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Paper 9
Entered: March 10, 2023

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

APOTEX INC.,
Petitioner,

v.

REGENERON PHARMACEUTICALS, INC.,
Patent Owner.

IPR2022-01524
Patent 11,253,572 B2

Before SUSAN L. C. MITCHELL, ROBERT A. POLLOCK, and RYAN H. FLAX, *Administrative Patent Judges*.

FLAX, *Administrative Patent Judge*.

DECISION
Denying Institution of *Inter Partes* Review
35 U.S.C. § 314

I. INTRODUCTION

Regeneron Pharmaceuticals, Inc. ("Patent Owner") is the owner of U.S. patent 11,253,572 B2 ("the '572 patent"). Paper 5, 1. On September 9, 2022, Apotex Inc. ("Petitioner") filed a Petition for *inter partes* review challenging the patentability of claims 1–14 and 26–30 of the '572 patent (claims 15–25 are not challenged). Paper 1, 1 ("Pet."). On December 23, 2022, Patent Owner filed a Preliminary Response to the Petition. Paper 7 ("Prelim. Resp."). No further briefing was requested or authorized.

Under 37 C.F.R. § 42.4(a), we have authority to determine whether to institute trial in an *inter partes* review. We may institute an *inter partes* review if the information presented in the petition filed under 35 U.S.C. § 311, and any preliminary response filed under § 313, shows that there is a reasonable likelihood that Petitioner would prevail with respect to at least one of the claims challenged in the petition. 35 U.S.C. § 314.

After reviewing the parties' submissions, we conclude Petitioner does not demonstrate a reasonable likelihood it would prevail in showing that any challenged claim of the '572 patent is unpatentable under the presented grounds. Therefore, we deny institution of *inter partes* review.[1] Our reasoning is discussed below.

A. REAL PARTIES-IN-INTEREST

Petitioner lists Apotex Inc., Apotex Corp, Apotex Pharmaceutical Holdings Inc, and Aposherm Delaware Holdings Corp. as real parties-in-

[1] We note that there are disputed issues in this proceeding under 35 U.S.C. § 325(d) and § 314(a). *See* Pet. 6–11; Prelim. Resp. 47–57. However, because we determine institution should be denied on the merits, we do not address these matters.

interest. Pet. 2. Patent Owner identifies itself as the only real party-in-interest. Paper 5, 1.

B. RELATED MATTERS

Petitioner identifies the following as related matters: IPR2021-00881 (concerning U.S. Patent 9,254,338 ("the '338 patent"); IPR2022-00258 (also concerning the '338 patent); IPR2022-00298 (also concerning the '338 patent); IPR2021-00880 (concerning U.S. Patent 9,669,069 ("the '069 patent)); IPR2022-0257 (also concerning the '069 patent); IPR2022-00301 (also concerning the '069 patent); IPR2022-01225 (concerning U.S. Patent 10,130,681 ("the '681 patent"); and IPR2022-01226 (concerning U.S. Patent 10,888,601 ("the '601 patent"). Pet. 3–4. Petitioner also identifies as related *Regeneron Pharms., Inc. v. Mylan Pharms. Inc.,* No. 1:22-cv-00061-TSK (N.D. W.Va), and PGR2021-00035 (concerning U.S. Patent 10,828,345). *Id.* at 5. In addition to the above-listed patents, Petitioner identifies U.S. Patent Application Nos. 17/072,417; 17/112,404; 17/112,063; and 17/350,958 as related. *Id.* Patent Owner identifies the same matters, patents, and applications as related. Paper 5, 2–3.

C. THE '572 PATENT

The '572 patent issued on February 22, 2022, from U.S. Application 17/352,892, which was filed on June 21, 2021. Ex. 1001, codes (45), (21), (22). The '572 patent ultimately indicates priority to U.S. Provisional Application 61/432,245, filed on January 13, 2011. *Id.* at code (60), 1:7–29. Petitioner declines to challenge whether the '572 patent is entitled such priority. *See, e.g.*, Pet. 1 ("Long before the patent's alleged 2011 priority date . . . .").

The '572 patent's abstract states:

> The present invention provides methods for treating angiogenic eye disorders by sequentially administering multiple doses of a VEGF antagonist to a patient. The methods of the present invention include the administration of multiple doses of a VEGF antagonist to a patient at a frequency of once every 8 or more weeks. The methods of the present invention are useful for the treatment of angiogenic eye disorders such as age related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion, branch retinal vein occlusion, and corneal neovascularization.

Id. at Abstract.

As background, the '572 patent states that "[r]elease of vascular endothelial growth factor (VEGF) contributes to increased vascular permeability in the eye and inappropriate new vessel growth," and "inhibiting the angiogenic-promoting properties of VEGF appears to be an effective strategy for treating angiogenic eye disorders." *Id.* at 1:60–65. As further background, the '572 patent identifies that "FDA-approved treatments of angiogenic eye disorders such as AMD and CRVO include the administration of an anti-VEGF antibody called ranibizumab (Lucentis®, Genentech, Inc.) on a monthly basis by intravitreal injection." *Id.* at 1:66–2:2. The '572 patent indicates that its invention is a response to the need for "new administration regimes" of "less frequent dosing while maintaining a high level of efficacy." *Id.* at 2:6–9.

In summarizing its invention, the '572 patent states:

> The present inventors have surprisingly discovered that beneficial therapeutic effects can be achieved in patients suffering from angiogenic eye disorders by administering a VEGF antagonist to a patient at a frequency of once every 8 or more weeks, especially when such doses are preceded by about three doses administered to the patient at a frequency of about 2

> to 4 weeks. Thus, according to the methods of the present invention, each secondary dose of VEGF antagonist is administered 2 to 4 weeks after the immediately preceding dose, and each tertiary dose is administered at least 8 weeks after the immediately preceding dose.

Id. at 2:22–33. Relating to this, the '572 patent defines certain terms. For example, "the VEGF antagonist comprises one or more VEGF receptor-based chimeric molecule(s), (also referred to herein as a 'VEGF-Trap' or 'VEGFT')," and an example of this includes a product called "aflibercept," marketed as "EYLEA" by Regeneron Pharmaceuticals, Inc. and approved by the FDA in November 2011 at a dose of 2 mg via intravitreal injection every 4 weeks for three months and then every 8 weeks. *Id.* at 2:47–67.

On the aforementioned FDA-approved dosing regimen, the '572 patent further defines the terms (ultimately used in the claims) "initial dose, "secondary doses," and "tertiary doses" as follows:

> the "initial dose" is the dose which is administered at the beginning of the treatment regimen (also referred to as the "baseline dose"); the "secondary doses" are the doses which are administered after the initial dose; and the "tertiary doses" are the doses which are administered after the secondary doses.

Id. at 3:51–58.

The '572 patent describes a series of Examples detailing clinical trials conducted to validate the VEGFT drug and the dosing regimen. *Id.* at 8:12–18:3. Example 4 details two "Phase III Clinical Trials of the Efficacy, Safety, and Tolerability of Repeated Doses of Intravitreal VEGFT in Subjects with Neovascular Age-Related Macular Degeneration" (AMD) (Study 1 and Study 2), which followed dosing regimens using 2 mg doses of aflibercept at the aforementioned initial dose, then two 4-week doses, and then doses every 8-weeks through the end of the 52-week study (the "2Q8"

regimen). *Id.* at 9:29–14:30. The results of this and other regimens were compared to subjects administered 0.5 mg ranibizumab every 4 weeks (the "RQ4" regimen) by assessing patients' visual acuity based on a Best Corrected Visual Acuity (BCVA) test, which is based on the ability to identify letters. *Id.* at 9:35–10:7. This disclosure describes the inclusion criteria and exclusion criteria for the participating patients. *Id.* at 10:50–12:22.

Results of the Example 4 clinical trials are described in TABLE 1, which we reproduce below:

TABLE 1

	Ranibizumab 0.5 mg monthly (RQ4)	VEGFT 0.5 mg monthly (0.5Q4)	VEGFT 2 mg monthly (2Q4)	VEGFT 2 mg every 8 weeks[a] (2Q8)
Maintenance of vision* (% patients losing <15 letters) at week 52 versus baseline				
Study 1	94.4%	95.9%**	95.1%**	95.1%**
Study 2	94.4%	96.3%**	95.6%**	95.6%**
Mean improvement in vision* (letters) at 52 weeks versus baseline (p-value vs RQ4)***				
Study 1	8.1	6.9 (NS)	10.9 (p <0.01)	7.9 (NS)
Study 2	9.4	9.7 (NS)	7.6 (NS)	8.9 (NS

[a]Following three initial monthly doses
*Visual acuity was measured as the total number of letters read correctly on 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 Study 1 and Study 2, respectively)
***Test for superiority
NS = non-significant

Id. at 13:9–27. The '572 patent describes that these results showed that the VEGFT therapies usually maintained or improved visual acuity in patients and were not inferior to the ranibizumab treatment based on similar criteria. *Id.* at 13:28–38.

As Example 5, the ’572 patent describes a phase 2 clinical trail using the same drug, also administered at 2 mg doses and, in one arm, at a regimen of three initial doses every four weeks followed by doses every eight weeks, but treating patients with diabetic macular edema (DME). *Id.* at 14:32–15:5. The ’572 patent describes that visual acuity in this trial was maintained or improved for all VEGFT study groups. *Id.*

The ’572 patent concludes with 30 claims, of which claims 1, 15 (not challenged), 26, and 29 are independent claims. Ex. 1012, 62:12–64:20. Claim 1 is illustrative and reproduced below:

> 1. A method of treating an angiogenic eye disorder in a patient in need thereof comprising sequentially administering to the patient by intravitreal injection a single initial dose of 2 mg of aflibercept, followed by one or more secondary doses of 2 mg of aflibercept, followed by one or more tertiary doses of 2 mg of aflibercept;
>
> wherein each secondary dose is administered approximately 4 weeks following the immediately preceding dose; and
>
> wherein each tertiary dose is administered approximately 8 weeks following the immediately preceding dose;
>
> wherein the patient achieves a gain in visual acuity within 52 weeks following the initial dose.

Ex. 1001, 23:2–14.

Independent claim 26 is similar to claim 1 in reciting the same drug, at the same dose, and administered the same way, on the same schedule, but adds that the method treats “age related macular degeneration” (AMD) and that “the method is as effective in achieving a gain in visual acuity as monthly administration of 0.5 mg of ranibizumab by intravitreal injection in human subjects with age-related macular degeneration at 52 weeks

following the initial dose." *Id.* at 24:26–44. Independent claim 29 is also similar to claim 1, and essentially the same as claim 26, but differs in requiring effectiveness in "maintaining visual acuity" rather than a *gain* therein. *Id.* at 24:50–67.

D. ASSERTED GROUNDS FOR UNPATENTABILITY

Petitioner asserts the following grounds for the unpatentability of claims 1–14 and 26–30 of the '572 patent:

Ground	Claims Challenged	35 U.S.C. §[2]	Reference(s)/Basis
1	1–5, 8–11, 14, 26–30	102	Dixon[3]
2	1–5, 8–11, 14, 26–30	102	Regeneron 2008[4]
3	1–5, 8–11, 14, 26–30	102	NCT-795[5]
4	1–5, 8–11, 14, 26–30	102	NCT-377[6]

[2] The '572 patent has an uncontested January 13, 2011, priority date, which is before the AIA revisions to 35 U.S.C. §§ 102 and 103 took effect on March 16, 2013. 35 U.S.C. § 100 (note). Therefore, pre-AIA §§ 102 and 103 apply. Our decision is not impacted by which version of the statute applies.

[3] James A. Dixon et al., *VEGF Trap-Eye for the treatment of neovascular age-related macular degeneration*, 18(10) EXPERT OPIN. INVESTIG. DRUGS 1573–80 (2009) (Ex. 1006, "Dixon").

[4] Regeneron, News Release: *Bayer and Regeneron Dose First Patient in Second Phase 3 Study for VEGF Trap-Eye in Wet Age-Related Macular Degeneration -International study to evaluate efficacy and safety in treating a leading cause of blindness* 1–3 (May 8, 2008) (Ex. 1009, "Regeneron 2008").

[5] NIH, U.S. National Library of Medicine, ClinicalTrials.gov archive, *History of Changes for Study: NCT00509795, Vascular Endothelial Growth Factor(VEGF)Trap-Eye:Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration(AMD) (VIEW1)* (Dec. 20, 2012), accessed January 7, 2021, at https://clinicaltrials.gov/ct2/history/NCT00509795?A=8&B=9&C=merged#StudyPageTop (Ex. 1010, "NCT-795").

[6] NIH, U.S. National Library of Medicine, ClinicalTrials.gov archive, *History of Changes for Study: NCT00637377, VEGF Trap-Eye:*

Ground	Claims Challenged	35 U.S.C. §[2]	Reference(s)/Basis
5a[7]	6, 7, 12, 13	103	Dixon, Hecht[8]
5b	6, 7, 12, 13	103	Regeneron 2008, Hecht
5c	6, 7, 12, 13	103	NCT-795, Hecht
5d	6, 7, 12, 13	103	NCT-377, Hecht

See Pet. 12.

In support of these grounds for unpatentability Petitioner submits, *inter alia*, the Declaration of Angelo P. Tanna, MD (Ex. 1002). In the absence of evidence to the contrary, we find Dr. Tanna competent to testify on the subject matter of his declaration. *See infra* Section II.A; *see* Ex. 1002 ¶¶ 3–11, 15–18; Ex. 1003. We understand that Patent Owner has not submitted a similar witness declaration specifically directed to this proceeding, nor was it required to do so. Patent Owner has, however, submitted witness declarations from related proceedings before the Board, including the Declaration of Lucian V. Del Priore, MD, PhD, which was submitted in related matters IPR2021-00880 and IPR2021-00881 (and notes that IPR2022-00257, IPR2022-00258, IPR2022-00298, and IPR2022-00301 were joined therewith). *See* Ex. 2021; *see also* Prelim. Resp. viii, 37, 40; *see*

Investigation of Efficacy and Safety in Wet AMD (VIEW 2) (Nov. 28, 2014), accessed Dec. 29, 2020, at https://clinicaltrials.gov/ct2/history/NCT00637377?A=1&B=1&C=merged#StudyPageTop (Ex. 1011, "NCT-377").

[7] Grounds 5a–5d listed here are presented by Petitioner as a single "Ground 5"; however, because that ground actually asserts four separate challenges for unpatentability premised on separate combinations of the references of Grounds 1–4 in combination with Hecht, we separate these into separate grounds.

[8] Gerald Hecht, PhD, *Ophthalmic Preparations*, in II REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY, 19th ed., Ch. 89, 1563–76 (Alfonso R. Gennaro ed., 1995) (Ex. 1025, "Hecht").

supra Section I.B (Related Matters). In the absence of evidence to the contrary, we also find Dr. Del Priore to be competent to testify on the subject matter of his declaration, which is related to the subject matter of this proceeding. *See* Ex. 2021 ¶¶ 3–10, 16–18; *see also infra* Section II.A (identifying the parties' proposed definition of the ordinarily skilled artisan, which is the same as that addressed by Dr. Del Priore).

II. DISCUSSION

A. LEVEL OF ORDINARY SKILL IN THE ART

In determining the level of ordinary skill in the art, we consider the types of problems encountered in the art, the prior art solutions to those problems, the rapidity with which innovations are made, the sophistication of the technology, and the educational level of active workers in the field. *Custom Accessories, Inc. v. Jeffrey-Allan Indus., Inc.*, 807 F.2d 955, 962 (Fed. Cir. 1986).

Petitioner states,

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

> including through the use of VEGF antagonists, or (ii) treating of same, including through the use of VEGF antagonists.

Pet. 23 (citing Ex. 1002 ¶ 16).[9] Patent Owner neither contests this proposed definition of the ordinarily skilled artisan nor offers its own. *See generally* Prelim. Resp.

For the purposes of this decision, we accept Petitioner's proposed definition of the person of ordinary skill in the art (or ordinarily skilled artisan), which appears to be consistent with the level of skill in the art reflected in the prior art of record and the disclosure of the '572 patent. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) ("the prior art itself [may] reflect[]" evidence of the ordinary level of skill in the art) (quoting *Litton Indus. Prods., Inc. v. Solid State Sys. Corp.*, 755 F.2d 158, 163 (Fed. Cir. 1985)).

B. CLAIM CONSTRUCTION

The Board interprets claim terms in an *inter partes* review using the same claim construction standard that is used to construe claims in a civil action in federal district court. 37 C.F.R. § 42.100(b). In construing claims, district courts and the Board here, by default, give claim terms their ordinary and customary meaning, which is "the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312–13 (Fed. Cir. 2005) (en banc).

Should claim terms require express construction, sources for claim interpretation include "the words of the claims themselves, the remainder of the specification, the prosecution history [i.e., the intrinsic evidence], and extrinsic evidence concerning relevant scientific principles, the meaning of

[9] Petitioner uses "POSA" to refer to the person of ordinary skill in the art.

technical terms, and the state of the art." *Id.* at 1314 (quoting *Innova/Pure Water, Inc. v. Safari Water Filtration Sys., Inc.*, 381 F.3d 1111, 1116 (Fed. Cir. 2004)). "[T]he claims themselves [may] provide substantial guidance as to the meaning of particular claim terms." *Id.* However, the claims "do not stand alone," but are part of "'a fully integrated written instrument' . . . consisting principally of a specification that concludes with the claims," and, therefore, the claims are "read in view of the specification." *Id.* at 1315 (quoting *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 978–79 (Fed. Cir. 1995) (en banc)). Any special definition for a claim term must be set forth in the specification "with reasonable clarity, deliberateness, and precision." *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994). Without such a special definition, however, limitations may not be read from the specification into the claims. *In re Van Geuns*, 988 F.2d 1181, 1184 (Fed. Cir. 1993).

"[W]e need only construe terms 'that are in controversy, and only to the extent necessary to resolve the controversy.'" *Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999)).

We now turn to the parties' positions on claim construction.

1. "initial dose," "secondary doses," and "tertiary doses"

One or all of the terms "initial dose," "secondary doses," and "tertiary doses," appear in claims 1, 4, 9, 15, 16, 20, 24–27, and 29 (as noted, not all of these claims are challenged). *See* Ex. 1001, 23:1–25:5 (claims).

Petitioner asserts that the '572 patent expressly defines the claim terms "initial dose," "secondary doses," and "tertiary doses," in its Specification, as follows:

> The terms "initial dose," "secondary doses," and "tertiary doses," refer to the temporal sequence of administration of the VEGF antagonist. Thus, the "initial dose" is the dose which is administered at the beginning of the treatment regimen (also referred to as the "baseline dose"); the "secondary doses" are the doses which are administered after the initial dose; and the "tertiary doses" are the doses which are administered after the secondary doses. The initial, secondary, and tertiary doses may all contain the same amount of VEGF antagonist, but will generally differ from one another in terms of frequency of administration. In certain embodiments, however, the amount of VEGF antagonist contained in the initial, secondary and/or tertiary doses will vary from one another (e.g., adjusted up or down as appropriate) during the course of treatment.

Pet. 16 (quoting Ex. 1001, 3:51–65; citing Ex. 1002 ¶ 62).

Patent Owner "does not propose a construction of 'initial dose,' 'secondary dose[s],' or 'tertiary dose[s]' that is different than that proposed by Petitioner," although it also does not concede Petitioner's proposal is correct. Prelim. Resp. 18.

"When the specification explains and defines a term used in the claims, without ambiguity or incompleteness, there is no need to search further for the meaning of the term." *Multiform Dessicants Inc. v. Medzam Ltd.*, 133 F.3d 1473, 1478 (Fed. Cir. 1998). We agree with Petitioner's unopposed position that the Specification of the '572 patent expressly and unequivocally defines the claim terms "initial dose," "secondary doses," and "tertiary doses," as set forth in the quote above, as meaning, respectively, (1) *the dose which is administered at the beginning of the treatment regimen*; (2) *the doses administered after the initial dose*; and (3) *the doses*

administered after the secondary doses. We interpret these terms consistent with the Specification's definitions.

2. "4 weeks" and "8 weeks" after the immediately preceding dose

Petitioner contends that "[a] skilled artisan would understand the phrase "'4 weeks'—as it appears in the Challenged Claims—to be synonymous with monthly administration" and "'8 weeks' . . . to be synonymous with bi- monthly (or every-other-month administration)." Pet. 17 (citing Ex. 1001, 8:9–11, 15:19–30; Ex. 1002 ¶¶ 65–66). Patent Owner does not challenge this construction. Prelim. Resp. 18.

We determine that express construction of these claim terms is unnecessary for purposes of rendering this Decision. *See Nidec Motor Corp.*, 868 F.3d at 1017.

3. "wherein the patient achieves/gains"

Claim 1 recites as its concluding clause, "*wherein the patient achieves a gain in visual acuity within 52 weeks following the initial dose*." Ex. 1001, 23:13–14 (italics added). Claims 2–4 and 8–10 further define this "gain in visual acuity." *Id.* at 23:15–25, 23:32–38. Independent claim 15 and its dependent claims 16–26 are not challenged in this proceeding, and, although claim 15 has no *gain in visual acuity* requirement, claims 16–23 do. *Id.* at 23:53–24:21. Independent claim 26 recites as its concluding clause, "*wherein the method is as effective in achieving a gain in visual acuity as monthly administration of 0.5 mg of ranibizumab by intravitreal injection in human subjects with age-related macular degeneration at 52 weeks following the initial dose*," and dependent claim 28 further defines this "gain in visual acuity." *Id.* at 24:40–44, 24:47–49 (italics added). Finally, independent claim 29 recites as its concluding clause, "*wherein the method*

is as effective in maintaining visual acuity as monthly administration of 0.5 mg of ranibizumab by intravitreal injection in human subjects with age-related macular degeneration at 52 weeks following the initial dose," and dependent claim 30 further defines this "gain in visual acuity." *Id.* at 24:63–25:5 (italics added). Collectively we refer to these clauses, particularly of independent claims 1, 26, and 29, as the "*results limitations*."

Petitioner asserts that the *results limitations* merely state the intended results of the otherwise claimed methods of administering aflibercept and, as such, have no patentable weight because they do not alter the steps of the methods. Pet. 17. Petitioner's position is that the *results limitations* should not be treated as limitations. *Id.* 17–20 (citing Ex. 1002 ¶ 67; *Syntex (U.S.A.) LLC v. Apotex, Inc.*, 407 F.3d 1371, 1378 (Fed. Cir. 2005); *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1376 (Fed. Cir. 2001); *In re Copaxone*, 2016 WL 873062, at *2 n.1–2 (D. Del. Mar. 7, 2016); *Endo Pharm. Inc. v. Watson Labs., Inc.*, 2014 WL 2859349, at *6, *8 (E.D. Tex. Jun. 23, 2014)). Petitioner, however, accounts for the possibility that we find its position incorrect and alternatively argues under Grounds 1–4 that, if the *results limitations* are given patentable weight, then the asserted prior art inherently anticipated these limitations. *See, e.g.*, *id.* at 38–39, 44–45 (citing Ex. 1002 ¶ 148; *In re Montgomery*, 677 F.3d 1375, 1382 (Fed. Cir. 2012)).

Patent Owner argues that the *results limitations* require that the claimed patients and methods achieve particular "endpoints as assessed by the physician," and that the *results limitations* are "'condition[s] material to patentability,' and therefore 'cannot be ignored.'" Prelim. Resp. 18–19 (citing *Hoffer v. Microsoft Corp.*, 405 F.3d 1326, 1329 (Fed. Cir. 2005)).

Patent Owner argues that "[t]he Visual Acuity [i.e., *results*] *limitations* in the Challenged Claims add additional requirements that may be—but are not necessarily—met upon performance of the dosing steps recited earlier in the claim," and adds that the *results limitations* requirements are "not met unless the patient receiving the doses does, in fact, experience the required gain." *Id.* at 20, 25 (italics added).

The facts here are similar to those of *Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center v. Eli Lilly & Co.*, 849 F.3d 1049 (Fed. Cir. 2017) ("*Los Angeles Biomed*."), where claims covered administering a pharmaceutical according to a certain regimen, to a person in need of treatment, and included a limitation in the body of the independent claim to a treatment result of "arresting or regressing" a tissue fibrosis by the administration of the recited dosage. *Id.* at 1053–54. Similarly here, as can be seen from claim 1 reproduced above at Section I.C (and each challenged independent claim), the claims are similarly directed to administering a pharmaceutical (aflibercept) to patients in need thereof, at a specified regimen and dosage, where a result of that treatment is expressly recited in the body of the independent claims. *See* Ex. 1001, 23:2–14 (claim 1), 24:26–43 (claim 26), 24:50–67 (claim 29).

In *Los Angeles Biomed*, in an *inter partes* review the Board construed the "arresting or regressing" clause to have no limiting role and to merely state an intended result, ultimately finding the claims unpatentable as obvious. *Id.* at 1054–57. The Federal Circuit disagreed and the Board's decision was vacated and the case was remanded on, *inter alia,* that issue. *Id.* at 1067–68.

Relating to the claim construction, the Federal Circuit found that patent at issue was "clear" that the tissue fibrosis, recited by the claim as arrested or regressed by the otherwise recited treatment, was not the same as and did not *necessarily* accompany the symptom of erectile disfunction (taught in and the focus of the relied-upon prior art), although the former (fibrosis) may frequently result in the latter (disfunction). *Id.* at 1059. The Federal Circuit held that the "arresting or regressing" clause was more than a mere statement of intended result, but was a limitation carrying patentable weight because the phrase was drafted as a part of a separate step of the method rather than of the preamble, the "arresting or regressing" language demanded efficacy, and the efficacy was linked to specific treatment minimum duration and dosage. *Id.* at 1060–61. The patients exhibiting these two issues were not necessarily the same.

In part because the Board did not consider the arresting/regressing result limitation in its unpatentability analysis, the Federal Circuit agreed with the patent owner that the Board's findings were insufficient. *Id.* at 1064, 1067. The Federal Circuit found that that prior art reference relied upon in the Board's decision for teaching the claimed treatment, and also relied upon to link the condition of fibrosis with the symptom of erectile dysfunction, did not teach treating a population of patients suffering from erectile dysfunction *only* because of a fibrosis condition and, even though such patients *may* have had fibrosis, *it was not certain*; and further found that other cited prior art did not make certain a link between fibrosis and such dysfunction. *Id.* at 1065–66. This, the Federal Circuit found, was error.

We find in agreement with Patent Owner that the *results limitations* of the challenged claims are limitations and must be given patentable weight for the same reasons *arresting or regressing a tissue fibrosis* was a limitation in *Los Angeles Biomed*.

Similarly, here the claims are directed to expressly required results of the administration of aflibercept to patients at 2 mg at an initial dose, in at least one secondary dose 4 weeks later, and in at least one tertiary dose 8 weeks later. Therefore, we find that in claim 1, "*wherein the patient achieves a gain in visual acuity within 52 weeks following the initial dose,*" is a limitation. Further, in claim 26, "*wherein the method is as effective in achieving a gain in visual acuity as monthly administration of 0.5 mg of ranibizumab by intravitreal injection in human subjects with age-related macular degeneration at 52 weeks following the initial dose,*" is a limitation. And, in claim 29, "*wherein the method is as effective in maintaining visual acuity as monthly administration of 0.5 mg of ranibizumab by intravitreal injection in human subjects with age-related macular degeneration at 52 weeks following the initial dose,*" is a limitation.

4. "wherein exclusion criteria for the patient include both of . . ."

Claim 14, which depends from claim 1, recites "exclusion criteria for the patient include both of: (1) active ocular inflammation; and (2) active ocular or periocular infection." Ex. 1001, 23:49–53.

Petitioner asserts that this recited subject matter should be entitled to no patentable weight under the printed matter doctrine because it is directed only to a mental step on the basis of information, i.e., deciding whether to treat a patient based on an instruction, with no functional relationship to the rest of the claimed method. Pet. 20–23.

Patent Owner argues that the printed matter doctrine does not apply and the exclusion criteria should be given patentable weight because it defines the scope of patients to be treated and requires an assessment by the clinician. Prelim. Resp. 28–30.

We determine that express construction of this claim term is unnecessary for purposes of rendering this Decision. *See Nidec Motor Corp.*, 868 F.3d at 1017.

C. APPLICABLE LEGAL STANDARDS

"In an IPR, the petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable." *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016) (citing 35 U.S.C. § 312(a)(3) (requiring *inter partes* review petitions to identify "with particularity . . . the evidence that supports the grounds for the challenge to each claim")). This burden of persuasion never shifts to Patent Owner. *See Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015) (discussing the burden of proof in *inter partes* review).

An *inter partes* review may be instituted if the information presented by Petitioner in the Petition, in view of Patent Owner's Preliminary Response and the preliminary record, shows that there is a reasonable likelihood that Petitioner would prevail with respect to at least one of the claims challenged in the Petition. 35 U.S.C. § 314.

"Anticipation requires that all of the claim elements and their limitations are shown in a single prior art reference." *In re Skvorecz*, 580 F.3d 1262, 1266 (Fed. Cir. 2009). To anticipate "it is not enough that the prior art reference discloses part of the claimed invention, which an ordinary artisan might supplement to make the whole, or that it includes multiple,

distinct teachings that the artisan might somehow combine to achieve the claimed invention." *Net MoneyIN, Inc. v. VeriSign, Inc.,* 545 F.3d 1359, 1371 (Fed. Cir. 2008). "However, a reference can anticipate a claim even if it 'd[oes] not expressly spell out' all the limitations arranged or combined as in the claim, if a person of skill in the art, reading the reference, would 'at once envisage' the claimed arrangement or combination." *Kennametal, Inc. v. Ingersoll Cutting Tool Co.*, 780 F.3d 1376, 1381 (Fed. Cir. 2015) (quoting *In re Petering*, 301 F.2d 676, 681 (CCPA 1962)).

A prior art reference without express reference to a claim limitation may anticipate by inherency. *See In re Cruciferous Sprout Litig.,* 301 F.3d 1343, 1349 (Fed. Cir. 2002). "Under the principles of inherency, if the prior art necessarily functions in accordance with, or includes, the claimed limitations, it anticipates." *Id.* (quoting *MEHL/Biophile Int'l Corp. v. Milgraum,* 192 F.3d 1362, 1365 (Fed. Cir. 1999)).

Regarding obviousness, the Supreme Court in *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398 (2007), reaffirmed the framework for determining obviousness set forth in *Graham v. John Deere Co.*, 383 U.S. 1 (1966). The *KSR* Court summarized the four factual inquiries set forth in *Graham* (383 U.S. at 17–18) that are applied in determining whether a claim is unpatentable as obvious under 35 U.S.C. § 103 as follows: (1) determining the scope and content of the prior art; (2) ascertaining the differences between the prior art and the claims at issue; (3) resolving the level of

ordinary skill in the art;[10] and (4) considering objective evidence indicating obviousness or non-obviousness.[11] *KSR*, 550 U.S. at 406.

"The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *Id.* at 416. "[W]hen the question is whether a patent claiming the combination of elements of prior art is obvious," the answer depends on "whether the improvement is more than the predictable use of prior art elements according to their established functions." *Id.* at 417.

With these standards in mind, and in view of the definition of the ordinarily skilled artisan, we address Petitioner's challenges below.

D. PETITIONER'S ASSERTED PRIOR ART

1. Dixon

Dixon is an article that indicates on its face its publication in 2009. Ex. 1006, 1573. There is currently no dispute that Dixon is prior art. *See generally* Prelim. Resp.; *see also* Pet. 26 n.4 ("the asserted prior art reference all qualify as publications that were available to—and indeed cited by—interested, skilled artisans before the '572 patent's earliest, purported priority date.").

Dixon is a review of clinical trials regarding administering VEGF Trap-Eye to treat neovascular AMD. Ex. 1006, 1573. Dixon discloses that "VEGF Trap-Eye is a novel anti-VEGF therapy, with Phase I and II trial data indicating safety, tolerability and efficacy for the treatment of neovascular AMD." *Id.* Dixon describes VEGF Trap-Eye as "a fusion

[10] *See supra* Section II.A.
[11] There is no evidence pertaining to objective indicia of non-obviousness. *See* Prelim. Resp.

protein of key binding domains of human VEGFR-1 and -2 combined with a human IgG Fc fragment." *Id.* at 1575. Dixon discloses that "VEGF Trap-Eye and aflibercept (the oncology product) have the same molecular structure, but there are substantial differences between the preparation of the purified drug product and their formulations." *Id.*

Dixon discloses that current therapy requires "frequent intraocular injections, as often, as monthly, without a defined stopping point," and that "[t]he time and financial burden of monthly injections has led to the initiation of studies to examine the efficacy of alternative dosing schedules." *Id.* at 1574, 1577. Dixon discloses that:

> [d]ue to its high binding affinity and the ability to safely inject high doses into the eye, VEGF Trap-Eye may have longer duration of effect in the eye. Two Phase III studies in wet AMD, VIEW 1 and VIEW 2, are currently under way and seek to compare monthly ranibizumab to monthly or bimonthly VEGF Trap-Eye.

Id. at 1577. Specifically, Dixon discloses that the Phase III trial initiated in August of 2007 "will evaluate the safety and efficacy of intravitreal VEGF Trap-Eye at doses of 0.5 and 2.0 mg administered at 4-week dosing intervals and 2.0 mg at an 8 week dosing interval (following three monthly doses), compared with 0.5 mg of ranibizumab administered every 4 weeks." *Id.* at 1576. Dixon discloses that in a previous Phase II trial, patients treated with monthly doses of 2.0 or 0.5 mg VEGF Trap-Eye achieved improvements according to the Early Treatment of Diabetic Retinopathy Study ("ETDRS") scale. *Id.*

2. Regeneron 2008

Regeneron 2008 is a press release by Bayer HealthCare and Regeneron dated May 8, 2008. Ex. 1009, 1. There is currently no dispute

that Regeneron 2008 is prior art. *See generally* Prelim. Resp.; *see also* Pet. 26 n.4.

Regeneron 2008 states that a "first Phase 3 trial, VIEW 1, began enrolling patients in August 2007 in the United States and Canada," and announces "that the first patient has been dosed in the VIEW 2 trial, a second Phase 3 clinical study in a development program evaluating VEGF Trap-Eye for the treatment of the neovascular form of Age-related Macular Degeneration (wet AMD)." Ex. 1009, 1. Regeneron 2008 discloses that "[b]oth VIEW 1 and VIEW 2 are designed to evaluate the efficacy and safety of VEGF Trap-Eye administered by intravitreal injection, at dosing intervals of 4 and 8 weeks" and "will include visual acuity endpoints and anatomical endpoints, including retinal thickness, a measure of disease activity. The trial is intended to establish non-inferiority of VEGF Trap-Eye with Lucentis®* (ranibizumab), an antiangiogenic agent approved for use in wet AMD in major markets globally." *Id.* Regeneron 2008 more specifically states that the VIEW2 study "will evaluate the safety and efficacy of VEGF Trap-Eye at doses of 0.5 milligrams (mg) and 2.0 mg administered at 4-week intervals and 2.0 mg at an 8-week dosing interval, including one additional 2.0 mg dose at week four." *Id.*

Regeneron 2008 discloses that in a Phase 2 trial announced in October 2007, "VEGF Trap-Eye met both primary and secondary key endpoints: a statistically significant reduction in retinal thickness (a measure of disease activity) after 12 weeks of treatment compared with baseline and a statistically significant improvement from baseline in visual acuity (ability to read letters on an eye chart)." *Id.* at 1–2.

3. NCT-795

NCT-795 discloses clinical trial information for the VIEW1 study and indicates it is the "[l]atest version (submitted December 20, 2012)," but also indicates it discloses "Changes (Merged) for Study: NCT00509795, March 3 2009 (v8) -- April 28, 2009 (v9)." Ex. 1010, 1, 3. Petitioner asserts this document "was publicly available on the ClinicalTrials.gov website prior to January 13, 2011." Pet. 30–31 (citing Ex. 1002 ¶¶ 108–116, 123; Ex. 1006, 1579; Ex. 1010, 8; Ex. 1022, 1–2, 8–11). There is currently no dispute that NCT-795 is prior art. *See Generally* Prelim. Resp.; *see also* Pet. 26 n.4.

NCT-795 describes the VIEW1 study as "a phase III, double-masked, randomized, study of the efficacy and safety of VEGF Trap-Eye in patients with neovascular age-related macular degeneration." Ex. 1011, 5. NCT-795 discloses "Experimental: 3" arm, which includes "2.0 mg VEGF Trap-Eye administered every 8 weeks (including one additional 2.0 mg dose at week 4) during the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks." *Id.* at 6. For such an experimental arm, NCT-795 discloses "Key Inclusion Criteria" and "Key Exclusion Criteria." *Id.* at 9–11.

4. NCT-377

NCT-377 discloses clinical trial information for the VIEW2 study and indicates it is the "[l]atest version (submitted November 28, 2014)," but also indicates a "Submitted Date [of] March 17, 2008 (v1)," and Petitioner asserts it "was publicly available and accessible to interested, skilled artisans prior to January 13, 2011." Ex. 1011, 1, 3; Pet. 32 (citing Ex. 1002 ¶¶ 108–123; Ex. 1006, 1579; Ex. 1011, 1–3; Ex. 1020, 95–96; Ex. 1022, 1–2, 4–7).

There is currently no dispute that NCT-377 is prior art. *See generally* Prelim. Resp.; *see also* Pet. 26 n.4.

NCT-377 describes the VIEW2 study as "phase III, double-masked, randomized, study of the efficacy and safety of VEGF Trap-Eye in patients with neovascular age-related macular degeneration." Ex. 1011, 5. NCT-377 discloses "Experimental: Arm 3," which includes "2.0 mg VEGF Trap-Eye administered every 8 weeks (including one additional 2.0 mg dose at Week 4) during the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks." *Id.* at 6. For such an experimental arm, NCT-377 discloses "Inclusion Criteria" and "Exclusion Criteria." *Id.* at 7–8.

E. PETITIONER'S PATENTABILITY CHALLENGES

As summarized above, Petitioner asserts eight grounds (with ground 5 separated into its four alternatives) for unpatentability of the claims of the '572 patent. *See supra* Section I.D; *see also* Pet. 12. We review Petitioner's challenges and Patent Owner's arguments below.

1. Anticipation by Dixon, Regeneron 2008, NCT-795, or NCT-377 (Grounds 1–4)

Petitioner's Grounds 1–4 assert the challenged claims are anticipated by each of Dixon, Regeneron 2008, NCT-795, and NCT-377. *See* Pet. 35–68. Petitioner asserts each of these prior art references in substantially similar ways against the challenged claims, Patent Owner argues against them together as a group, and the same facts and law are determinative for each of Grounds 1–4. Therefore, we address Grounds 1–4 together.

Petitioner asserts that independent claims 1, 26, and 29, as well as dependent claims 2–5, 8–11, 14, 27, 28, and 30, are anticipated by each of (individually) Dixon Regeneron 2008, NCT-795, and NCT-377. Pet. 35–68

(citing, concerning the independent claims, Ex. 1001, 2:51–56, 5:23–26, 5:30–48, 9:29–14:30 (Example 4), 23:2–14 (claim 1); Ex. 1002 ¶¶ 137–138, 140–141, 143–145, 157–168, 170–171, 174–179, 181, 183–185, 187–192, 194, 197–201; Ex. 1005, Table 1; Ex. 1006, 1573, 1575–77; Ex. 1009, 1–2; Ex. 1010, 3, 4, 8–9; Ex. 1011, 3–4, 6; Ex. 1014, 2537; Ex. 1019, 2; Ex. 1023, 3; Ex. 1026; Ex. 1030 (App'x 2); Ex. 1031, 15–16; Ex. 1032, 67, 69, 76, 81, 85). Foundationally, it is Petitioner's position that each of these references discloses the same clinical trials identified in the '572 patent at Example 4—the VIEW1 and VIEW2 trials—including the same drug (aflibercept/VEGF Trap-Eye), dose (2 mg), administration (intravitreal injection), and dosing regimen (initial, 4-week secondary, and 8-week tertiary doses) of that Example 4 and as recited by the independent claims. *Id*. This point is not currently disputed by Patent Owner. *See generally* Prelim. Resp.

Petitioner does not assert that any of Dixon, Regeneron 2008, NCT-795, and NCT-377 expressly discloses "[t]he last clause of claim 1" (and of claims 26 and 29), i.e., the *results limitations* addressed above in the Claim Construction Section of this Decision (*see supra* Section II.B.3), as the Petitioner identifies Dixon, for example, as stating, "Two Phase III studies in wet AMD [VIEW1/VIEW2] are currently under way and seek to compare monthly ranibizumab to monthly or bimonthly VEGF Trap-Eye," meaning the visual acuity gain (or maintenance) results required by the claims, including comparative results with respect to ranibizumab, were not yet established by the cited art's disclosed clinical trials or otherwise reported. Pet. 36, 38–39, 41–44, 53, 55, 60–61, 63–64 (citing Ex. 1002 ¶¶ 140–141, 145, 167, 170–171, 187–189; Ex. 1006, 1577–78 (describing

DME and RVO studies); Ex. 1008; Ex. 1010, 9; Ex. 1011, 6). Petitioner makes similar statements directed to Regeneron 2008, NCT-795, and NCT-377. *Id.* at 51, 60–61. Thus, Petitioner concedes the *results limitations* are not expressly disclosed. *Id.*

As a first position, Petitioner asserts that this lack of express disclosure matters not because the results limitations are "not given patentable weight," invoking Petitioner's claim construction arguments. *See, e.g.*, *id.* at 38. For the reasons discussed above at Section II.B.3, Petitioner's position is not persuasive because we find the *results limitations* of the claims are limitations and must be given patentable weight.

As a second position, Petitioner asserts that "even if the Board finds that this last element should be given patentable weight," which we do, "Dixon [and Regeneron 2008, NCT-795, and NCT-377] still anticipates" because the reference "inherently anticipates this element." *Id.* at 38, 50, 60. The Petition, respectively, includes two essentially identical paragraphs explaining why Dixon, and each other reference, inherently disclose the results limitations. *Id.* at 38–39, 50–51, 60–61. As an example, Petitioner asserts that

> Although final results of the phase 3 clinical trial were not reported in the literature until after the priority date of the '572 patent, Dixon's description of the trial protocol nevertheless anticipates the present claims. The Federal Circuit has "repeatedly held that 'newly discovered results of known processes directed to the same purpose are not patentable because such results are inherent.'" *In re Montgomery*, 677 F.3d [1375,] 1381 [(Fed. Cir. 2012)] (holding that clinical data obtained from a known method of administering a known

> compound to treat a known indication is not patentable because "efficacy is inherent in carrying out the claim steps.").

Id. at 38–39. Petitioner specifically cites as evidence (under Ground 1) only paragraphs 140 and 141 of Dr. Tanna's Declaration, but, for the sake of completeness, we note paragraphs 139–142 address whether Dixon inherently discloses the *results limitations*. *See* Ex. 1002 ¶¶ 139–142, 144; *see also id.* ¶¶ 163–167 (regarding Ground 2, which are essentially the same as those addressing Ground 1), ¶¶ 187–191 (regarding Grounds 3 and 4, which are also essentially the same as those addressing Ground 1).

As Dr. Tanna's testimony is substantially the same for each of Grounds 1–4 on this issue, we use Ground 1 as an example. Dr. Tanna testifies (concerning claim 1) that Dixon discloses phase 2 clinical trial results for the VEGF Trap-Eye pharmaceutical, at the same dose as in the VIEW trials and as claimed, were "favorable" and showed those patients "'achieved mean improvements of 9.0 ($p < 0.0001$) and 5.4 ($p < 0.085$) ETDRS letters with 29 and 19% gaining, respectively, ≥ 15 ETDRS letters at 52 weeks.')." *Id.* ¶ 140. Next, Dr. Tanna testifies that the phase 3 clinical trials, the VIEW 1 and 2 trials, then proceeded with "the primary outcome [being] the proportion of patients who maintain vision at week 52 (defined as a loss of < 15 ETDRS letters).')." *Id.* ¶ 141. And, finally, Dr. Tanna concludes that, "[a]lthough final results of the phase 3 clinical trial were not reported in the literature until after the priority date of the '572 patent, it is my opinion that Dixon's description of the trial protocol anticipates the present claims." *Id.* ¶ 142.

For the other independent claims 26 and 29, Dr. Tanna similarly testifies that Dixon's disclosure that the Phase 3 trials were non-inferiority studies comparing the claimed dose and regimen of aflibercept to (monthly)

0.5 mg ranibizumab treatment, where the primary outcome was "the proportion of patients to maintain vision at week 52 (defined by a loss of < 15 ETDRS letters)," sufficed to show Dixon inherently disclosed the *results limitations*. *Id.* ¶ 145 (claim chart).

Turning to Patent Owner's positions, Patent Owner argues that the asserted prior art fails to expressly or inherently disclose the "recited visual acuity" elements of the claims, or the *results limitations*, as we have termed such herein. Prelim. Resp. 30–42 (citing Ex. 1001, 10:63–12:14, 13:8–27 (Table 1); Ex. 1010, 4; Ex. 1011, 4; Ex. 1014, 1, 6, 7; Ex. 1030, 1–4, 9; Ex. 2020, 1860, Figs. 3B, 4, 5A; Ex. 2021 ¶¶ 109–111, 113–120; Ex. 2022, 1; Ex. 2023, 128:6–129:8, 132:4–133:10; *Galderma Labs, L.P. v. Teva Pharms. USA, Inc.*, 799 Fed. App'x 838 (Fed. Cir. 2020); *Allergan, Inc. v. Sandoz Inc.*, 726 F.3d, 1286 (Fed. Cir. 2013); *In re Montgomery*, 677 F.3d 1375 (Fed. Cir. 2012); *Bettcher Indus., Inc. v. Bunzl USA, Inc.*, 661 F.3d 629 (Fed. Cir. 2011); *King Pharms., Inc. v. Eon Labs, Inc.*, 616 F.3d 1267 (Fed. Cir. 2010); *Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 471 F.3d 1369 (Fed. Cir. 2006); *Perricone v. Medicis Pharm. Corp.*, 432 F.3d 1368 (Fed. Cir. 2005); *Transclean Corp. v. Bridgewood Serv., Inc.*, 290 F.3d 1364 (Fed. Cir. 2002); *Bristol-Myers Squibb Co. v. Ben Venue Labs, Inc.*, 248 F.3d 1368 (Fed. Cir. 2001); *Rapoport v. Dement*, 254 F.3d 1053 (Fed. Cir. 2001); *Glaxo Inc. v. Novopharm Ltd.*, 52 F.3d 1043 (Fed. Cir. 1995); *Cont'l Can Co. USA, Inc. v. Monsanto Co.*, 948 F.2d 1264 (Fed. Cir. 1991); *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628 (Fed. Cir. 1987); *Hospira, Inc. v. Amneal Pharms., LLC*, 285 F. Supp. 3d 776 (D. Del. 2018), *aff'd* 748 Fed. App'x 1024 (Fed. Cir. 2019); *Gilead Sci., Inc. v. United*

States, IPR2019-01456, Paper 17 (PTAB 2020); *Celltrion, Inc. v. Genentech, Inc.*, IPR2016-01667, Paper No. 15 (PTAB 2017)).

This argument is subdivided into the following more specific arguments: (1) the actual VIEW clinical trials are not prior art (Petitioner does not assert they are); (2) the VIEW trials' published results do not show the recited visual acuity outcomes are necessary results from the dosing regimen; (3) the recited results limitations are not the same (do not correspond) to the results of the clinical trials; (4) the patient population reported in the asserted prior art did not disclose the same exclusion criteria as, and taught a different patient population compared to, the invention; and (5) different doses/formulations of aflibercept produce different results. *Id.* Of these arguments, at least (2) and (4) are persuasive on the record, and we deny institution in view thereof. We discuss these below.

Patent Owner argues that Petitioner's position that the *results limitations* are inherently disclosed by Dixon (or Regeneron 2008, NCT-795, or NCT-377) is not supported by evidence that the claimed results of visual acuity gains/maintenance "necessarily result" from the prior art's disclosed dosing regimen, because the prior art "show[s] that some patients achieve the endpoint," that is, the result of "losing fewer than 15 ETDRS letters at week 52, as compared to monthly ranibizumab," "but others did not." *Id.* at 34. Patent Owner argues that the clinical trial arms directed to the claimed dosing regimen, i.e., the VIEW1 and VIEW2 2Q8 arms, are shown by the '572 patent itself to include "some patients" who received the claimed drug at the claimed dosing regimen, but did not meet the endpoint (showing a gain in visual acuity, such a gain as effective as ranibizumab treatment, or maintenance as effective as ranibizumab).

Patent Owner points to the data described in the '572 patent's Table 1, which "summarizes" "[t]he results from both [clinical trial] studies," and shows that for the 2Q8 arms, 95.1% (study 1) and 95.6% (study 2) of the patients maintained their vision at week 52, and that the "[m]ean improvement in vision" based on letters gained at 52 weeks was 7.9 (study 1) and 8.9 (study 2). *Id.* at 34–35 (citing Ex. 1001, 13:8–27). Patent Owner argues that such data shows that some patients did not meet the primary endpoint, as there was variation in patient's responses to the claimed dosing and, in both clinical trials, "the mean improvement in vision . . . was lower for the 2[Q]8 aflibercept arm as compared to the monthly ranibizumab arm." *Id.* at 35–36 (citing Ex. 1001, 13:8–27, Ex. 1014, 6–7).

Patent Owner also points to Petitioner's Exhibit 1030 (appendices disclosing criteria and results from VIEW 1 and 2 clinical trials) as evidencing that (about) 1 in 5 patients failed to show any visual acuity gains at all. *Id.* (citing Ex. 1030, 9 (Appendix 5)). Patent Owner also points to a "retrospective analysis" of the VIEW clinical trials as evidencing that in some patients "approximately 20% of eyes treated with aflibercept and 30% of eyes in the monthly ranibizumab arm—2q8 aflibercept resulted in worse visual acuity results compared to those receiving monthly ranibizumab or aflibercept." *Id.* at 36–37 (citing Ex. 2020, 1860, Figs. 3B, 4, 5A; Ex. 2021 ¶¶ 109–111; Ex. 2022, 1). This retrospective analysis concluded that some patients required a different, more frequent, dosing regimen than claimed for clinical benefits and that some patients could expect a loss of letters in visual acuity testing when dosed as claimed. *See* Ex. 2020, 1856 (Abstract), 1863.

Patent Owner correctly argues that "inherency . . . 'may not be established by probabilities or possibilities.'" *Id.* at 37 (citing *Gilead*,

IPR2019-01456, at 42; *Bettcher Indus.*, 661 F.3d at 639). Based on the above, Patent Owner argues that, whether measuring absolute visual acuity (claim 1) or comparing the claimed treatment dosing regimen to monthly ranibizumab (claims 26 and 29), "visual acuity outcomes vary by patient, [which] show[s] the Visual Acuity [*results*] *limitations* are not inherently met" by Dixon (or the other references). *Id.* (italics added). Patent Owner points out that Petitioner does not (substantively) address this issue. *Id.*

In a related argument, Patent Owner contends that the patient population disclosed in Dixon's report (and Regeneron 2008's, NCT-795's, and NCT-377's reports) on the VIEW clinical trials did not exclude certain subpopulations that the '572 patent describes as excluded in the invention's dosing regimens. *Id.* at 40 (citing Ex. 1001, 10:63–12:14; Ex. 2021 ¶ 113). Patent Owner argues that the potential patient populations described in the '572 patent as excluded from the treated-patient population to achieve the reported (and claimed) results, including those with a history of uveitis, a prior trabeculectomy or other filtration, and patients with a history of aphakia or pseudophakia, "can be expected to clear injected drugs more quickly" than other patients, which means that doses every 8 weeks as claimed would likely result in lower efficacy and a decreased likelihood of meeting the results limitations of the claims. *Id.* (citing Ex. 2021 ¶¶ 114–120; Ex. 2023, 128:6–129:8, 132:4–133:10; *Gilead*, IPR2019-01456, at 42 n.26). Patent Owner's point is that, because the specific patients being treated in the prior art disclosure and those treated as described in the '572 patent (Example 4) may not have been the same, and because the evidence shows that certain of the invention-excluded patients could be expected to experience inferior results compared to others, the results from the claimed

treatment regimen could not be expected to necessarily always occur; to the contrary, the results would be expected to be different for some patients and the prior art does not evidence otherwise; therefore, "preclude[ing] a finding of inherency." *Id.* Patent Owner correctly points out that this issue is not (substantively) addressed by Petitioner, even though Petitioner submits evidence that supports Patent Owner's position. *Id.* (citing Ex. 1030, 1–4).

As we noted above, we are persuaded by Patent Owner's arguments. As an initial matter, we find Petitioner has insufficiently addressed the issue of inherent anticipation by Dixon (or any other prior art) and has done so in a merely conclusory manner.

There is no dispute that Dixon (as well as the other asserted prior art) discloses angiogenic eye disorder treatment using the same drug (aflibercept), at the same dose (2 mg), administered in the same way (intravitreal injection), and administered at the same dosing regimen (an initial, a secondary, and a tertiary dose), as required by all challenged claims. *See generally* Pet.; Prelim. Resp. Petitioner relies on these facts, and the results of a phase 2 clinical trial that followed a different dosing protocol (one not claimed) to establish that the *results limitations* of claims 1, 26, and 29 are inherent to the phase 3 clinical trials (VIEW 1 and 2) with a dosing regimen that is claimed. *See* Pet. 38–39. Petitioner calls the claimed *results limitations* mere newly discovered results of a known process. *Id.* (citing *Montgomery*, 677 F.3d at 1381).

As Patent Owner identifies, it is not so simple. The evidence of the results of the VIEW 1 and 2 trials itself (found in the '572 patent) shows that some, but not all, patients treated with the claimed dosing regimen achieved "*a gain in visual acuity*" as recited by claim 1, "*a gain in visual acuity*" that

is "*as effective*" "*as monthly administration of 0.5 mg of ranibizumab*" as recited by claim 26, or "*maintaining visual acuity*" "*as effective[ly]*" "*as monthly administration of 0.5 mg of ranibizumab*" as recited by claim 29. *See* Ex. 1001, 13:5–38 (Table 1). As Patent Owner points out, the '572 patent's described studies 1 and 2, when following the claimed dosing regimen (2Q8), were not always effective treatments—achieving mere maintenance (as opposed to improvement or "gains") of vision 95.1% and 95.6% (respectively) of the time. *Id.*; *see* Prelim. Resp. 34–37 (citing Ex. 1001, 13:8–27; Ex. 1014, 4, 6; Ex. 1030, 9; Ex. 2021 ¶¶ 109–111; Ex. 2022).

Thus, the evidence shows that, although most would, about 4–5% of patients (or, possibly, an even higher number based on Patent Owner's cited evidence—Ex. 1030, 9) would *not* see the *gains* in visual acuity required by claims 1 and 26 or the *maintenance* in visual acuity required by claim 29. It is well established that "[i]nherency . . . may not be established by probabilities or possibilities" and "[t]he mere fact that a certain thing may result from a given set of circumstances is not sufficient." *In re. Oelrich*, 666 F.2d 578, 581 (CCPA 1981) (quoting *Hansgirg v. Kemmer*, 102 F.2d 212, 214 (CCPA 1939)). Here, the evidence shows that the claimed *results limitations* may *typically* flow from the claimed method, but not *necessarily*.

We also agree with Patent Owner that the treated patient population described in the '572 patent as achieving the claimed results and the patient population of the clinical trials disclosed by Dixon, Regeneron 2008, NCT-795, and NCT-377, if such references disclose any particular patients at all, are not identical, that some patients (not mentioned by the prior art)

would be expected to *not* achieve the claimed gains or maintenance results, and that this matters to our inherency analysis.

Petitioner asserts "Dixon also discloses pertinent details regarding Phase 3 trials (VIEW1/VIEW2) and the dosing regimens used therein. *Id.*, 1573, 1575-76, 1579 (Bibliography Nos. 46-47); Ex.1002, ¶¶136-138," and also "the promising results of the Phase 2 CLEAR-IT-2 study of VEGF Trap-Eye in AMD. Ex.1006, 1576." Pet. 27. Moreover, Petitioner asserts "Regeneron (8-May-2008) reports VIEW1/VIEW2 Phase 3 AMD trials and sets out the dosing regimen encompassed by the Challenged Claims" and "also reports that '[r]esults from the Phase 2 study have shown that VEGF Trap-Eye has the potential to significantly reduce retinal thickness and improve vision.' Ex.1009, 1; Ex.1002, ¶158." Pet. 28–29. And further, Petitioner asserts regarding the NCT-795 and NCT-377 publications that they "disclose[] Regeneron's Phase 3 VIEW1 trial. Ex.1010, 3-5. Specifically, NCT-795 discloses the treatment arms of the VIEW1 [and VIEW2] study, including the every-8-week treatment regimen: '2.0 mg VEGF Trap-Eye administered every 8 weeks (including one additional 2.0 mg dose at week 4) during the first year.' Ex.1010, 4-5, 8; Ex.1002, ¶¶184-185." Pet. 31–33 (also citing Ex. 1011, 5–6).

Petitioner is clear that the phase 2 clinical trial (called "CLEAR-IT-2"), cited for its promising results indicating the potential to improve vision with aflibercept, did not apply the claimed dosing regimen for the drug. Pet. 26 ("Monthly or quarterly doses through wk-12, followed by PRN"). Petitioner and Dr. Tanna are also clear that "final results of the phase 3 clinical trial were not reported in the literature until after the priority date of the '572 patent." Ex. 1002 ¶¶ 142, 165, 188. Therefore, the

evidence Petitioner relies upon to conclude that the claimed *results limitations* naturally and necessarily flow from the asserted prior art's (the VIEW 1 and 2 clinical trials) dosing regimen is merely the fact that the phase 3 trials used the same drug, dose, administration method, and dose timing of the claims, and that a different dosing regimen with that drug was promising. *See id.* ¶¶ 139–143, 163–164, 187–188 (note, Dr. Tanna does not cite any other evidence beyond Dixon, Regeneron 2008, NCT-795, and NCT-377 to support that the *results limitations* of the independent claims are inherent); *see also* Pet. 38–39, 50–51, 60–61 (constituting all of Petitioner's assertions and citations to supporting evidence on the inherency of the *results limitations* of the independent claims).

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

Further, there is evidence that the patient population treated in the VIEW 1 and 2 clinical trials reported by Dixon, Regeneron 2008, NCT-795, and NCT-377 was not necessarily the same as the patient population described in the '572 patent where visual acuity gains or maintenance results were described, and this evidence also supports that selection and exclusion criteria for patient populations matters for expected results. Dixon and Regeneron 2008 do not specify any patient populations treated with aflibercept. Ex. 1006; Ex. 1009. NCT-795 and NCT-377 do. However, as Patent Owner argues, certain conditions, such as uveitis, a prior

trabeculectomy, or aphakia, cause patients to clear injected drugs (in the eye) more quickly than other patients and a dosing regimen as claimed (8-week tertiary doses) may result in lower efficacy. Prelim. Resp. 40 (citing Ex. 1001, 10:63–12:14, Ex. 2021 ¶¶ 113–120; Ex. 1030, 1–4; Ex. 2023, 128:6–129:8, 132:4–133:10). These conditions are described in the '572 patent as reasons certain patients were excluded from treatment (*see* Ex. 1001, 10:63–12:14), a fact validated by witness testimony in related proceedings (Ex. 2021 ¶¶ 113–120; Ex. 2023, 128:6–129:8, 132:4–133:10); however, none of the asserted prior art mentions these conditions or the possibility that they will result in less effective treatment (Ex. 1006; Ex. 1009; Ex. 1010; Ex. 1011). Such patients were not identified as excluded in the trials disclosed by NCT-795 and NCT-377. *See* Ex. 1010; Ex. 1011.

These facts further illustrate that the claimed *results limitations* (visual acuity gains or maintenance) do not necessarily occur just by following the claimed dosing regimen disclosed in the prior art. *See Perricon*, 432 F.3d at 1376–79 (if providing the claimed treatment may have different results based upon the specific patient (with or without sunburn) treated, the results are not inherent). There is evidence of potential variance in results based on patients generally and patient populations specifically, which negates the inherency of the *results limitations*. Thus, for such reasons also, are not persuaded that the asserted prior art's disclosure of the same dosing regimen as claimed would necessarily lead to the claimed *results limitations* of independent claims 1, 26, and 29.

For the reasons above, we determine that Petitioner has not established a reasonable likelihood that it would prevail in showing that

claims 1, 26, and 29 are unpatentable as anticipated by Dixon, Regeneron 2008, NCT-795, or NCT-377.

The challenge to dependent claims 2–5, 8–11, 14, 27, 28, and 30 depends on Petitioner first establishing that independent claims 1, 26, and 29 are anticipated by the prior art, and we are unpersuaded that Petitioner's contentions on these dependent claims make up for the deficiencies discussed above. Pet. 44–48, 54–58, 65–68; *Alcon Research, Ltd. v. Apotex Inc.*, 687 F.3d 1362, 1367 (Fed. Cir. 2012) ("It is axiomatic that a dependent claim cannot be broader than the claim from which it depends."). Thus, we also determine that Petitioner has not met its burden in establishing a reasonable likelihood that it would prevail in establishing the challenged dependent claims are unpatentable under 35 U.S.C. § 102.

2. Obviousness (Grounds 5a–5d)

Under Grounds 5a–5d Petitioner asserts that combining the teachings of Hecht with any of Dixon, Regeneron 2008, NCT-795, and NCT-377, respectively, renders dependent claims 6, 7, 12, and 13 obvious. Pet. 69–71. Petitioner asserts that "[c]laims 6 and 1[2] require that the 'aflibercept is formulated as an isotonic solution,'" and that "[c]laims 7 and 13 require that the 'aflibercept is formulated with a nonionic surfactant.'" *Id.* at 69; *see* Ex. 1001, 23:28–31, 23:45–48. Petitioner cites Hecht for teaching such "unremarkable limitations," and no more. Pet. 69–71. Petitioner does not address other claim limitations under Grounds 5a–5d, except to state that "each of Dixon, Regeneron (8-May-2008), NCT-795, and NCT-377 discloses each and every element of the claims upon which claims 6, 7, 10, and 13 depend." *Id.* at 69.

For the same reasons set forth above concerning the asserted prior art's failure to inherently disclose the *results limitations* of the challenged claims (limitations which are incorporated into these challenged dependent claims), we find the prior art also fails to render dependent claims 6, 7, 12, and 13 obvious. These dependent claims require the *results limitations*, Petitioner does not assert that such would have been obvious over any asserted prior art, and we do not discern that Petitioner shows Hecht remedies the shortcomings of the other prior art, as discussed above.

For the reasons above, we determine that Petitioner has not established a reasonable likelihood that it would prevail in showing that claims 6, 7, 12, and 13 are unpatentable.

III. CONCLUSION

Petitioner does not demonstrate a reasonable likelihood of prevailing at trial in showing that any of claims 1–14 and 26–30 of the '572 patent is unpatentable over the cited prior art. Our decision derives from our review of the preliminary record before us. Accordingly, we do not institute *inter partes* review of the '572 patent on the grounds asserted by Petitioner. This decision does not reflect a final determination on the patentability of the claims.

ORDER

Accordingly, it is hereby:

ORDERED that the Petition is denied and we do not institute *inter partes* review of any claim of the '572 patent based on the grounds asserted in the Petition.

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