berliner, a Regeneron employee, did so based on her knowledge of DA VINCI. (Ex.2066, ¶42; Ex.2064, ¶41; Ex.2021; *compare* Ex.2022 with Ex.1010.) Dr. Berliner gave the draft abstract to Drs. Major and Brown for submission to ARVO once they had reviewed. (Ex.2066, ¶¶38, 40-45; Exs.2021-2023.) As Dr. Brown explained, he “did not make any material changes” to the parts of the draft on which Samsung

now relies. (Ex.2066, ¶44 (comparing Ex.2022 with Ex.1010); Exs.2078-2079.)

And as for Dr. Major, he appeared on the abstract because Dr. Brown already had submitted one abstract to the ARVO conference and was ineligible, as first author, to submit another. (Ex.2066, ¶45.)

Because the relevant parts of 2010 ARVO are Dr. Yancopoulos's work alone, and because its publication date is less than 1 year before the '572 Patent's priority date, it is not prior art under Pre-AIA §§ 102(a) or (b).¹⁵

E. Ground VI

The Board should reject Ground VI for two reasons. First, Samsung's references either do not teach or suggest the claimed results limitations or do not qualify as prior art. Second, Samsung has failed to show that claims 6-7 and 12-13's "isotonic solution" and "nonionic surfactant" limitations were obvious.

¹⁵ Even if the AIA applies, 2010 ARVO is not prior art under § 102(b)(1)(A) because Drs. Major and Brown obtained the subject matter disclosed in 2010 ARVO from Dr. Yancopoulos via Dr. Berliner. *See also* MPEP 717.01(a)(1). Because Regeneron publicly disclosed the 24-week DA VINCI results in a press release on February 18, 2010, which predates 2010 ARVO, it is also not prior art under AIA § 102(b)(1)(B).

1. Samsung's Ground VI Arguments Fail for the Same Reasons as for Grounds II and IV

Dixon & the 2006 PR. As discussed for Ground IV, Dixon and the 2006 PR neither teach nor render obvious the claimed visual acuity results. (*Supra* §VI.C.) Dependent claims 6-7 and 12-13, which inherit the visual acuity results limitations of their parent claims, are not unpatentable over Samsung's combinations including Dixon and/or the 2006 PR for that reason.

December 2010 PR. As discussed for Ground II, the December 2010 PR is not prior art to claims 6-7 and 12-13. (*Supra* §VI.A.)

2. Neither Dixon Nor Hecht Shows the Claimed Formulations Were Obvious

Dixon. Samsung identifies no disclosure of an isotonic solution or a non-ionic surfactant in Dixon. (Ex.2065, ¶104.) Instead, Samsung and its expert gesture at Dixon's teaching about "comfortable, non-irritating" buffers and argue that shows an isotonic solution was obvious. (Pet. 49-50.)

Samsung has not carried its burden of proof. The paragraph of expert testimony Samsung cites is worth little because that expert has no experience formulating drugs. (Ex.2090, 336:13-338:10, 354:1-7, 355:21-356:1.) As for the cited statement from Dixon, "comfortable" and "non-irritating" did not mean isotonic; to the contrary, Samsung's own art states that hypertonic solutions were "well within the comfort tolerance of the eye." (Ex.1016, 11.) So did Samsung's

own expert. (Ex.2090, 360:5-20 (“[I]t’s hypertonic. Would that solution be tolerated by the eye? Certainly.”) Finally, Samsung does not even argue that Dixon suggests a non-ionic surfactant, foreclosing such a finding. (Pet. 49-50.)

Hecht. Samsung is wrong that Hecht teaches that ophthalmic solutions “must” be “formulated to be ... isotonic.” (Pet. 50 (quoting Ex.1016, 11); *see* Ex.1065, ¶¶106-109.) Instead, according to Hecht, “[t]he calculation of tonicity at one time was stressed rather heavily,” but was no longer “an overriding concern” by Hecht’s date. (Ex.1016, 13; Ex.2065, ¶105.) And while Hecht teaches using non-ionic surfactants, it teaches using them in “steroid suspensions,” (Ex.1016, 13), which are a different kind of drug than aflibercept. (Ex.2065, ¶33.) It also teaches that non-ionic surfactants have downsides. (Ex.1016, 13 (“[n]onionic surfactants ... may ... inactivate much of the preservative system”).) Moreover, it teaches that “[c]ationic surfactants are used frequently,” and that one such surfactant was “used in the large majority of commercial ophthalmic solutions....” (Ex.1016, 13.)

Perhaps aware of these deficiencies, Samsung tries to supplement Hecht’s disclosures with two more references, Randolph and Fraser. (Pet. 50-51 (citing Exs.1032-33).) The Board should not consider these references because they are not “listed under the numbered obviousness ground.” (DI, 15; Pet. 12.) Regardless, neither proves Samsung’s point. (Ex.1065, ¶¶110-111.) Randolph

teaches using non-ionic surfactants as stabilizing agents in some protein formulations, but it says nothing about aflibercept. (Ex.1032, 4.) Instead, it teaches that a non-ionic surfactant might not work: “non-ionic surfactants can also have the opposite effect” and can “destabilize the conformation of a protein.” (*Id.*, 13.) As for Fraser, that reference involved intravenous administration in monkeys to reduce ovulation. (Ex.1033.) The POSA would not have assumed that formulation was appropriate for intravitreal injection in humans to ameliorate angiogenic eye disorders. (Ex.2065, ¶111.)

The *Mylan* Order. Regeneron anticipates that, on reply, Samsung will ask the Board to follow a recent district court order finding claim 6 invalid over Dixon and Hecht. *Regeneron Pharms., Inc. v. Mylan Pharms. Inc. et al*, No. 22-cv-00061, Dkt. No. 692 (N.D.V.A. Jan. 31, 2024) (Ex.2093). For three reasons, the *Mylan* court’s approach is flawed and the Board should not adopt it.

First, the Board should discount the *Mylan* court’s reasoning because the *Mylan* court held, contrary to the DI here, that the *results limitations* lacked patentable weight. (Ex.2093, 51-52.) The *Mylan* court therefore never resolved whether achieving the result required by claim 6 (or those required by any other claim including a *results limitation*) was obvious. (Ex.2093, 51-52.) Its finding that the POSA would have had a reasonable expectation of success in using the claimed formulation was thus not a finding that the POSA would have reasonably

expected to achieve the claimed gain. (*Id.*, 240-42, 262-64.) For example, a successful formulation might only *slow* visual acuity loss by *some* amount, which is less than the *results limitations* require. (Ex.1001.)

Second, the Board should discount the *Mylan* court’s specific finding that an isotonic formulation was obvious over Hecht because the *Mylan* court misread the reference. The district court assumed that Hecht instructs using isotonic formulations. (Ex.2093, 279.) But Hecht doesn’t: Hecht teaches that, by 1995, isotonicity no longer was an “overriding concern” because the eye tolerates hypertonicity. (Ex.1016, 13.) The *Mylan* court’s reasoning that an isotonic solution was obvious to try because the POSA only had three options for tonicity (isotonic, hypertonic, and hypotonic) is also flawed because it oversimplifies the POSA’s choices. (Ex.2093, 279.) Hecht teaches the eye can tolerate tonicities “equivalent to a range of 0.5% to 1.8% sodium chloride,” or roughly anywhere between 50% to 200% the tonicity of an isotonic solution. (Ex.1016, 13.) Thus, the POSA had a wide range of options for tonicity, not just three.

Third, the Board also should not extend the *Mylan* court’s findings for claim 6 to other claims. Even had the *Mylan* court found some visual acuity gains obvious, it never found what *magnitude* gain the POSA could expect or *when* the POSA could expect to achieve it. (Ex.2093, 240-42 (reciting evidence of certain gains at certain times, but only finding a general “expectation of success at using

the claimed treatment regimens”); *id.*, 262-64 (same).) Its findings do not reach claims 3, 8, 10, 17, and 21, which require specific gains, nor claims 1-14, 16-23, and 26-30, which require gains within 24 weeks, within 52 weeks, or at 52 weeks.

* * *

Because Samsung has failed to carry its burden of proof for the formulation limitations, the Board should confirm patentability of claims 6-7 and 12-13.

F. Ground VII

The Board should reject this ground because Samsung did not plead it with particularity. *See* 35 U.S.C. § 312(a)(2). Under *Magnum Oil*, a conclusory assertion that “[t]he same analysis for [one reference] also applie[s] to [another] ... cannot satisfy the petitioner’s burden of demonstrating obviousness.” 829 F.3d at 1380. And that is all Samsung offers: its one-paragraph argument just points to three other grounds and asks the Board to fill in the blanks. (Pet. 51.) Samsung incorporates “the same reasons set out in Ground VI,” (*id.*), but that ground involved different references and a different disease. (*Compare* Pet., 49-51 (Ground IV art; angiogenic eye disorders) *with id.*, 51 (Ground V art; DME).) As in *Magnum Oil*, Samsung’s “the same reasons” argument does not provide the Board “sufficient evidence on which to base [a] legal conclusion of obviousness.” 829 F.3d at 1380. And once again, Samsung cannot fix these deficiencies on reply. 84 FR 64280, 73.

Alternatively, the Board also should reject Ground VII on the merits for the same reasons as the arguments Samsung incorporated by reference: neither 2010 ARVO nor the December 2010 PR is prior art (*supra* §§VI.A, VI.D.2); none of the 2009 PR, Dixon, or 2007 ARVO render obvious the *results limitations*, which claims 18-19 and 22-23 inherit from claims 16 and 17 (*supra*, §VI.D.1); and the formulation limitations were not obvious over Dixon and Hecht (*supra* §VI.E).

G. Ground VIII

1. Dixon Does Not Disclose the Claimed Results

As discussed above, Dixon neither discloses nor renders obvious the claimed visual acuity results. (*Supra* §VI.C.) Because claim 14 includes the limitations of its parent claims, Samsung’s obviousness theory based on Dixon fails.

2. The December 2010 PR Is Not Prior Art

The December 2010 PR is not prior art to claim 14. (*Supra* §VI.A.)

H. Ground IX: The 2009 PR, 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.” Samsung argues that this regimen was obvious over the 2009 PR, Shams, and Elman. (Pet. 52-56.) But these references do not disclose the recited five monthly loading doses, and Samsung fails to articulate how and why the POSA would have modified the art to arrive at the recited

regimen. The Board also should not follow the *Mylan* district court's recent, flawed order finding claim 25 obvious.

1. 2009 PR

The 2009 PR discloses that Regeneron's DA VINCI clinical trial included an arm with two—not four—secondary doses followed by every-eight-week dosing. (Ex.1005, 1.) Samsung argues that the POSA would have selected that regimen from the 2009 PR and then added two more monthly loading doses because some patients *might* benefit. (Pet. 52-54.) For the following reasons, no POSA would have blazed the path Samsung proposes.

To begin with, Samsung never justifies the starting point of its combination: selection of the DA VINCI's three-monthly-loading dose, 2q8-maintenance-dosing arm for modification. By the critical date, attempts at dosing Lucentis on a fixed extended interval had failed, so monthly and PRN dosing were common. (Ex.2066, ¶¶22-34.) And even setting that aside, Samsung identifies no motivation to increase the number of loading doses. (Ex.1005, 1.) At most, it speculates that five loading doses might have helped some patients. (Pet. 54.) But, if anything, the POSA would have been motivated to *decrease* the number of injections to reduce the treatment burden on patients, not *increase* them. (Ex.2065, ¶94.) Nor, if the POSA wanted to change the regimen, is there any reason they would have varied the loading doses rather than the every-eight-week maintenance doses. As

Samsung acknowledges, the POSA might have adopted PRN dosing. (Pet. 54.) So even accepting that the POSA might have modified DA VINCI's 2q8 arm protocol, Samsung never shows the 2009 PR would have motivated the POSA to use five monthly loading doses, specifically. (Ex.2065, ¶¶115-118.)

2. Shams

Shams does not help Samsung. The POSA would not have relied on Shams to optimize the 2009 PR's 2q8 dosing regimen because, by 2011, Shams' own extended dosing regimen proposed for Lucentis® had been shown not to work. (Ex.2065, ¶¶119-124; *compare* Ex.1017, 22:30-23:7 *with* Ex.1017, 23:13-23:28, 31:8-11, Fig.2.) As Dr. Brown explains, the extended dosing regimen in Shams led to losses in visual acuity. (Ex.2066, ¶¶3, 12, 22-34.) The POSA would have recognized, given that outcome, that optimizing an extended-interval dosing regimen was anything but "routine." (Ex.2065, ¶123.)

Nor does Shams' vague statement about adjusting doses "to minimize adverse effects while maintaining a maximum therapeutic effect" support obviousness. (Pet. 54-55 (quoting Ex.1017, 23-24); *see* Ex.2065, ¶¶125-129.) For one thing, the pages from Shams that Samsung cites recommend "typically three" monthly doses. (Ex.1017, 24:14-28.) Sham's teaching that "the first dose may be administered, for example, one, two or three times, typically three times," would have motivated the POSA to use three or fewer doses, not more. (*Id.*; Ex.2065,

¶119.) For another, “where the prior art[] at best gives only general guidance as to the particular form of the claimed invention or how to achieve it, relying on an obvious-to-try theory to support an obviousness finding is impermissible.” *Roxane Lab’ys, Inc. v. Vanda Pharms. Inc.*, No. IPR2016-00690, 2016 WL 5226531 (P.T.A.B. Aug. 30, 2016) (cleaned up). As that is at most all Samsung contends Shams provides (to the extent Samsung even made that contention in its cursory Ground) (Pet. 54-55), the Board should reject Samsung’s argument for this reason, too (*see also* Ex.1065, ¶¶130-143).

3. Elman

Samsung’s combination of the 2009 PR with Elman fails for three reasons. First, Samsung misreads the reference. Samsung relies on Elman’s disclosure that 22% of patients did not receive a fifth dose at 16 weeks to conclude that 78% of patients did receive five initial monthly doses. (Pet. 55.) But this is not disclosure that 78% of patients received *only* five initial monthly doses, as claim 25 requires. (Ex.2065, ¶149.) In fact, there is no way to tell from Elman whether *any* patient received exactly five monthly doses, nor whether all patients in the 78% received six or more initial monthly doses. (Ex.2065, ¶¶149-151.) And given that Elman reported worsening visual acuity and retinal thickness at week 20 compared to week 16, it is likely that the 78% of patients who received a fifth dose also received a sixth—or more. (Ex.2065, ¶151; Ex.1018, 6 Fig.3, 10 Fig.6, 25.)

Second, Elman 2010 identifies no benefit from five loading doses. Visual acuity and retinal thickness both worsened between weeks 16 and 20. (Ex.1018, 35 Fig. 8, 6 Fig. 3; Ex.2065, ¶153.) And nearly all the improvement was seen by week 12. (Ex.1018, 35 Fig. 8, 6 Fig. 3; Ex.2065, ¶153.) So even though many subjects received five or more monthly doses, Elman does not teach that exactly five is any better than three, four, six, or more. (Ex.2065, ¶¶152-157.) Elman also does not disclose individualized data, so it is impossible to determine whether exactly five loading doses would be helpful or ideal for any individual. (*Id.*, ¶155.)

Third, Elman tested ranibizumab, and the POSA would not have reasonably expected the optimal ranibizumab and aflibercept dosing regimens to be identical. Aside from understanding that different drugs have different properties, the POSA would have believed that aflibercept might dry the retina differently than ranibizumab. (Ex.2065, ¶¶159-160.) Regeneron's VEGF Trap molecules (including aflibercept) had been shown to have higher binding affinity than existing therapies. (Ex.1009, 5; Ex.2065, ¶161.) And 2mg of aflibercept contains more protein molecules than 0.5mg ranibizumab (the ranibizumab dose in the 2009 PR and Elman 2010). (Ex.2065, ¶160.) Thus, the POSA would be skeptical about relying on a ranibizumab dosing regimen to determine the optimal aflibercept regimen. (Ex.2065, ¶159.) The Board should reject Samsung's hindsight-driven attempt to reconstruct claim 25. (*See also* Ex.2065, ¶¶144-148, 162-177.)

4. The *Mylan* Order

For claim 25, Regeneron anticipates that Samsung will ask the Board to follow the *Mylan* court's recent finding that four secondary doses was obvious over the 2009 PR. (Ex.2093, 256-311.) The Board should not do so.

The *Mylan* court's opinion regarding claim 25 rests on two contradictory findings. The *Mylan* court first acknowledged an undisputed fact: that "there was market pressure to employ extended (*i.e.*, less frequent than monthly) dosing regimens for aflibercept." (*Id.*, 258.) Then, it pivoted and found five loading doses obvious because some doctors using PRN dosing might have administered five doses or that amount was obvious to try. (*Id.*, 259-80.) These findings are irreconcilable: if POSAs were motivated to avoid monthly doses, then they would not have optimized PRN regimens for monthly doses or routinely tried the same.

In resolving this tension, the *Mylan* court got the law wrong. It wrote about the teaching away standard, "[a]bsent evidence that the prior art 'invariably' would have led to a different path, the prior art does not teach away." (Ex.2093, 266 (quoting *PAR Pharm.*, 773 F.3d at 1199).) But that is not what *PAR Pharm.* held. There, because a technology did not "invariably" produce an unfavorable result, the Federal Circuit found no flaw in a district court's rejection of a teaching away argument under the deferential, clear error standard. 773 F.3d at 1199. The legal standard for teaching away is different: it requires only a suggestion "that the line

of development flowing from [its] disclosure is unlikely to be productive.” *Id.* at 1198 (cleaned up). Under that standard, the fact that the POSA would have avoided increasing the number of loading doses refutes obviousness.

I. Grounds X & XI: The *Results Limitations* Have Patentable Weight

Samsung’s Grounds X and XI depend on the premise that the *results limitations* lack patentable weight. (Pet. 60-61.) The Board should reject these grounds because that premise is false. (*Supra* §V.A.; DI, 30.)

VII. EYLEA®’S COMMERCIAL SUCCESS OBJECTIVELY DEMONSTRATES NON-OBVIOUSNESS

A. Eylea® has as nexus to the challenged claims

The challenged claims and Eylea® have a nexus that supports a finding of commercial success. *See Cont’l Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1273 (Fed. Cir. 1991); *Volvo Penta of the Ams., LLC v. Brunswick Corp.*, 81 F.4th 1202, 1211 (Fed. Cir. 2023).

Eylea® is commercially successful because doctors know that the claimed extended dosing regimens yield the claimed benefits to visual acuity in patients with wAMD and DME. (Ex.2065, ¶¶179-189; Ex.2067, ¶¶36-39.) Eylea®’s patented, effective 2q8 dosing regimen is a key differentiator that has led to its commercial success. (Ex.2065, ¶190; Ex.2067, ¶35.) Patients and physicians value effective treatments that involve fewer needlesticks in the eye, and administering Eylea® according to the 2q8 dosing regimen allows for an effective treatment with

fewer needlesticks compared to other options. (Ex.2065, ¶¶180-181; Ex.2067, ¶¶32-35.) Physicians report switching to Eylea® from competing products because of the effective extended dosing regimen. (Ex.2065, ¶188; Ex.2067, ¶28.) In a 2014 survey, [REDACTED] named dosing as a key benefit of Eylea® while only [REDACTED] named dosing as a key benefit of Lucentis®. (Ex.2067, ¶35.) Eylea®'s other claimed features, like its formulation, its efficacy at both three and five loading doses, and its efficacy within as short a span as 24 weeks, also led physicians to prescribe Eylea® and thereby drive sales. (Ex.2065, ¶¶189-190; Ex.2067, ¶35.)

B. Eylea® is a commercial success

Eylea®'s significant market share and sales volume shows commercial success of the claimed methods. *See Chemours Co. FC, LLC v. Daikin Indus., Ltd.*, 4 F.4th 1370, 1377 (Fed. Cir. 2021).

Eylea® is the most common anti-VEGF treatment option: [REDACTED] practitioners use Eylea® more than other treatment options. (Ex.2067, ¶30.) Eylea®'s share of sales across all indications rose year-over-year, [REDACTED] [REDACTED] (Ex.2067, ¶20.) Eylea® has gained [REDACTED] [REDACTED] in sales share since its launch through 2021, while Avastin® and Lucentis® have each lost [REDACTED] sales share. (Ex.2067, ¶29.)

Across all angiogenic eye disorders, Eylea® had a sales share [REDACTED] in 2014 that has jumped to [REDACTED] by 2021. (Ex.2067, ¶20.) Eylea® also has the highest share among anti-VEGF products for the treatment of both DME and wAMD. (Ex.2067, ¶¶22, 24.) For both DME and wAMD, Eylea® garnered a sales share [REDACTED] by 2014, which by 2021 had grown [REDACTED] [REDACTED] (Ex.2067, ¶¶22, 24.)

Eylea® also is the dominant option for second-line treatments, in which a patient switches to a new therapy because initial therapy doesn't work or stopped working. (Ex.2067, ¶28.) About [REDACTED] are in their second line of therapy. (Ex.2067, ¶28.) Eylea®'s patient shares for second line of therapy were [REDACTED]. (Ex.2067, ¶28.) Even when doctors use multiple treatment options for a patient, [REDACTED] of doctors depend on Eylea® as their primary treatment choice. (Ex.2067, ¶30.)

Sales volume from Medicare also shows Eylea®'s commercial success. From 2012 to 2021, the number of patients taking Eylea® increased from [REDACTED] [REDACTED]. (Ex.2067, ¶27.) During that time, the number of Medicare patients receiving Avastin® and Lucentis® decreased [REDACTED] for Avastin® and [REDACTED] for Lucentis®, [REDACTED]. (Ex.2067, ¶27.) In the last two years, Eylea® sale volume has increased [REDACTED] while Avastin® and Lucentis® volume has dropped [REDACTED] (Ex.2067, ¶26.)

The commercial success of Eylea® due to the claimed regimen refutes unpatentability. (Ex.2065, ¶¶189-190; Ex.2067, ¶16.)

VIII. CONCLUSION

For the foregoing reasons, the Board should confirm patentability of all challenged claims.

Date: February 23, 2024

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I hereby certify that this PATENT OWNER’S RESPONSE has 13,896 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: February 23, 2024

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Certificate of Service (37 C.F.R. § 42.6(e)(4))

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