

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SAMSUNG BIOEPIS CO., LTD.,
Petitioner,

v.

REGENERON PHARMACEUTICALS, INC.,
Patent Owner.

Case IPR2023-00442

U.S. Patent No. 10,130,681

**PETITIONER'S REPLY TO
PATENT OWNER'S RESPONSE**

TABLE OF CONTENTS

I.	INTRODUCTION	1
II.	CLAIM CONSTRUCTION	2
	A. The Board Should Apply Collateral Estoppel to Its Construction of the “Method of Treating” Term	2
	B. Consistent with the Board’s Prior Decisions, the Challenged Claims Do Not Require Efficacy	4
	1. There Is No Support for “High Level of Efficacy” Comparable to Monthly Lucentis and Avastin.....	4
	2. Patent Owner’s Cases on “Treat” Support Petitioner’s Position.....	5
	C. Exclusion Criteria 2 and Exclusion Criteria 3.....	7
III.	THE CHALLENGED CLAIMS ARE OBVIOUS	9
	A. The CATT, MACTEL, and/or PIER Studies Render the Claimed Exclusion Criteria Obvious	9
	1. MACTEL and CATT Studies Either Alone or In Combination Render Obvious EC3	10
	2. A POSA Would Have Been Motivated to Look to the Exclusion Criteria of Prior Clinical Trials of Available Intravitreal Injectables, including MACTEL and CATT Studies.....	14
	B. Dixon Discloses the Claimed Q8 Dosing.....	18
	1. Dixon Discloses the Claimed Sequences.....	19
	(a) The Board Should Apply Collateral Estoppel.....	19
	(b) Dixon Discloses the Claimed Sequences	19
	2. A POSA Would Have a Reasonable Expectation of Success	20
IV.	NO SECONDARY CONSIDERATIONS SUPPORT NON- OBVIOUSNESS OF THE CHALLENGED CLAIMS.....	23
V.	CONCLUSION.....	26

TABLE OF AUTHORITIES

	<u>Page</u>
<u>Cases</u>	
<i>Amneal Pharms. LLC v. Jazz Pharms. Ireland Ltd.</i> , No. IPR2016-00546, 2016 WL 5222883 (P.T.A.B. July 28, 2016).....	18
<i>B&B Hardware, Inc. v. Hargis Indus.</i> , 575 U.S. 138 (2015).....	2, 3
<i>In re Chapman</i> , 595 F.3d 1330 (Fed. Cir. 2010)	17
<i>In re Fulton</i> , 391 F.3d 1195 (Fed. Cir. 2004)	15
<i>Galderma Lab'ys, L.P. v. Tolmar, Inc.</i> , 737 F.3d 731 (Fed. Cir. 2013)	14
<i>Helsinn Healthcare S.A. v. Dr. Reddy's Lab'ys</i> , No. 14-4274, 2018 WL 623642 (D.N.J. Jan. 30, 2018)	21
<i>Hoffmann-La Roche Inc. v. Apotex Inc.</i> , 748 F.3d 1326 (Fed. Cir. 2014)	20, 22
<i>Infineum USA L.P. v. Chevron Oronite Co. LLC</i> , No. 2020-1333, 2022 WL 3147683 (Fed. Cir. Aug. 8, 2022)	15
<i>Medtronic Inc. v. Teleflex Life Sciences Limited</i> , IPR2020-01343 (February 23, 2022).....	2, 3, 9, 19
<i>Merck & Co. v. Teva Pharms. USA, Inc.</i> , 395 F.3d 1364 (Fed. Cir. 2005)	24
<i>Mobile Tech, Inc. v. Invue Security Prods. Inc.</i> , IPR2018-00481, Paper 29 (PTAB July 16, 2019)	3
<i>Pfizer Inc. v. Sanofi-Aventis Deutschland GmbH</i> , IPR2019-00979, POR, 93 (P.T.A.B. Aug. 11, 2020)	25

<i>Prometheus Lab ’ys, Inc. v. Roxane Lab ’ys,</i> 805 F.3d 1092 (Fed. Cir. 2015)	24
<i>Sanofi Mature IP v. Mylan Lab ’ys. Ltd.,</i> 757 F. App’x 988 (Fed. Cir. 2019)	6
<i>Vanda Pharmaceuticals, Inc. v. Teva Pharmaceuticals USA, Inc.,</i> 2022 WL 17593282 (D. Del. 2022).....	21
<i>Volvo Penta of the Americas, LLC v. Brunswick Corp.,</i> 81 F.4th 1202 (Fed. Cir. 2023)	23

Statutes

35 U.S.C. § 315(e)(1).....	4
----------------------------	---

Other Authorities

37 C.F.R. § 42.1(b)	4
Institution Decision, Paper 10.....	17, 18
Restatement (Second) of Judgments	2, 3

TABLE OF EXHIBITS

Exhibit	Description
1001-1063	<i>Previously presented.</i>
1064	Board's May 11, 2023 Email
1065	Declaration of Zachariah Summers in Support of Motion for Admission <i>Pro Hac Vice</i>
1066	Declaration of Elliot Choi in Support of Motion for Admission <i>Pro Hac Vice</i>
1067	Declaration of Sarah M. Cork in Support of Motion for Admission <i>Pro Hac Vice</i>
1068	Final Written Decision in <i>Mylan Pharmaceuticals Inc. v. Regeneron Pharmaceuticals, Inc.</i> , IPR2022-01225 [Paper 96] (“’681 FWD”)
1069	Videotaped Deposition Transcript of Diana Do, M.D. dated June 2, 2023, submitted in IPR2022-01225 and IPR2022-01226 on June 28, 2023 [Ex. 1109]
1070	Videotaped Deposition Transcript of Diana V. Do, M.D. dated December 8, 2023
1071	Eligibility Criteria for ANCHOR Study, Appendix to Ex. 2108, available at: https://www.nejm.org/doi/suppl/10.1056/NEJMoa062655/suppl_file/nejm_brown_sal.pdf
1072	Eligibility Criteria for MARINA Study, Appendix to Ex. 2109, available at: available at https://www.nejm.org/doi/suppl/10.1056/NEJMoa054481/suppl_file/nejm_rosenfeld_sal.pdf
1073	Videotaped Deposition Transcript of Dr. David M. Brown dated December 13, 2023
1074	Videotaped Deposition Transcript of David Brown, M.D. dated May 17, 2023, submitted in IPR2022-01225 and IPR2022-01226 on June 28, 2023 [Ex. 1110]
1075	Videotaped Deposition Transcript of Richard Manning, Ph.D. dated June 1, 2023, submitted in IPR2022-01225 and IPR2022-01226 on June 28, 2023 [Ex. 1121]
1076	Videotaped Deposition Transcript of Richard Manning, Ph.D. dated December 12, 2023
1077	Videotaped Deposition Transcript of Richard Manning, Ph.D. dated May 4, 2022, submitted in IPR2021-00881 on May 27, 2022 [Ex. 1151]

1078	Eylea Label 2016 available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/125387s051lbl.pdf
1079	Regeneron 2022 Press Release, available at: https://investor.regeneron.com/news-releases/news-release-details/regeneron-receives-six-months-us-pediatric-exclusivity-eylea#:~:text=(NASDAQ%3A%20REGN)%20today%20announced,months%20through%20May%2017%2C%202024%20.
1080	International Nonproprietary Names for Pharmaceutical Substances (INN), 20 WHO DRUG INFORMATION 118 (2006)
1081	Videotaped Deposition Transcript of Alexander Klibanov, dated December 20, 2023

I. INTRODUCTION

The Challenged Claims are directed to methods for treating an angiogenic disorder comprising intravitreally administering aflibercept on an 8-week extended dosing regimen after three initial monthly doses (“2Q8 Dosing Regimen”) that are disclosed in Dixon. The Challenged Claims further comprise three exclusion criteria directed to reducing the risk associated with intravitreal injections of any drug.

The 2Q8 Dosing Regimen has been the focus of two related *inter partes* review proceedings before the Board. Exs.1004, 1068. In both proceedings, the Board determined that the 2Q8 Dosing Regimen was disclosed by the Dixon reference, and that the preamble of the Challenged Claims does not require a particular level of efficacy. Nothing has changed here, and the only question to resolve is whether the exclusion criteria—which require excluding patients with current or recent infections and inflammation—are an obvious addition to the claims. They are.

The claimed exclusion criteria are basic safety precautions designed to minimize known risks associated with intravitreal injections. As demonstrated by the prior art exclusion criteria for studies of the major intravitreally injected drugs at the time, POSAs recognized that the presence of active or recent infection or inflammation would further increase the risk of injection complications due to heightened bacterial load. Accordingly, POSAs would have found obvious to adopt

the claimed exclusion criteria to achieve the best treatment and safety outcome for patients.

As set forth in the Petition and below, Patent Owner's arguments to the contrary are legally and factually unsupported, premised on incorrect claim constructions, and reliant on artificial distinctions not recognized in the art. The Board should cancel the Challenged Claims as obvious.

II. CLAIM CONSTRUCTION

A. The Board Should Apply Collateral Estoppel to Its Construction of the "Method of Treating" Term

"When an issue of fact or law is actually litigated and determined by a valid and final judgment, and the determination is essential to the judgment, the determination is conclusive in a subsequent action between the parties, whether on the same or a different claim." *B&B Hardware, Inc. v. Hargis Indus.*, 575 U.S. 138, 148 (2015) (quoting Restatement (Second) of Judgments § 27). "It is well-established that a final written decision issued by the Board can trigger collateral estoppel in subsequent PTAB trials." *Medtronic Inc. v. Teleflex Life Sciences Limited*, IPR2020-01343 (February 23, 2022, Paper 85 at 67) ("Medtronic")(J. Paulrag concurring).

Every requirement of collateral estoppel is met here. The prior '681 FWD addressed the identical claim construction issue, that issue was both actually litigated and necessary to the final determination, and Patent Owner was fully represented.

Indeed, Patent Owner has had multiple opportunities to litigate the construction of the '681 patent preamble, which is identical to the '338 patent preamble. Patent Owner's arguments have been rejected by the Board at least twice already, and should be collaterally estopped here.

Patent Owner is likely to argue that it will appeal the '681 FWD and therefore the '681 FWD is not sufficiently final. But, while unresolved by the PTAB (*Medtronic*, IPR2020-01343, at 31, 71), the weight of authority holds that collateral estoppel applies once a court or agency issues a final decision, regardless of possible appeals. *Id.*, 71 (collecting cases). Indeed, the Board has recognized that “[t]he fact that an appeal is pending does not prevent the application of collateral estoppel,” though it has generally declined to apply it out of an “abundance of caution.” *Mobile Tech, Inc. v. Invue Security Prods. Inc.*, IPR2018-00481, Paper 29 at 33 (PTAB July 16, 2019).

Additionally, the Supreme Court regularly turns to Restatement (Second) of Judgments when analyzing collateral estoppel. *B&B Hardware, Inc.*, 575 U.S. at 148. The Restatement explains: that “‘final judgment’ includes any prior adjudication of an issue in another action that is determined to be sufficiently firm to be accorded conclusive effect.” Restatement (Second) of Judgments § 13. Finding that a FWD is sufficiently final also is consistent with the IPR estoppel

statute, which attaches estoppel following “a final written decision,” not after all appeals are exhausted. 35 U.S.C. § 315(e)(1).

Confirming the application of collateral estoppel would be consistent with “secur[ing] the just, speedy, and inexpensive resolution of every proceeding.” 37 C.F.R. § 42.1(b). The Board and parties should not need to relitigate the construction of the ’681 patent preamble to conclusion again.

B. Consistent with the Board’s Prior Decisions, the Challenged Claims Do Not Require Efficacy

Even if collateral estoppel does not apply, there is no reason for the Board to depart from its prior construction of the “treating” term in the ’338 and 681 FWDs. The Board correctly found that the plain and ordinary meaning of the term “treating” does not require a specific level of efficacy—just that the method be administered *for the purpose of* providing an improvement of or beneficial effect. Ex.1068, 33-37; Ex.1004, 17-23. Patent Owner’s proposed “high level of efficacy” construction would require “improperly importing limitations into the claims.” *Id.* Below Petitioner briefly addresses Patent Owner’s arguments, which are substantively identical to those rejected by the Board in the ’681 and ’338 FWDs.

1. There Is No Support for “High Level of Efficacy” Comparable to Monthly Lucentis and Avastin

There is no support for Patent Owner’s construction requiring a high level of efficacy comparable to monthly Lucentis and Avastin. The Challenged Claims do

not mention “efficacy,” and the term “a high level of efficacy” is mentioned only once in the “Background” section of the specification, without further definition or guidance for a POSA to determine, measure, or distinguish what constitutes “a high level of efficacy.” *See* Ex.1001, 1:55-62. Moreover, the claims do not specify the dosage amount, and the specification broadly discusses a range of doses some of which do not produce a “high degree of efficacy” or any detectable improvement *Id.*, 6:29-7:14; Ex.1002, ¶¶84-88; Pet., 19-22.

Patent Owner also fails to explain what a “high level of efficacy” across each of the angiogenic eye disorders covered by the claims would be. For instance, Patent Owner’s expert Dr. Do could not define which of the VIEW subjects had received “highly effective” treatment and which had not; she also could not specify the standard of care for disorders such as diabetic retinopathy that were not yet approved for treatment with an anti-VEGF agent. Ex.1069, 125:22-25; 116:7-117:4; *see also*, Ex.1070, 61:25-62:18; 72:10-73:1.

2. Patent Owner’s Cases on “Treat” Support Petitioner’s Position

Stymied by the lack of support in the specification and art, Patent Owner instead argues that courts “have consistently found” that claims with limiting “method for treating” preambles “require *effective* treatment.” POR., 9. That is incorrect, and Patent Owner’s cases in fact support requiring only a *purpose* to treat.

For instance, in *Eli Lilly & Co. v. Teva Pharms. Int’l GmbH*, the only issue was whether the preamble was limiting. 8 F.4th 1331 (Fed. Cir. 2021). The Federal Circuit affirmed the Board’s finding that the preamble, which recited “a method for treating” headache or vasomotor symptoms, required an “intended ***purpose***” that would not be met by “the performance of the same method step to treat other conditions”—i.e. that lacked that purpose. *Id.*, 1343. But, despite the body of the claims referring to an “effective amount” being administered, the Federal Circuit affirmed the Board’s finding “that while the claims encompass a clinical result, ***they do not require such a result.***” *Id.* (emphasis added). *See also Sanofi Mature IP v. Mylan Lab’ys. Ltd.*, 757 F. App’x 988, 993 (Fed. Cir. 2019) (holding “the preamble expresses the ‘intentional ***purpose***—increasing survival—for which the method must be performed” but not requiring specific level of efficacy).

And in *Manning v. Paradis*, the preamble of an interference count specifically recited “an amount effective to deliver oxygen to the heart,” distinguishing the case from the preamble here. 296 F.3d 1098 (Fed. Cir. 2002). Notably, consistent with the Board’s construction in the ’681 FWD, the Federal Circuit recognized that the plain meaning of the word “‘treat’ requires that the invention of the count is used to ***seek or*** to achieve a therapeutic effect.” *Id.*, 1103.

C. Exclusion Criteria 2 and Exclusion Criteria 3

Petitioner proposed three plain and ordinary meanings for the conditions recited in the exclusion criteria in its Petition including “active, on-going infection in or on the eye” for exclusion criteria 2 (“EC2”) and “recent infection within the prior two weeks” for exclusion criteria 3 (“EC3”). Pet., 23; Ex.1002, ¶¶91-93.

Patent Owner argues, however, that the Board should replace the word “any” used in EC3 with the word “resolved,” thereby limiting EC3 to only recent infections that are “no longer active at the time of treatment.” POR, 18-21. Patent Owner also argues on the basis of its incorrect claim construction that Petitioner’s expert, Dr. Chaum, misinterpreted and misapplied the claims. Patent Owner is incorrect on both counts.

Patent Owner’s construction is contrary to plain language and unsupported by the specification. EC3 applies to “*any* ocular or periocular infection” within the prior two weeks—not “resolved” infections only (whatever “resolved” means). And Patent Owner’s only alleged support in the specification is the repetition of these two exact criteria as part of a broader list—nothing more. Interjecting “resolved” into the claims thus interjects ambiguity, as there is no guidance in the specification as to what “resolved” means in context.

Patent Owner’s construction also unnecessarily interjects an artificial distinction between “active” and “resolved” into the claims. POSAs were not

concerned with “active” versus “resolved” infections, but, as the claims reflect, with active infections or “any” other infection that might present a heightened risk of complications when giving an intravitreal injection—in particular, endophthalmitis. Ex.1002, ¶¶59-66, 146-160; Ex.2384, 123:11-125:8, 135:15-136:10. EC2-3, read in conjunction, reflect that concern, teaching that patients with the potential for increased bacterial flora on their eye surface—i.e. those with active infections or any infection at all in the past two weeks—should be excluded from treatment, so that there is a lower risk of carrying that bacteria into the eye. *Id.*

In particular, as Dr. Chaum explains and Patent Owner’s expert agrees, POSAs assessed for and excluded active and recent infections—whether or not they were “resolved”—by a variety of means, including physical examination and review of medical history before proceeding with any intravitreal injections. Ex.2056, ¶¶111-112; Ex.1002, ¶¶146-147; Ex.1070, 27:10-29:34:10, 186:20-187:6, 200:4-201:18; Ex.2384, 125:16-25, 135:15-136:10, 233:22-234:5. The purpose was to avoid eyes that might have a higher bacterial load and thus a higher risk of complications. *Id.* That is how the claims should be understood, and that is how Petitioner and its expert applied them.

Patent Owner’s reference to Dr. Chaum’s testimony implying EC2-3 are “substantially the same” is thus taken out of context. POR, 18. In referring to EC2 and EC3 as “substantially the same,” Dr. Chaum was simply making the observation

about the alignment of the two exclusion criteria with the standard of care: “And the presence of infection, whether it's active or recent, puts that patient at risk for increased risk of infection. Therefore, ... I would think of those two concepts of recent infection and active infection in a similar fashion they both put the patient at risk and would be a contraindication to potential treatment.” Ex.2384, 123:11-19. Dr. Chaum’s testimony is consistent with the claims and does not ignore EC2 as Patent owner alleges.

III. THE CHALLENGED CLAIMS ARE OBVIOUS

As the Board has found in prior decisions, Dixon discloses the claimed dosing steps, aflibercept molecule sequences, and every element of dependent claims. Pet., 32-42; Exs.1004 and 1068. Even if those findings are not given collateral estoppel effect, the Board should deem them “highly relevant” as it has in the past. *Medtronic*, IPR2020-01343, at 31, 71.

The primary question presented here is whether excluding patients with current or recent infections or inflammation from treatment was obvious. It was. While Patent Owner launches a kitchen sink’s worth of collateral attacks on the petitioned ground, none of them address this core question.

A. The CATT, MACTEL, and/or PIER Studies Render the Claimed Exclusion Criteria Obvious

Petitioner showed, and Patent Owner does not dispute, that the CATT, MACTEL, and/or PIER Studies disclose EC1 and EC2. POR, 32-52; Pet. 41-44.

Patent Owner argues only that EC3 was not obvious. Patent Owner’s arguments ignore the standard of care and introduce unsupported readings of the claims and prior art.

1. MACTEL and CATT Studies Either Alone or In Combination Render Obvious EC3

The MACTEL and CATT Studies, either alone or in combination render obvious excluding “any ocular or periocular infection within the last 2 weeks prior to treatment” as shown below.

Table 1	
EC3	Prior Art Exclusion Criteria Relied on by Petitioner for EC3
“(3) any ocular or periocular infection within the last 2 weeks prior to treatment” – i.e. a recent infection anywhere on/in or surrounding the eye.	<i>“History within the past 30 days of a chronic ocular or periocular infection (including any history of ocular herpes zoster)” and “[c]urrent acute ocular or periocular infection.”</i> Exs. 1032-33. “Active or <i>recent (within 4 weeks) intraocular inflammation</i> (grade trace or above) in the study eye.” Ex. 1031.

For instance, the MACTEL Study’s exclusion of patients with a “history” of a chronic infection within the past 30 days would exclude any infection in the past 14 days that was present long enough to be considered “chronic” (or had otherwise reoccurred). Additionally excluding “acute” infections would necessarily exclude

any other infections that had presented within the weeks immediately before treatment (i.e. generally one to three weeks) whether resolved or ongoing through treatment. Pet. 42-47; Ex.1002, ¶¶141-149; Exs.1023-1024. Similarly, the CATT Study excludes patients with “[r]ecent (within 4 weeks) intraocular inflammation (grade trace or above) in the study eye.” Ex. 1002, ¶¶137-139. As explained by Dr. Chaum, intraocular inflammation is a “hallmark” indicator for ocular and periocular infections. *Id.*, ¶¶138-139; *see e.g.* Ex. 1018, 1394. Patent Owner’s experts, Drs. Do and Brown, admit as much. *See*, Ex. 1017, 62; Ex. 2056, ¶158.

Patent Owner argues the criteria do not specifically exclude “resolved” (or “prior”) acute periocular infections and thus do not render EC3 obvious. POR, 45-50. Specifically, Patent Owner argues that while MACTEL excludes ocular and periocular acute infections, and recent chronic infections, it allegedly does not exclude recent resolved acute infections. *Id.*, 45-48. And, while CATT discloses excluding recent (including “resolved”) infections causing intraocular inflammation, Patent Owner argues some resolved periocular infections allegedly would not cause inflammation and thus not be excluded. *Id.*, 48-50.

First, Patent Owner is wrong regarding MACTEL. Read in conjunction, MACTEL’s criteria teach excluding both chronic infections and acute infections that presented in the prior 1-3 weeks. Pet., 42-47; Ex.1002, ¶¶140-149; Ex.1070, 175:17-24, 185:3-5, 186:20-187:6. A POSA would understand this to teach excluding “any”

infection presenting in the prior two weeks (whether or not resolved). *Id.* This understanding is also bolstered further by CATT’s teaching to exclude any patient with intraocular inflammation—a hallmark of infection—within the prior four weeks. *Id.*; Ex. 1017, 62; Ex. 2056, ¶158.

Second, Patent Owner argues that the CATT Study permits treatment of patients with a recent history of periocular infection (but not ocular infection) because Patent Owner alleges periocular infection does not manifest as intraocular inflammation. POR, 48-49. But even if Patent Owner was correct (it is not (*see* Ex. 1002, ¶¶138-139)), a POSA would have evaluated both inflammation and infection as part of the standard care because intravitreal injections necessarily involve penetrating both ocular and periocular structures. Ex.1002, ¶151-153; Ex.2384, 117:23-118:10. Thus, even if it does not use the exact language of the claims, a POSA reading the CATT Study exclusion criterion would therefore have found it obvious to exclude not only ocular infection (based on exclusion of intraocular inflammation), but also periocular infection based on the POSAs understanding of the injection procedure and associated risk of complications.¹ Pet., 46-47; Ex.1002,

¹ Patent Owner’s contention that the rationale for excluding historical inflammation is different from the rationale for excluding historical infection in the

¶¶65, 140-148. Indeed, the MACTEL and PIER Studies show that it was well known to evaluate a patient for both intraocular and periocular conditions prior to injecting intravitreally. Ex.1032, 4; Ex.1033, 2-3; Ex.1034, 13.

Moreover, even if Patent Owner's arguments regarding the conditions excluded by MACTEL and CATT are accepted, Patent Owner's argument fails because it misses the basic point: EC3 and the other criteria were obvious as basic safety precautions taken as part of the standard of care, which are taught by the CATT and MACTEL exclusion criteria. Pet. 48-53; Ex.1002, ¶¶146-60. The CATT and MACTEL exclusion criteria reflect the fact that POSAs understood that intravitreal injections can introduce flora into the vitreous cavity and potentially cause endophthalmitis, a blinding complication, as well as intraocular inflammation. *Id.*; *see also* Ex.1070, 35:15-18; Ex 2056, ¶124. As the criteria show, POSAs recognized that the presence of active *and* recent infection (whether chronic/acute or active/resolved or ocular/periocular) would increase bacterial load and thus increase the risk of bringing bacteria into the vitreous cavity. *Id.*; Ex.1002, ¶¶76, 141-144. Accordingly, POSAs would have found it obvious that the exclusion

context of clinical trials is contradicted by the close relationship between infection and inflammation. Ex. 1018, 1394; Ex. 1017, 62; Ex. 2056, ¶158.

criteria disclosed in the prior art taught to exclude patients with active and recent infections and inflammation. *Id.*

Finally, Patent Owner does not (and cannot) demonstrate that there is anything novel or unexpected about the two-week waiting period for EC3. Pet. 11; Ex.1002, ¶¶76, 145. The 30-day or four-week waiting period of the MACTEL and CATT Studies necessarily encompasses the two-week waiting period. Exs.1031-33. And even without an *in haec verba* disclosure, POSAs have found it routine to exclude ocular or periocular infections generally without reference to the specific timing of the infection at the time of '681 patent. *See, e.g.*, Ex. 1026; Ex.1002, ¶¶76, 141-144.

Accordingly, the MACTEL and CATT Studies render the claimed exclusion criteria obvious. *Galderma Lab'ys, L.P. v. Tolmar, Inc.*, 737 F.3d 731, 736 (Fed. Cir. 2013) (finding patent obvious in view of prior art that encompassed claimed range).

2. **A POSA Would Have Been Motivated to Look to the Exclusion Criteria of Prior Clinical Trials of Available Intravitreal Injectables, including MACTEL and CATT Studies**

Patent Owner first contends that POSAs would not have been motivated to consider the MACTEL and CATT Studies because the disclosed exclusion criteria were allegedly untested and teach away from EC3. POR, 36-52. Patent Owner argues that POSAs would have looked instead to the exclusion criteria of MARINA and ANCHOR—prior clinical trials for Lucentis[®]—that had published results at the time of the '681 patent. *Id.* Patent Owner is wrong for a number of reasons.

First, the claimed exclusion criteria are from trials of each of the major intravitreally injected drugs at the time, and demonstrate the standard of care. Pet. 48-53, Ex.1002, ¶¶130-160. POSAs understood that it was the method of administration—intravitreal injection—not the specific anti-VEGF agent being administered or eye disorder being treated that raised risks of complications. *Id.*; see also Ex.1002, ¶156. Petitioner’s prior art PIER, MACTEL, and CATT Studies simply reflect this standard of care for intravitreal injections and further confirm a POSA’s desire to minimize injection complications through the claimed exclusion criteria. *Id.*

Patent Owner’s focus on MARINA and ANCHOR is misplaced. First, the Federal Circuit repeatedly “rejected the notion that a patent challenger seeking to demonstrate obviousness must prove that a person of ordinary skill would have been motivated to select one prior art disclosure over another.” *Infineum USA L.P. v. Chevron Oronite Co. LLC*, No. 2020-1333, 2022 WL 3147683, at *6 (Fed. Cir. Aug. 8, 2022). The proper inquiry “is whether there is something in the prior art as a whole to suggest the *desirability*, and thus the obviousness, of making the combination, not whether there is something in the prior art as a whole to suggest that the combination is the *most desirable* combination available.” *In re Fulton*, 391 F.3d 1195, 1200 (Fed. Cir. 2004) (emphasis original).

Here, the prior art clearly indicated to a POSA the desirability of minimizing injection complications through the claimed exclusion criteria. Dixon states that “[e]ach [intravitreal] injection subjects patients to risks of cataract, intraocular inflammation, retinal detachment and endophthalmitis.” Ex. 1006, 1577; *see also* Ex. 1034, 247 (noting relationship between endophthalmitis and intravitreal injections); Ex. 2109, 1429 (same). The Lucentis® label also warned that “[e]ndophthalmitis and retinal detachments may occur following intravitreal injections. Patients should be monitored during the week following the injection.” Ex. 1026, 2. The standard of care at the time thus required assessing for active and recent infections and inflammation and ensuring they were cleared before any intravitreal injections of anti-VEGF agents were made. Ex.1002, ¶¶146-160. The MACTEL, CATT, and PIER Studies expressly disclose those known safety precautions.

Patent Owner’s own VIEW trials also undercut its contention that a POSA would have looked to and adopted the specific exclusion criteria of the MARINA and ANCHOR Studies over those of other available prior art: they used MARINA and ANCHOR as comparators but used different exclusion criteria. *Compare* Ex.1001, 10:57-12:15 with Ex.1071 and Ex.1072; Ex.1070, 154:20-155:13; 165:10-23. This is not surprising: as the Board has correctly noted, “the guiding principle

for all such studies are the particular objectives of that study and the general standards of medical care.” Institution Decision, Paper 10, 38; Ex.1002, ¶150-160.

Finally, even if a POSA relied upon the exclusion criteria of the MARINA and ANCHOR Studies, these studies disclose EC2-3. Ex.1072, 1-3; Ex.1071, 12-14. Both studies also exclude patients with “history of other diseases...giving reasonable suspicion of a disease or condition...that might affect interpretation of the results of the study or *render the subject at high risk for treatment complications.*” *Id.* They are not inconsistent with the prior art relied on by Petitioner.

Second, Patent Owner argues that the MACTEL and CATT references exclude *more patients* than the EC3 and thus teach away from EC3. POR, 40-44. Patent Owner is wrong. Nothing in the Challenged Claims of the ’681 patent precludes the exclusion of additional patients beyond the claimed exclusion criteria. In fact, the Challenged Claims recite that “exclusion criteria for the patient *include*” the three claimed exclusion criteria—an open ended claim. Ex.1001, Claims 1 and 14. The VIEW1 and 2 trials described in the specification, for example, included thirty four exclusion criteria *in addition to* the three recited exclusion criteria. Ex.1001, 10:58-12:15; *see also* Ex.1070, 141:17-142:1.

Because the Challenged Claims are not limited by the three recited exclusion criteria, there is no teaching away. *See, e.g., In re Chapman*, 595 F.3d 1330, 1337

(Fed. Cir. 2010) (rejecting patent owner's theory that prior art disclosing more attachment points than claimed teaches away from the claimed invention).

Patent Owner's cited case law is also inapposite. In *Amneal Pharms. LLC v. Jazz Pharms. Ireland Ltd.*, No. IPR2016-00546, 2016 WL 5222883, (P.T.A.B. July 28, 2016), the Board considered a prior art drug label for an oral administration of sodium oxybate (i.e., a GHB salt) with a black box warning—the strictest safety warning issued by the FDA—against the claimed use. The Board found these explicit warnings as teaching away from the claimed invention. *Id.*, at *5 (quotation omitted). There is no such warning here: the MACTEL and CATT Studies exclude a broader population that *encompasses* the patient population excluded by EC3.

B. Dixon Discloses the Claimed Q8 Dosing

There is no dispute that the Challenged Claims, including the dependent claims, are identical to those of the '338 patent except for the recitation of the exclusion criteria in independent claims 1 and 14 of the '681 patent. Pet., 13; Institution Decision, Paper 10, 14-15. And there is no dispute Dixon discloses the claimed dosing steps and every element of dependent claims. Patent Owner merely raises previously rejected and irrelevant arguments about the aflibercept molecule sequences and reasonable expectation of success. Pet., 32-42; Exs.1004, 1068.

1. Dixon Discloses the Claimed Sequences

(a) The Board Should Apply Collateral Estoppel

For the same reasons articulated in Section II, the Board should apply collateral estoppel to bar Patent Owner's argument that Dixon does not inherently disclose the claimed sequences. That factual finding was fully litigated in both the '681 and '338 FWDs. Exs.1004, 1068. Patent Owner raises identical arguments here that have been rejected at least twice. *Id.* It should be collaterally estopped.

(b) Dixon Discloses the Claimed Sequences

Even if collateral estoppel does not apply, the Board should find its prior factual findings "highly relevant" (*Medtronic*, IPR2020-01343, at 31, 71) and should confirm them on the same grounds. Dixon also expressly discloses in its Abstract that "[o]ne promising new drug is *afibercept (VEGF Trap-Eye)*," confirming POSAs were aware that VEGF Trap-Eye and afibercept (whose sequence was reported in the 2006 WHO index (Ex.1080)), to refer to the same molecule. *See, e.g.,* Pet., 34-39; Ex.1002, ¶¶121-129; Ex.1081, 73:12-22. And Dixon further teaches that "VEGF Trap-Eye and afibercept (the oncology product) have the same molecular structure." Ex.1006, 1575. This is sufficient to teach a POSA that they have the same, known amino acid sequence, even without considering that "Patent Owner has acknowledged, repeatedly, that the VEGF Trap-Eye used in [VIEW1/VIEW2] studies disclosed by Dixon is the same drug disclosed by the '338

patent, with the same amino acid sequence recited by claim 1,” and therefore the same sequence recited in claim 1 of the ’681 patent. Ex.1004, 39-40.

2. A POSA Would Have a Reasonable Expectation of Success

Patent Owner also claims POSAs lacked a reasonable expectation of success that the Q8 dosing regimen disclosed in Dixon would be effective. POR, 22-32. Patent Owner’s argument is premised entirely on its faulty claim construction of the preamble and factually wrong.

First, Patent Owner’s reasonable expectation of success argument is entirely premised on its faulty construction of the preamble reading in a particular efficacy requirement. POR, 22-29; Ex.1073, 81:18-85:5. As set forth in Sections II.A-B, the Board should reject Patent Owner’s construction. It can thus reject Patent Owner’s arguments regarding reasonable expectation of success on this basis alone.

Second, even if the Challenged Claims required efficacy (they do not) and even if a reasonable expectation of achieving that efficacy is required, it is present here. The Federal Circuit repeatedly found that: “Conclusive proof of efficacy is not necessary to show obviousness. All that is required is a reasonable expectation of success.” *Hoffmann-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1331 (Fed. Cir. 2014).

As set forth in the Petition, Phase III trials were ongoing and *less frequent* dosing regimen than the claimed dosing regimen in a Phase 2 trial achieved positive

results by 2011. Pet., 53; Ex.1002, ¶¶55-58, 161-163. In view of this teaching in the art, a POSA would have had a reasonable expectation of success that the use of the claimed dosing regimen disclosed in Dixon in the Phase III trials would show efficacy. *Id.*; see also, *Vanda Pharmaceuticals, Inc. v. Teva Pharmaceuticals USA, Inc.*, 2022 WL 17593282, at *16 (D. Del. 2022) (initiation of a Phase III trial provided a reasonable expectation of success); *Helsinn Healthcare S.A. v. Dr. Reddy's Lab's*, No. 14-4274, 2018 WL 623642, at *6 (D.N.J. Jan. 30, 2018) (Phase 3 studies evidence the “basis for believing” that the claimed method would work.).

Patent Owner relies on a *post hoc* re-evaluation of the CLEAR-IT-2 trial to claim there was no reasonable expectation of success. But Dixon reports that CLEAR-IT-2 resulted in mean gains of 9.0 letters in the 2Q4 arm, where those patients needed just 1.6 injections over the entire 40-week PRN phase, confirming aflibercept’s durability at an extended dosing interval. Ex.1006, 1576; Ex.1002, ¶¶162-163, 181. Moreover, some patients required *zero* injections over the 40-week PRN phase, and average time to first re-injection was over 85 days (approximately *three months*) for all cohorts. Ex.2366, 12-13. The data also shows that retinal thickness improved with three monthly loading doses. See, e.g., Ex.2366, 18. Visual acuity likewise improved in the cohorts receiving monthly loading doses, suggesting the desirability and feasibility of drying the retina and achieving initial visual acuity gain with of monthly loading doses before moving to extended dosing. Ex.2366, 17.

Indeed, while Patent Owner's expert now claims CLEAR-IT-2 results "strongly suggested" that extended maintenance dosing would not work, he admitted he was aware of no contemporaneous evidence in which he made such a statement. And the contemporaneous statements he did make show the data was, in his own words, "very encouraging" and "incredibly positive," and supported "that dosing with 2 mg every 8 weeks may be as effective as monthly dosing." Ex.1073, 176:24-177:5; Ex. 2296, 1095; Ex.1074, 100:16-23. Dr. Brown also admitted at depositions that the CLEAR-IT-2 OCT data on which Patent Owner now relies was not discussed contemporaneously in evaluating whether the CLEAR-IT-2 data supported extended dosing, while the positive visual acuity results were. Ex.1073, 161:13-162:3, 167:19-174:14; Ex.2296.

Accordingly, a POSA reading the CLEAR-IT-2 data would have had a reasonable expectation of success for the administration of the VEGF antagonist for the purpose of providing an improvement of or beneficial effect on the angiogenic disorder as claimed.² *Hoffmann-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1331 (Fed. Cir. 2014).

² Patent Owner's argument that there is no reasonable expectation of success to support an intent to treat likewise fails for the same reasons.

IV. NO SECONDARY CONSIDERATIONS SUPPORT NON-OBVIOUSNESS OF THE CHALLENGED CLAIMS

No Nexus: There are no secondary considerations here because Eylea does not embody the Challenged Claims. The claimed exclusion criteria are not recited in the Eylea label, and notably when opining that physicians using Eylea practice the claimed methods, Dr. Do did not cite the Eylea label even once when describing the alleged practice of the exclusion criteria.³ Ex.2056, ¶184; *see, e.g.*, Exs.1062, 1078. By failing to show as a threshold matter that Eylea practices the claims, Patent Owner has failed to establish the required nexus to any alleged secondary considerations. *Volvo Penta of the Americas, LLC v. Brunswick Corp.*, 81 F.4th 1202 (Fed. Cir. 2023).

No Commercial Success: For commercial success, Patent Owner cannot establish that the claimed dosing regimen is what drives Eylea sales. For instance, Patent Owner's expert failed to apportion or otherwise analyze whether the reported Eylea sales were in fact associated with the claimed dosing regimen, despite the fact

³ Dr. Do instead describes her alleged clinical practice (and those of retina specialists generally) in evaluating patients prior to intravitreal injections. Ex.2056, ¶184. She admitted that she conducted the same clinical evaluation that she says practices the claims prior to the critical date, which highlights the obviousness of the claimed exclusion criteria. Ex.1070, 114:2-118:25.

there are multiple other regimens on the label and in practice. Ex.1076, 90:6-11, 106:2-108:11. Indeed, Patent Owner’s own evidence shows the majority of the Eylea sales **were not** attributable to the claimed 8-week dosing regimen. Ex.2250, 17 (showing over 70% of Eylea injections for AMD were on PRN, monthly, or treat and extend regimen); Ex.2244, 29; Ex.2138, 15; Ex.2140, 22.

Patent Owner also did not account for other patents covering Eylea and regulatory exclusivity periods. *See* Ex.1077, 209:24-212:16; Ex.1076, 125:7-132:4. Patent Owner’s patents covered various aspects of Eylea, including the aflibercept molecule, formulation, and variations of extended dosing regimens that not only precluded market entry of competitors, but also were significant factors to Eylea sales. Ex.1075, 146:9-148:14; *see also*, Ex.1062, 15; Ex.1078, 26. Eylea’s regulatory exclusivity, which expires on May 17, 2024, also prevented market entry. Ex.1079. “Because market entry by others was precluded on those bases, the inference of non-obviousness of [the Challenged Claims], from evidence of commercial success, is weak.” *Merck & Co. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1377 (Fed. Cir. 2005).

Finally, Patent Owner has invested an enormous amount of marketing spend on Eylea—over \$1.5 billion dollars—involving thousands of physicians. *See*, Ex.2059, Attachment D-3; Ex.1077, 74:1-20. *Prometheus Lab’ys, Inc. v. Roxane Lab’ys*, 805 F.3d 1092, 1101 (Fed. Cir. 2015) (commercial success of drug

attributable to patentee’s marketing and sales practices, rather than from the claimed treatment method).

Accordingly, Patent Owner “has not sufficiently demonstrated that [Eylea’s] ‘tremendous success’ can fairly be attributed to the claimed invention.” *Pfizer Inc. v. Sanofi-Aventis Deutschland GmbH*, IPR2019-00979, POR, 93 (P.T.A.B. Aug. 11, 2020).

No Unexpected Results/Long Felt Need/Failure of Others: Patent Owner’s argument that there were unexpected results or a long felt need/failure of others is premised on the idea that the claims require efficacy—a premise the Board already has rejected. POR, 67-68. In fact, Patent Owner’s expert admitted that in evaluating these factor he applied only Patent Owner’s construction requiring efficacy on par with monthly Lucentis. Ex.1073, 80:21-85:3. But the Challenged Claims do not require any particular level of efficacy, and the 2Q8 dosing regimen Patent Owner cites as the basis for these factors was known in the art. *See* Sections II.A-B, III.B. The Board can ignore Patent Owner’s arguments on this ground alone. Patent Owner has failed to carry its burden. Pet. 53-54.

Second, even if the claims required a particular level of efficacy, as set out in Section III.B, by 2009, POSAs were aware that aflibercept had a “higher binding affinity” than other established anti-VEGF therapies and it may “have longer duration of effect in the eye.” Ex.1006, 1577. In fact, it was established that

aflibercept on a less frequent dosing interval than the claimed regimen achieved positive efficacy outcomes. Ex.1002, ¶¶161-163, 181. POSAs expected that the 2Q8 dosing regimen would work for at least some patients, based on trials such as PIER and Lucentis, which showed visual acuity gains even on greater extended dosing.

V. CONCLUSION

For the foregoing reasons, Petitioner respectfully requests the Challenged Claims of the '681 patent be found unpatentable.

DATED: January 16, 2024

Respectfully submitted,

By /Raymond N. Nimrod/
Raymond N. Nimrod (Reg. No. 31,987)
raynimrod@quinnemanuel.com
QUINN EMANUEL URQUHART
& SULLIVAN LLP
51 Madison Avenue, 22nd Floor
New York, NY 10010
Tel: (212) 849-7000
Fax: (212) 849-7100

Attorneys for Petitioner Samsung Bioepis

CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(a) and (d), the undersigned hereby certify that the forgoing Reply to Patent Owner's Response complies with the type-volume limitation of 37 C.F.R. § 42.24(c) permitting a reply of up to 5,600 words because, exclusive of the exempted portions, it contains 5,598 words as counted by the word processing program used to prepare the paper.

Date: January 16, 2024

Respectfully submitted,

By: /Raymond N. Nimrod/
Raymond N. Nimrod (Reg. No. 31,987)
QUINN EMANUEL URQUHART
& SULLIVAN, LLP
51 Madison Avenue, 22nd Floor
New York, New York 10010
raynimrod@quinnemanuel.com
Attorney for Petitioner Samsung Bioepis

CERTIFICATE OF SERVICE

In accordance with 37 C.F.R. § 42.6(e), I hereby certify that on January 16, 2023, true and correct copies of Petitioner's Reply to Patent Owner's Response and Exhibits 1068-1081 were served via electronic mail to Patent Owner at the following email addresses of record:

Deborah.Fishman@arnoldporter.com
David.Caine@arnoldporter.com
David.Denuyl@arnoldporter.com
Alice.Ho@arnoldporter.com
Victoria.Reines@arnoldporter.com
Jeremy.Cobb@arnoldporter.com
Abigail.Struthers@arnoldporter.com
Daniel.Reisner@arnoldporter.com
Matthew.Wilk@arnoldporter.com
RegeneronEyleaIPRs@arnoldporter.com

DATED: January 16, 2024

Respectfully submitted,

By /Raymond N. Nimrod/
Raymond N. Nimrod (Reg. No. 31,987)
raynimrod@quinnemanuel.com
QUINN EMANUEL URQUHART
& SULLIVAN, LLP
51 Madison Ave., 22nd Floor
New York, NY 10010
Tel: (212) 849-7000
Fax: (212) 849-7100