

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ALVOTECH USA INC. and ALVOTECH HF,
Petitioners,

v.

REGENERON PHARMACEUTICALS, INC.,
Patent Owner.

Case: PGR2025-00085
U.S. Patent No. 12,168,036

PATENT OWNER'S PRELIMINARY RESPONSE

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2036	Gerard A. Rodrigues, <i>Functional Characterization of Abicipar-Pegol, an Anti-VEGF DARPIn Therapeutic That Potently Inhibits Angiogenesis and Vascular Permeability</i> , 59 <i>Investigative Ophthalmology & Visual Science</i> 5836 (2018) (“Rodrigues 2018”)

I. Preliminary Statement

Alvotech's obviousness Grounds are a poster child for impermissible hindsight. For starters, each of Alvotech's combinations relies on the AU Label (Ex.1009) for its supposed teaching of the claimed "at least about 8 mg" dose. But—astonishingly—the Petition never once acknowledges the AU Label's express warning to physicians that, in case of "overdose[]" with 8 mg of aflibercept, "[i]t is advisable to contact the Poisons Information Centre ... for recommendations on the management and treatment of overdose." Ex.1009, 35. The AU Label itself is the product information for "Eylea 2 mg"—a far lower dose of aflibercept—and its sole reference to "8 mg" is found not in the "DOSAGE AND ADMINISTRATION" section (which refers exclusively to a 2 mg dose), but in a separate "OVERDOSAGE" section warning about "isolated cases of overdoses." *Id.*, 29-35. Only with hindsight can Alvotech suggest that this passage supports the POSA's motivation and reasonable expectation of success. Pet. 21-22, 25.

There is more. To satisfy the claimed viscosity limitation, every obviousness Ground relies upon Larson (Ex.1010). But Larson teaches to reduce viscosity in one specific way: using "water soluble organic dyes." *E.g.*, Ex.1010, ¶21. Larson teaches that, "[i]n the absence of a viscosity-lowering water soluble dye, the viscosity of a protein formulation increases exponentially as the concentration is increased." *Id.*, ¶75. Alvotech, however, makes no attempt to prove that these

“dyes” required by Larson are suitable for administration into the eye. Nor could it: Larson is directed to other types of administration, including subcutaneous and intramuscular; and Larson’s sole mention of “intravitreal” accompanies a passing reference to Eylea[®] in a laundry list of over 700 other biological products. *E.g., id.*, abstract, ¶¶88-190. Nevertheless, as with the AU Label, Alvotech brazenly plucks the Larson disclosure it prefers and continues on its hindsight-driven quest to assemble a mishmash of isolated prior-art passages in support of its spurious obviousness combinations. To be clear, neither Larson nor any of Alvotech’s other cited art discloses any viscosity value for a VEGF antagonist formulation, much less one for a formulation meeting the dose, concentration, and volume limitations of the challenged claims.

And while Alvotech’s obviousness Grounds are riddled with these and other deficiencies, its sole written-description Ground is even flimsier. Its argument rests on the baseless contention that Regeneron’s U.S. Patent 12,168,036 (the “’036 patent”) “lists only a few examples.” Pet. 80. But the ’036 patent discloses an extensive set of working formulation embodiments encompassing different protein concentrations, viscosity reducers, thermal stabilizers, surfactants, and other ingredients—in total, over thirty specific formulations with concentrations at or above 100 mg/ml and viscosity data under 15 cP. Only by disregarding these disclosures can Alvotech baldly proclaim that “[t]he facts are similar to” a district-

court case involving a patent disclosing only a single operative embodiment. Pet. 81. The numerous and diverse representative formulations disclosed by the '036 patent more than satisfy written description.

Neither the obviousness nor written-description Grounds in Alvotech's Petition come remotely close to demonstrating a reasonable likelihood of prevailing on the merits. The Director should deny institution.

II. Background

Regeneron's scientists invented aflibercept, the fusion protein used in its marketed products Eylea[®] and Eylea HD[®]. "Aflibercept is known as a 'VEGF antagonist' or 'VEGF trap' due to its ability to bind, or 'trap,' a protein called vascular endothelial growth factor (VEGF) before VEGF can bind to receptors in the human body and stimulate blood-vessel growth. Aflibercept formulations have been approved by the FDA for the treatment of several angiogenic eye diseases (*i.e.*, diseases related to blood-vessel growth in the eye) via intravitreal administration." *Regeneron Pharm., Inc. v. Mylan Pharm. Inc.*, 127 F.4th 896, 903 (Fed. Cir. 2025) ("SB"). Aflibercept has a molecular weight of approximately 115 kilodaltons (kDa), including glycosylation. *Regeneron Pharm., Inc. v. Mylan Pharm. Inc.*, 714 F. Supp. 3d 652, 740-41 (N.D.W. Va. 2024) ("Mylan"); Ex.1050 (Eylea Label), 9.

Eylea was the first fusion-protein ophthalmic drug product. Fusion proteins are formed by fusing together different domains of multiple proteins. Ex.2015

(Mylan Trial Transcript), 448:1-12 (Furfine). The leading ophthalmic VEGF antagonist in development before Eylea was Genentech's ranibizumab. *Id.*, 448:18-449:6, 450:14-19 (Furfine). Whereas aflibercept is a synthetic fusion protein, ranibizumab is an antibody fragment. *Id.*, 451:5-14, 456:6-9 (Furfine), 1035:4-9 (Rabinow).

“[F]usion proteins are fundamentally different from antibodies in that fusion proteins are synthetic molecules made by humans, while antibodies have evolved over time to be stable.” *Mylan*, 714 F. Supp. 3d at 737 (citing Ex.2015, 2013:14-17, 2014:21-2015:16 (Trout), 448:1-6, 456:6-9 (Furfine)); Ex.2027 (Fast), 15 (“In comparison with native IgG proteins, wherein interdomain interactions presumably have evolved to provide mutual stabilization, fusion proteins may lack such stabilizing interdomain stabilization.”); *In re Aflibercept Pat. Litig.*, 2024 WL 3422971, at *31 (N.D.W. Va. June 24, 2024).

Although aflibercept is most commonly used today to treat ophthalmic diseases, aflibercept originally was developed to treat cancer by systemic administration into the bloodstream, leveraging the prolonged serum half-life aflibercept possessed. *Mylan*, 714 F. Supp. 3d at 691-92. Aflibercept was approved to treat certain cancers under the trade name Zaltrap[®]. Ex.2028 (Zaltrap[®] Label), 1.

A. Regeneron's Eylea and Eylea HD Products

Regeneron's Eylea product contains 40 mg/ml of aflibercept (among other ingredients) in a 50 microliter volume, yielding a 2 mg dose. Ex.1050, 9. Eylea was initially approved in 2011. *Id.*, 1. In comparison to Genentech's Lucentis® (ranibizumab)—the previous leading anti-VEGF ophthalmic product—"Eylea demonstrated three critical and unexpected properties: comparable (1) safety and (2) efficacy to ranibizumab, along with (3) the durability to be dosed half as frequently as ranibizumab (after three loading doses for wet AMD). Extended dosing with Eylea was not only unexpected, but revolutionary, providing 'immediate benefits to patients who have a difficult time with intravitreal dosage administration' for the first time." *Mylan*, 714 F. Supp. 3d at 746 (quoting Ex.2029 (Thomas), 498). Thus, in contrast to ranibizumab, which is administered monthly, Eylea could be administered bimonthly after three loading doses. *Id.* This greater durability was achieved largely because of Eylea's 40 mg/ml concentration, which (1) "maximize[d] the half-life of aflibercept in the eye while minimizing toxicity and stability concerns," and (2) was already a high concentration, as it was "four times higher than the 10 mg/ml concentration of ranibizumab" in Lucentis, the only other anti-VEGF protein formulation then in development. *Id.* at 731, 746. Ultimately, "Eylea became the new gold standard of care" in treating multiple ophthalmic

disorders. *In re Aflibercept Pat. Litig.*, 2024 WL 3423047, at *1 (N.D.W. Va. July 9, 2024) (“*Formycon*”).

Numerous entities have sought to market biosimilar versions of Eylea. Over the past three years, Regeneron asserted U.S. Patent 11,084,865 (the “’865 patent”) covering Eylea against those biosimilars. The ensuing litigation resulted in numerous decisions involving the ’865 patent—four from the U.S. District Court for the Northern District of West Virginia, three from the Federal Circuit, and four from the Board or Director.

Building on the success of Eylea, Regeneron’s scientists continued to pursue advances in treating patients with angiogenic eye diseases. Regeneron recognized that patients would benefit greatly from a further extension of the dosing interval beyond the bimonthly dosing achieved with Eylea. Striving toward this objective, Regeneron’s scientists invented Eylea HD, containing 114.3 mg/ml aflibercept in a 70 microliter injection volume to deliver an 8 mg dose. Eylea HD thus delivers a dose four times greater than Eylea, by using a formulation with a nearly three-fold greater concentration of aflibercept but only a 20 microliter greater injection volume. Eylea HD was approved by FDA in 2023 and has been marketed by Regeneron since then. Ex.2035 (Eylea HD FDA Approval Letter), 6.

Following the approval and release of Regeneron's Eylea HD, Alvotech announced its plans to develop a proposed biosimilar to Eylea HD. Ex.2030 (Alvotech Press Release), 5.

B. Other Attempts at Extended Dosing with Anti-VEGF Products

Regeneron's scientists faced daunting odds in their quest to achieve extended dosing with a higher-dose aflibercept formulation beyond the bimonthly dosing achieved with Eylea. Indeed, multiple entities have attempted to further extend VEGF antagonist dosing, and multiple of these efforts failed.

Abicipar. Allergan developed the anti-VEGF molecule abicipar "to help fulfill the unmet need for a long-acting anti-VEGF that decreases the treatment burden for patients with nAMD." Ex.2022 (Khurana 2021), 1036. Unlike aflibercept, a 115 kDa fusion protein, abicipar is a 34 kDa molecule comprising a recombinant protein coupled to a polyethylene glycol moiety. Ex.2036 (Rodrigues 2018), 5837. Although a much smaller molecule, abicipar showed comparable affinity to aflibercept in a preclinical study. *Id.* The "small" molecular weight of abicipar "allow[ed] a high molar dose by intravitreal injection, and abicipar has a long intraocular half-life." Ex.2022, 1028. Abicipar was administered at the same 50 microliter volume as Eylea, *id.*, and owing to its lower molecular weight, the 2 mg dose of abicipar (*id.*) delivered an over threefold higher molar concentration of abicipar as compared to Eylea's aflibercept. Investigators hoped that "[t]he

optimized combination of high affinity, high molar dose, and long half-life with abicipar may translate into an extended duration of effect after intravitreal injection.”

Id.

Yet abicipar ultimately was withdrawn and never obtained FDA approval. Abicipar resulted in “significantly higher” inflammation compared to ranibizumab. *Id.*, 1032; *see* Ex.2015, 861:1-15 (Albini). In 2020, FDA refused to approve abicipar because “the rate of intraocular inflammation observed following administration of Abicipar pegol 2mg/0.05 mL results in an unfavorable benefit-risk ratio in the treatment of neovascular (wet) age-related macular degeneration (AMD).” Ex.2008 (AbbVie Press Release), 1. The molecule was then abandoned. *See* Ex.2031 (Molecular Partners Press Release).

Brolucizumab. Brolucizumab is another anti-VEGF molecule; Novartis developed it “to lessen the treatment and monitoring-visit burden while maintaining treatment efficacy and safety.” Ex.2024 (Dugel), 90. Like abicipar, brolucizumab is a lower-weight molecule “with a molecular weight of 26 kDa, allowing for higher molar dosing than previous anti-VEGF therapies.” *Id.* However, in its principal clinical trials, brolucizumab exhibited higher intraocular inflammation than aflibercept: “(4.7% vs. 0.6%).” *Id.*, 92. While brolucizumab was approved at a 6 mg dose and 120 mg/ml concentration, Ex.2012 (Beovu Label), 1, Novartis ultimately discontinued multiple clinical trials due to inflammation and vision loss,

Ex.2032 (Novartis Press Release), 2. In 2020, given patients’ inflammation following brolucizumab injection and, in some cases, “irreversible severe vision loss,” prominent ophthalmologists issued a clear message: “*intravitreal injections of brolucizumab should stop.*” Ex.2013 (Rosenfeld 2020), A7 (emphasis added). “In the face of the known risk, its use is unwarranted.” *Id.*, A8. Accordingly, sales of Beovu have been relatively minimal. Ex.2011 (Liu 2021), 2 (quarterly sales of \$39M versus \$1.35B for Eylea).

Vabysmo. Approved in 2022, Vabysmo is an ophthalmic product containing the anti-VEGF protein faricimab (which also antagonizes angioiopoetin-2). Ex.2026 (Vabysmo Label), 1. Faricimab has a molecular weight of 149 kDa (higher than aflibercept) but is administered at a dose of 6 mg (lower than the 8 mg Eylea HD dose). *Id.*, 1, 13; Ex.2033 (U.S. Patent Application Pub. 2023/0416353), ¶¶92, 367; *see also* Ex.2034 (WO 2014/009465).

III. U.S. Patent 12,168,036

A. The '036 Patent's Specification

Developing any “therapeutically useful liquid formulation” is a difficult and uncertain endeavor that requires carefully selecting—and balancing the amounts of—active and inactive ingredients to achieve “a functional and stable delivery vehicle.” Ex.1001, 1:42-45. That is especially true for protein and antibody formulations, which “have long presented challenges to drug developers and

manufacturers, as antibody activity and administration typically require a pharmaceutically acceptable potency, osmolality, protein stability, viscosity, and proper pH.” *Id.*, 1:46-50. “These challenges are exacerbated when the antibody is at higher concentrations in the formulation, for example, beyond 20 to 40 mg/ml, the concentration of most pharmaceutically sold antibodies.” *Id.*, 1:50-54.

The '036 patent explains that high-concentration protein formulations offer potential benefits. For instance, with higher concentrations, “shorter injection times, smaller injection volumes, lower frequency of antibody administration, and more efficient manufacturing and storage utility” theoretically are possible. *Id.*, 1:55-58. However, higher concentrations also make it “more difficult ... to maintain the proper activity and delivery parameters for the formulation.” *Id.*, 1:58-61. “In particular, high concentration antibody and protein formulations often contend with increased protein aggregation and viscosity, which results in lower overall antibody or protein potency, and lower manufacturing and poorer storage stability.” *Id.*, 1:61-65. It is no surprise, then, that “few such pharmaceutically acceptable formulations have been developed” and that “high concentration, high stability, antibody and protein formulations that include the proper potency, stability, viscosity, osmolality and pH” have proved difficult to attain. *Id.*, 1:65-2:4; *see supra* §II.B.

The need for pharmaceutically acceptable high-concentration formulations is especially acute for angiogenic eye disorders. *See* Ex.1001, 2:5-14. Treating these

disorders has historically required “monthly or bi-monthly” intravitreal injections, but such frequent “injections represent a significant treatment burden on patients, caregivers, and physicians.” *Id.*, 51:19-25. Accordingly, “[t]here is a pressing need for more effective and durable therapies in clinical practice.” *Id.*, 51:25-26. And increasing the concentration of the protein or antibody in an ophthalmic formulation could help achieve increased durability, reduced injection frequency, and a reduced risk of side effects associated with increases in intraocular pressure. *Id.*, 2:10-14, 2:25-29 (“High concentration VEGF receptor fusion protein containing formulations could allow for shorter ocular injection times, smaller injection volumes, fewer possible injections per administration cycle, and more efficient manufacturing and storage,” as well as “pharmaceutically acceptable potency, long term manufacturing and storage stability, and viscosity and pH compatible with ocular injection.”); *id.*, 2:30-33 (higher concentrations “allow for reduced ocular administration volumes, a benefit for avoiding undesired effects on the limited volume of the eye”).

But higher concentrations may increase aggregation and viscosity, and these phenomena pose special challenges for intravitreally injected formulations. *See id.*, 20:34-38 (“Typically, high concentration protein solutions require viscosity reducing agents to avoid protein aggregation and higher viscosity, making the formulations difficult for intravitreal injection and reducing the potency of the VEGF receptor fusion protein.”); *see also id.*, 1:61-65. First, increased aggregation

may result in side effects like inflammation. *E.g., Mylan*, 714 F. Supp. 3d at 707 (“Preventing aflibercept from aggregating and coming out of solution is especially important in the context of intravitreal injections. Intravitreal injections use narrow needles, which lead to shear stress and enhanced risk of protein aggregation[.] Forcing protein solutions through a narrow-bore needle creates shear stress, which can cause a protein to aggregate and come out of solution.... A protein coming out of solution can lead to several potential problems, including protein inactivation, inflammation, and even adverse immune responses.” (quoting and citing Ex.2015, 472:21-473:8, 577:10-579:10 (Trout), 476:2-24 (Furfine), 1680:6-11 (Graham))). Increased viscosity, meanwhile, can make intravitreal injections—typically administered through narrow-bore needles—difficult to administer. Ex.1001, 13:33-39 (“Since small needle bores are preferred for performing intravitreal injections (due to decreased patient discomfort and eye trauma), a relative low viscosity is desirable. A lower viscosity formulation requires less force to push the formulation through the needle, thus making injection of the formulation through the needle easier for the treating physician.”).

The '036 patent inventors overcame these difficulties to achieve stable, high-concentration, low-viscosity aflibercept formulations. *Id.*, 2:20-40, 13:20-41, 20:31-41, 38:26-40:11, 42:14-22. One such formulation is Eylea HD, Ex.2007 (Eylea HD[®] Label), 1, and the specification discloses several dozen other exemplary

formulations. Ex.1001, 23:22-28:19. For instance, Figure 3B discloses nine different formulations with 155 mg/ml aflibercept, 5% sucrose, pH 5.8, and either no salt, 100 mM arginine, 200 mM arginine, 50 mM lysine, 200 mM lysine, 50 mM sodium chloride, or 100 mM sodium chloride, each of which achieves a viscosity less than 15 cP. *Id.*, 9:46-10:4, 38:32-54, 39:15-40:11, Fig. 3B. Figure 3C discloses sixteen formulations with 10 mM phosphate, 5% sucrose, pH 6.2, either 0 mM or 50 mM arginine, and aflibercept concentrations ranging from 10-160 mg/ml. *Id.*, 10:5-8, 38:55-67, Fig. 3C. Each formulation—except for 160 mg/ml formulations and the 140 mg/ml formulation with 0 mM arginine—had a viscosity of 15 cP or less. *Id.* Figure 5 discloses sixteen more formulations with 10 mM phosphate or histidine, pH 6.2 or 6.0, 5% sucrose, and aflibercept concentrations ranging from 10-170 mg/ml. *Id.*, 10:24-29, 42:17-22, Fig. 5. All but three had a viscosity of 15 cP or less. *Id.* Finally, Figure 9 discloses twelve formulations with 140 mg/ml aflibercept, 20 mM histidine, pH 5.8, 5% sucrose, 0.03% polysorbate 20, and either 50 mM sodium sulfate, 50 mM sodium thiocyanate, 40 mM sodium citrate, 50 mM glycine, 50 mM sodium chloride, 50 mM lysine, 50 mM sodium aspartate, 50 mM sodium glutamate, 50 mM sodium citrate plus 50 mM arginine-HCl, 50 mM glycine plus 50 mM arginine-HCl, 50 mM sodium aspartate plus 50 mM arginine-HCl, or 50 mM sodium glutamate plus 50 mM arginine-HCl. *Id.*, 10:45-11:26, 50:15-45, Fig. 9. All twelve had a viscosity of 15 cP or less. *Id.* In total, the '036 patent discloses at least

31 distinct formulations with 100 mg/ml or higher concentrations, viscosities of less than 15 cP, and over a dozen different ingredients and multiple concentrations thereof. *Id.*, 9:46-11:26, 38:47-67, 42:17-22, 50:15-45, Figs. 3B, 3C, 5, 9.

B. The '036 Patent's Prosecution History

The claims originally recited “[a] method for treating an angiogenic eye disorder in a human patient in need thereof comprising administering an intravitreal injection of at least about 8 mg of a VEGF receptor fusion protein ... to the eye of the patient.” Ex.2001 (Excerpted File History), 2. The Examiner rejected those claims as inadequately described, concluding that “the claim recites a high concentration of a VEGF receptor fusion protein without any recitation of the elements of the composition that permit such a high concentration of the protein” and found that “[t]he Specification discloses that L-arginine monohydrochloride increases the stability of high concentrations of the VEGF trap Aflibercept.” *Id.*, 230-31. The Examiner determined that “while the specification provides adequate written description for stable, high concentration formulations of a VEGF receptor fusion protein along with 5% sucrose, polysorbate, a histidine based buffer, and L-arginine, it does not provide adequate written description for the breadth of the formulation[s] encompassed by the claims.” *Id.*

The applicant amended the claims to recite a volume of about 100 microliters or less, a concentration of at least 100 mg/ml, and a viscosity of about 5-15 cP. *Id.*,

289. The applicant asserted that “[t]he amended claims are fully described” and explained how “[t]he formulation specified in the amended claims is optimal for delivery of at least 8 mg of VEGF receptor fusion protein to the vitreum in terms of several interrelated factors: protein concentration, injection volume[,] and viscosity.” *Id.*, 295. In general, “[i]ntravitreal injection of a liquid formulation into the eye should be done in a volume of about 100 microliters or less,” as “[t]he vitreous chamber is a closed system having a typical volume of about 4-5 ml,” such that introducing “excess volume into the eye risks damaging increases in intraocular pressure.” *Id.* “In order to inject the target amount of VEGF receptor fusion protein (8 mg) in an acceptably low volume (≤ 100 microliters), the concentration of the formulation must be relatively high, for example, greater than 100 mg/ml.” *Id.* At the same time, the formulation must “have a viscosity suitable for injection via syringe,” as high-viscosity formulations “require excess pressure on the syringe plunger,” which may cause “damaging shearing forces to the protein and difficulty for the clinician who delivers the injection.” *Id.* “A major factor affecting [the] viscosity of VEGF receptor fusion protein formulations is protein concentration,” but “[l]owering protein concentration to lower viscosity” is not an option, because then “delivery of ≥ 8 mg of VEGF receptor fusion protein to the eye would need to be done in a higher volume,” risking “an increase in intraocular pressure if 100 microliters is exceeded.” *Id.*, 295-96.

“In spite of being constrained by these factors”—*i.e.*, the difficulty associated with increasing protein concentration to achieve smaller injection volumes while avoiding increasing viscosity—the inventors “successfully developed several formulations that meet the[] criteria” recited by the claims. *Id.*, 296. For instance, in “Figures 3B, 3C[,] and 5 ... the viscosities of several formulations including a variety of excipients were measured to be within the 5-15 cP range specified in the claims.” *Id.* As a result, “a representative number of species encompassed by the claims have been disclosed,” and the applicant maintained “that the amended claims are fully described and respectfully request[ed] withdrawal of this rejection.” *Id.* The Examiner agreed, withdrawing his “rejection of claims 30-32, 35 and 39-52 under 35 U.S.C. 112(a) ... in view of Applicant’s amendment to claim 30[] [and] the persuasive arguments” and allowing the claims. *Id.*, 306, 308.

The Examiner did not issue any other rejection, including on anticipation or obviousness grounds. During prosecution Regeneron disclosed, and the Examiner considered, the Vitti (Ex.1007), Furfine (Ex.1005), Dix (Ex.1006), and Fiedler (Ex.1011) references, each a part of Alvotech’s obviousness Grounds, as well as the Fiedler ’126 (Ex.2002), Australian Public Assessment Report for Aflibercept (Ex.2003, “AusPAR”), Borwankar (Ex.2004), and Whitaker (Ex.2005) references. Ex.2001, 236-37, 240, 251, 324, 371, 396-97, 400, 411, 527. The Examiner issued no rejections based on those references.

C. Challenged Claims

Claim 1 of the '036 patent recites:

A method for treating an angiogenic eye disorder in a human subject in need thereof comprising administering, intravitreally into an eye of the subject, in a volume of about 100 microliters or less, at least about 8 mg of a VEGF receptor fusion protein comprising two polypeptides that comprise an immunoglobulin-like (Ig) domain 2 of VEGFR1, an Ig domain 3 of a VEGFR2, and a multimerizing component; wherein the VEGF receptor fusion protein is in an aqueous pharmaceutical formulation comprising at least 100 mg/ml of the VEGF receptor fusion protein and having a viscosity of about 5-15 centiPoise (cP) at 20° C.

Ex.1001, claim 1. The remaining dependent claims recite particular treatment outcomes (claims 2-3), specific viscosities (claims 4-8), additional limitations regarding the aqueous pharmaceutical formulation (claims 9-12, 15, 17, 19, 21, 23, 25-27, 31, and 35), and particular angiogenic eye disorders (claims 13-14, 16, 18, 20, 22, 24, 28-30, 32-34, and 36-38).

IV. Alvotech's Petition and Cited Prior Art

Alvotech's obviousness Grounds rely on the following references.

A. Furfine

Furfine is a Regeneron patent titled “VEGF Antagonist Formulations Suitable for Intravitreal Administration.” Ex.1005, (45), (54), (73). The patent includes eight examples of ophthalmic VEGF formulations, all with a VEGF concentration of 50 mg/ml or less. *Id.*, 7:60-11:24. Furfine’s disclosures are limited to ophthalmic formulations with a VEGF concentration less than or equal to 100 mg/ml.

B. Dix

Dix is a Regeneron patent titled “Stable Liquid VEGF Antagonist Formulations.” Ex.1006, (45), (54), (73). Dix is directed to VEGF formulations for cancer and discloses no formulations for intravitreal or ophthalmic use. Dix teaches that VEGF “is nearly ubiquitous in human cancer, consistent with its role as a key mediator of tumor neoangiogenesis,” and that “[b]lockade of VEGF function, by binding to the molecule or its VEGFR-2 receptor, inhibits growth of implanted tumor cells.” *Id.*, 1:29-34. Dix disclosed formulations of VEGF Trap antagonists that “can either be delivered subcutaneously or diluted and delivered by intravenous infusion.” *Id.*, 10:10-12. Dix nowhere teaches to use its formulations ophthalmically or that they were suitable for intravitreal injection.

Dix does not include stability data for any specific liquid VEGF formulations containing less than 20% sucrose. For instance, Example 1 discloses testing of a liquid formulation containing 20% sucrose. *Id.*, 7:40-8:34. Dix teaches another

formulation with 20% sucrose and instructs that “[d]ue to the high osmolality of this formulation, it is diluted 3-fold to achieve an iso-osmolar solution for intravenous administration.” *Id.*, 10:9-14. Dix nowhere suggests that such a formulation could be used ophthalmically or adapted for intravitreal injection. No evidence indicates that formulations containing 20% sucrose would be suitable for intravitreal use; to the contrary, trial testimony concerning the Furfine ’865 patent indicated that sucrose concentrations of 20% were inappropriate for ophthalmic use. Ex.2015, 1679:13-21 (Graham); *see generally Mylan*, 714 F. Supp. 3d at 745 (“Dix ’226 undisputedly did not disclose, suggest, or contemplate ophthalmic formulations or intravitreal injections....”).

C. Vitti

Vitti is a Regeneron patent application titled “Methods and Formulations for Treating Vascular Eye Diseases.” Ex.1007, (43), (54), (71). Vitti involves methods of treating vascular eye disease by administering a combination of an angiopoietin-2 (Ang-2) inhibitor (mAb1) and a VEGF antagonist. *Id.*, ¶2. Vitti discloses a broad range of potential VEGF antagonist concentrations, ranging from 5 ± 0.75 mg/ml to 150 ± 22.5 mg/ml. *Id.*, ¶87. Vitti also discloses a broad range of volumes that can be administered intravitreally—up to 100 microliters and up to 500 microliters. *Id.*, ¶127. These disclosures of total intravitreally injectable volume contemplate an aflibercept concentration of 10 mg/ml to 100 mg/ml. *Id.* There is no indication in

Vitti that an aflibercept formulation could be made with a volume of 100 microliters or less and an aflibercept concentration of 100 mg/ml or more.

Vitti discloses non-intravitreal methods of administering the combined mAb1/VEGF antagonist treatment using autoinjectors, oral administration, and subcutaneous injection via a microinfuser. *Id.*, ¶¶114-27. Vitti explains that “[m]icroinfusers are particularly useful for the delivery of large doses of therapeutic proteins contained within high concentration (e.g., about 100, 125, 150, 175, 200 or more mg/mL) or viscous solutions.” *Id.*, ¶125. Vitti contains no indication of the viscosity of a formulation containing VEGF antagonists with a volume of 100 microliters or less and an aflibercept concentration of 100 mg/ml or more.

Vitti discloses combining aflibercept with mAb1 to obtain “additional efficacy over treatment with an anti-VEGF therapy alone” and “provid[e] a longer duration of action resulting in a longer treatment interval.” *Id.*, ¶238. It was the combination that was intended to provide an increase in duration of action, not the increase of the dose of aflibercept. Indeed, in the only clinical trial disclosed in Vitti, five cohorts were given different drug formulations, and every aflibercept formulation contained 2 mg (40 mg/ml) aflibercept, *i.e.*, the same dose as commercially available Eylea. *Id.*, ¶¶260, 264-68.

D. AU Label

The AU Eylea Label (“AU Label”) is product information for the 2 mg, 40 mg/ml Eylea formulation. Ex.1009, 2, 35. It summarizes Eylea clinical trials and notes that “[a] total of 3102 patients treated with EYLEA constituted the safety population in eight Phase III studies. Amongst those, 2501 patients were treated with the recommended dose of 2 mg.” *Id.*, 27. It conveys that an increase in intraocular pressure was a serious adverse reaction. *Id.*, 27-28. An intraocular pressure increase was so concerning that it warranted its own section under “Precautions,” along with just three other specific potential adverse reactions. *Id.*, 24. The Precautions section instructs that ophthalmologists “must” monitor and manage intraocular pressure when treating patients with Eylea. *Id.* Ophthalmologists are again instructed to monitor their patients for “elevation in intraocular pressure” “[i]mmediately following [an] intravitreal injection” in the section titled “Method of Administration.” *Id.*, 30-31.

In a separate section titled “OVERDOSAGE,” the AU Label also reports “isolated cases of overdoses with 8 mg” of Eylea. *Id.*, 35. While these isolated incidents “were generally well tolerated,” the AU Label warns that “[o]verdosing was associated with increased injection volume and subsequently with increased intraocular pressure.” *Id.*, 35. In case of overdose, the AU Label instructs ophthalmologists to monitor intraocular pressure and advises “contact[ing] the

Poisons Information Centre (131126) for recommendations on the management and treatment of overdose.” *Id.* And Alvotech agrees (at 59) that the overdoses did not use either the required concentration or volume of the VEGF antagonist.

E. 2011 Eylea Clinical Review

The 2011 Eylea Clinical Review (“Clinical Review”) summarized the results of Phase I and Phase II clinical trials of aflibercept administered both intravenously and intravitreally. Ex.1008, 2. The Clinical Review explains that both diastolic blood pressure and systolic blood pressure increase after intravenous administration of a VEGF antagonist because the administration reduces the amount of free systemic VEGF. *Id.*, 10. These blood pressure effects were not found after the lower-concentration intravitreal injections, which were performed at concentrations up to 4 mg/eye. *Id.* However, “peak concentrations of bound aflibercept continue[d] to increase in a dose-dependent manner with increasing IVT doses.” *Id.*

F. Larson

Larson is a patent application directed generally to “liquid protein formulations containing water soluble organic dye.” Ex.1010, (54). More specifically, Larson discloses a technique to potentially decrease viscosity by formulating therapeutic protein formulations with “viscosity-lowering water soluble organic dyes.” *Id.*, ¶23. It is not directed to any specific protein and in fact mentions hundreds of proteins to which its disclosed formulations may be applicable. *Id.*,

¶¶92-190. These include fusion proteins, and Larson listed Eylea as one of over thirty different examples of fusion proteins. *Id.*, ¶¶164-81.

This isolated reference to Eylea is the only mention of intravitreal administration of protein formulations. Larson in fact excludes intravitreal injection as a potential method of administering the disclosed formulations “to an individual in need thereof.” *Id.*, ¶224 (“The protein formulations, including, but not limited to, reconstituted formulations, are administered to a person in need thereof by intramuscular, intraperitoneal (i.e., into a body cavity), intracerebrospinal, or subcutaneous injection”). Larson provides no indication that a formulation with water-soluble organic dyes would be safe or suitable for intravitreal use.

Larson also discloses a broad range of protein concentrations and viscosities. Specifically, Larson discloses protein concentrations of “between about 10 mg/mL and about 5,000 mg/mL,” *id.*, ¶22, and viscosities of protein formulations with viscosity-lowering water-soluble organic dyes of, at its broadest, “less than or about 100 cP,” *id.*, ¶75. The viscosities of the formulations in Larson’s only example ranged from 29.5 ± 0.9 cP to 1370 ± 3 cP. *Id.*, ¶258.

G. Fiedler

Fiedler is a patent application titled “Pre-Filled Plastic Syringe Containing a VEGF Antagonist.” Ex.1011, (54). It discloses a pre-filled syringe meant for intravitreal administration, *id.*, ¶83, with VEGF antagonist concentrations of “1 to

100 mg/ml,” *id.*, ¶19, and total formulation volumes of “about 0.05 ml to about 1 ml,” *id.*, ¶66. Fiedler explains that the actual volume administered to the patient from the pre-filled syringe would be lower, “between 0.01 ml and 1 ml.” *Id.*, ¶67. Fiedler provides no information concerning the volume of a VEGF antagonist formulation in any presentation other than a pre-filled syringe.

V. Person of Ordinary Skill

In this Preliminary Response, Regeneron applies Alvotech’s definition of a person of ordinary skill in the art (“POSA”). Pet. 10-11. Regeneron reserves the right to challenge this definition if PGR is instituted.

VI. Alvotech Fails To Show Preponderant Evidence That the ’036 Patent Claims Would Have Been Obvious or Lack Written Description

A. Ground 1: Alvotech Fails To Demonstrate Obviousness over Vitti, AU Label, and Larson

1. The Prior Art Motivated Against Using a High Dose of Aflibercept at a High Concentration

Claim 1 illustratively recites “[a] method for treating an angiogenic eye disorder ... comprising administering, intravitreally ... *at least about 8 mg* of a VEGF receptor fusion protein ... wherein the VEGF receptor fusion protein is in an aqueous pharmaceutical formulation comprising *at least 100 mg/ml of the VEGF receptor fusion protein* and *having a viscosity of about 5-15 centiPoise (cP)* at 20° C.” Ex.1001, claim 1 (emphases added). The prior art does not teach the use of such a high-dose, high-concentration formulation—to the contrary, it teaches that

accidental overdoses of a high dose of aflibercept led to increased intraocular pressure with no improved efficacy or durability, and the prior art further teaches that higher concentrations and dosages may lead to a host of issues like inflammation, aggregation, and adverse immune responses. Consistent with those teachings, multiple contemporaneous attempts at higher-concentration formulations of VEGF antagonists failed due to inflammation that led in some cases to “irreversible severe vision loss.” Ex.2013, A7; *see infra* §VI.A.3. Alvotech simply ignores the vast majority of these concerns, instead advancing a generic motivation to improve “patient benefits” like reducing injection frequency. Pet. 20-21. But neither Vitti nor the AU Label teaches to do so by using the claimed compositions, and the multiple failures of others to improve durability confirm the nonobviousness of the challenged claims, which require a higher dose of a VEGF antagonist than any other formulation that had succeeded. Because Alvotech cannot support a motivation to select—or a reasonable expectation of success in achieving—the high-concentration, high-dose compositions required by the challenged claims, institution should be denied.

a. The Prior Art Teaches No Formulations Meeting the Required Dose and Concentration and Motivated Against Using Them

Alvotech asserts that “[h]igh-concentration VEGF antagonist formulations (≥ 100 mg/ml) for treating angiogenic eye disorders were known in the art well,” Pet.

20, yet conspicuously omits any such concrete formulation coming anywhere close to the “at least about 8 mg” and “at least 100 mg/ml” dose and concentration limitations recited in claim 1. Contrary to Alvotech’s assertion, no intravitreal VEGF antagonist formulations in development met *either* limitation, and the prior art comprehensively taught against increasing dose and concentration as required by the ’036 patent claims.

Aflibercept and Ranibizumab. At the priority date, the sole marketed VEGF antagonist fusion protein product was Eylea, which contains a 40 mg/ml formulation of aflibercept that delivered a 2.0 mg dose in a 50 microliter injection volume. Ex.1050, 1; Pet. 58-59. Eylea’s 2.0 mg dose was not a low dose; to the contrary, the leading VEGF antagonist before Eylea was ranibizumab, which was ultimately approved (1) at a maximum dose of 0.5 mg and a concentration of 10 mg/ml, and (2) at an even lower 0.3 mg dose at a 6 mg/ml concentration. Ex.1055 (Lucentis Label), 1-3.

Genentech had attempted a higher-concentration formulation of ranibizumab—an antibody fragment, not a fusion protein—at 40 mg/ml, but that formulation was never commercialized. *See Mylan*, 714 F. Supp. 3d at 738. Rather, Genentech’s 40 mg/ml formulation exhibited “‘moderate to severe’ inflammation,” “an extremely concerning phenomenon for any intravitreal drug product to exhibit, as it could result in vision loss and thus defeat the purpose of using an ophthalmic

drug product in the first place.” *Id.* (citation omitted). In prior litigation involving Eylea, the District Court found that the inflammation resulting from Genentech’s 40 mg/ml formulation “persisted for seven days and was ‘problematic from an immune response standpoint’ and thus ‘would teach the [POSA] away from the 40 mg/ml’” concentration. *Id.* at 737 (quoting Ex.2015, 2041:1-10 (Trout)). In contrast, “the 10 mg/ml ranibizumab formulation did not exhibit such levels of inflammation, and the authors found that this lower ‘dose provides maximum inhibition of VEGF.’” *Id.* (quoting Ex.2015, 2041:22-2042:9 (Trout) (citing Ex.2014 (Gaudreault), 732)); *see* Ex.2014, 727 (10 mg/ml concentration resulted in “absent to moderate” inflammation).

The District Court considered the differences between aflibercept and ranibizumab and found that they would have further discouraged increasing aflibercept concentration. “[A]flibercept was much more potent than ranibizumab”; accordingly, “less aflibercept is needed to inhibit the same amount of VEGF as compared to ranibizumab.” *Mylan*, 714 F. Supp. 3d at 737. Furthermore, the Court found that because “fusion proteins are synthetic ‘Frankenstein’ molecules that, unlike antibodies, did not evolve to possess inherent stability, the POSA would expect fusion proteins like aflibercept to have lower stability than antibodies (or antibody fragments like ranibizumab).” *Id.* at 742 (quoting Ex.2015, 2068:18-2069:7 (Trout)). Importantly here, fusion proteins’ greater propensity for

aggregation would be exacerbated by increasing concentration, thereby further risking inflammation. *Id.* at 737 (noting “the greater risk of aggregation caused by a higher concentration” (citing Ex.2016 (Wang 2005), 9)); *see* Ex.2016, 9 (explaining that “[i]ncreasing protein concentration generally increases protein aggregation” and that “protein aggregates often have stronger immunogenicity or toxicity”); Ex.2017 (Wang 1999), 137 (“Protein aggregates may have ... altered immunogenicity.”).

Further clinical studies reinforced this risk of increasing VEGF antagonist dose. Patients in a ranibizumab clinical trial experienced dose-dependent increases in inflammation and “dose-limiting toxicity”—including, in one patient, transient vision loss—at a 1000 µg dose, which corresponds to a 20 mg/ml concentration using ranibizumab’s disclosed 50 µL volume, but not at lower doses. Ex.2018 (Rosenfeld 2005), 1049-52. Due to this observed dose-dependent inflammation, the investigators did not even attempt the 2.0 mg dose corresponding to a 40 mg/ml concentration at that volume. *Id.*

Alvotech acknowledges (at 21) that inflammation is undesirable but inexplicably ignores that increasing dose and concentration both risk higher inflammation and aggregation. That approach is erroneous. Alvotech must establish that it was not only “feasible” but also, “on balance, desirable” to increase dose and concentration, notwithstanding these known risks. *Winner Int’l Royalty Corp. v.*

Wang, 202 F.3d 1340, 1349 (Fed. Cir. 2000); *see also Orexo AB v. Actavis Elizabeth LLC*, 903 F.3d 1265, 1272-73 (Fed. Cir. 2018); *Henny Penny Corp. v. Frymaster LLC*, 938 F.3d 1324, 1331-32 (Fed. Cir. 2019). Alvotech shows neither: No evidence other than conclusory expert opinion even suggests that increasing dose and concentration of aflibercept as claimed would work to reduce “frequency of injections,” Pet. 21, let alone do so without a corresponding increase in inflammation and aggregation.

Alvotech’s other cited aflibercept and ranibizumab literature likewise does not support an 8 mg dose or a 100 mg/ml concentration. Alvotech cites the subsequent HARBOR clinical trial that again investigated a higher ranibizumab dose. Pet. 22, 50. Although Alvotech asserts that this study found that increasing dosage “increased the duration of action of the VEGF [inhibitor] in the eye,” Pet. 22 (citing Ex.1026 (Ho), 2182, 2190), it in fact teaches the opposite. Ho teaches that “[o]ver 2 years, *the 2.0 mg dose did not show any clinically meaningful difference* in efficacy, *durability*, or safety *compared with the 0.5 mg ranibizumab dose.*” Ex.1026, 2190 (emphases added); *see id.*, 2182 (“At 12 months (the primary end point), *the ranibizumab 2.0 mg monthly dose was not superior to the 0.5 mg monthly dose* and did not offer any incremental improvements in efficacy out-comes” (emphasis added)). Thus, Ho itself offered no reason to make a “4-fold increase in dosage,” *contra* Pet. 22. And although Ho did not observe dose-dependent effects

on safety, Ex.1026, 2182, 2190, it did not cite or contradict the earlier Gaudreault and Rosenfeld 2005 studies, which, as discussed *supra*, did disclose such drawbacks to using higher doses.

Alvotech also cites (at 22) Stewart (Ex.1039), which speculated that the HARBOR trial “suggest[ed], but d[id] not prove, that increasing the dose of a drug prolongs its duration of action.” Ex.1039, 1182. But Ho—the seminal paper by the HARBOR investigators published two years after Stewart—debunked that hypothesis and concluded that the study showed no “clinically meaningful difference in ... durability,” Ex.1026, 2190, thus flatly contradicting Alvotech’s characterization (in its second Ground) that Ho somehow “validated Stewart’s prediction.” Pet. 50.

Nor does Alvotech’s other cited art involve administration of a VEGF antagonist at doses even approaching 8 mg. Pet. 22. Nguyen (Ex.1035) investigated 4.0 mg of aflibercept compared to 0.15 mg; it did not evaluate any doses higher than 4.0 mg, did not disclose what concentration of aflibercept was used or the injection volume, and did not evaluate whether the 4.0 mg dose had any benefits over the approved, marketed 2.0 mg dose. Ex.1035, 581, 583. Ex.1030 is a presentation that mentions 6 tested dosages of only a “single intravitreal injection” between 0.05 and 4.0 mg but no higher dosages, and reports data only for the 1.0 mg dose. Ex.1030, 18-19. And finally, Ex.1058 is a foreign regulatory document that Alvotech does

not even indicate is prior art, and in any event, it does not teach an 8 mg dose either. Ex.1058, 20-21.

In support of a different obviousness Ground (Pet. 87), Alvotech cites the Clinical Review, which summarizes findings from Eylea clinical trials. This reference further teaches the POSA to use lower dosages in anti-VEGF formulations. In summarizing two studies comparing 0.5, 2, and 4 mg aflibercept doses, the Clinical Review explained that “the maximum improvement [was] achieved at a dose of 2 mg/eye,” that “[t]here was little further improvement observed at 4 mg/eye,” and that “4 mg[] was not associated with improvements in the efficacy parameters beyond those achieved with a dose of 2 mg.” Ex.1008, 10, 13. It further reported that none of the studied doses of 0.5, 2, or 4 mg “provide[d] a sustained [pharmacodynamics] improvement over the entire [twelve-week] dosing interval.” *Id.*, 10. With no improvement reported from 2 to 4 mg in duration or efficacy, the POSA would have been motivated against trying even higher doses of aflibercept, especially given the significant safety concerns with higher doses.

In sum, (1) the aflibercept and ranibizumab prior art does not teach the claimed dose or concentration, and (2) it teaches to use lower dosages and concentrations to reduce the risk of inflammation and aggregation.

Other VEGF Antagonists. Alvotech cites no other VEGF antagonists with an 8 mg dose or 100 mg/ml concentration. As explained *infra* §VI.A.3,

notwithstanding a long-felt need to increase dosing intervals, several contemporaneous attempts to deliver higher VEGF antagonist doses (each less than 8 mg) failed, strongly supporting nonobviousness under governing precedent. *E.g.*, *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1332 (Fed. Cir. 2016); *Amgen Inc. v. Sandoz Inc.*, 66 F.4th 952, 964 (Fed. Cir. 2023); *Millenium Pharm., Inc. v. Sandoz Inc.*, 862 F.3d 1356, 1369 (Fed. Cir. 2017). In particular, abicipar was a known VEGF antagonist in development at a 2.0 mg dose but with a much lower molecular weight (34 kDa versus 115 kDa for aflibercept), giving rise to an over threefold higher molar concentration than the aflibercept in Eylea. Ex.2010, 239. Yet abicipar exhibited substantial inflammation, *e.g.*, *id.*, and ultimately failed to obtain approval due to the “rate of intraocular inflammation observed,” which resulted in “an unfavorable benefit-risk ratio.” Ex.2008, 1. Similarly, brolucizumab (which has a 6 mg dose compared to Eylea’s 2 mg) caused significant inflammation and, in some circumstances, severe, permanent vision loss, and therefore was effectively abandoned. Ex.2024, 92; Ex.2012; Ex.2013, A7.

Viscosity. It was also known that, in addition to risking aggregation, inflammation, and an immune response, proteins like “[a]ntibodies tend to form viscous solutions at high concentration.” *Mylan*, 714 F. Supp. 3d at 743 (quoting Ex.2019 (Liu 2004), ¶6). Alvotech’s cited art is consistent, teaching that “[i]n the absence of a viscosity-lowering water soluble dye, the viscosity of a protein

formulation increases exponentially as the concentration is increased.” Ex.1010, ¶75. Furthermore, “high viscosity would be especially problematic for intravitreal injections because it leads to ‘very long injection times’ and even can make the formulation unusable.” *Mylan*, 714 F. Supp. 3d at 743 (quoting Ex.2015, 2066:2-21 (Trout)). Additionally, high-viscosity formulations are more difficult for ophthalmologists to inject and more uncomfortable or even harmful for patients. *E.g.*, Ex.1001, 13:33-39. Accordingly, the risk of increasing viscosity further motivates against increasing VEGF antagonist concentration, “because such increase would increase viscosity, which would have been particularly problematic for a formulation for intravitreal injection.” *Mylan*, 714 F. Supp. 3d at 743.

b. Alvotech’s Prior Art Teaches Away from the Claimed Dose and Concentration

Lacking any teaching of the claimed high-dose, high-concentration compositions, Alvotech cites Vitti and the AU Label in support of selecting both the claimed dose and concentration of the recited VEGF antagonist. However, neither reference teaches or suggests a particular composition with a 100 mg/ml (or higher) concentration and an 8 mg dose. To the contrary, Alvotech’s art teaches away from using the claimed high-dose, high-concentration compositions. Pet. 20-23.

The AU Label teaches away from 8 mg aflibercept. Alvotech’s sole reference to delivery of 8 mg of a VEGF antagonist comes from the section entitled “OVERDOSAGE” in the AU Label. Ex.1009, 35. Alvotech’s assertion that this

section would have motivated the POSA “to target an 8 mg dose of aflibercept” egregiously misreads the reference using hindsight rather than heeding the art’s teachings. Pet. 22. The AU Label describes “*isolated cases* of overdoses with 8 mg,” where patients were administered an “increased injection volume” and thus received a higher dose. Ex.1009, 35 (emphasis added). “Overdosing was associated ... subsequently with increased intraocular pressure.” *Id.* Increased intraocular pressure (“IOP”) is an adverse event requiring “[s]pecial precaution ... in patients with poorly controlled glaucoma,” a disease associated with increased IOP. *Id.*, 24, 27. The AU Label thus expressly discouraged overdosing with 8 mg: It advises that “in case of overdosage intraocular pressure should be monitored and if deemed necessary by the treating physician, adequate treatment should be initiated. *It is advisable to contact the Poisons Information Centre (131126) for recommendations on the management and treatment of overdose.*” *Id.*, 35 (emphasis added). That is Alvotech’s sole purported prior-art disclosure of 8 mg aflibercept.

Alvotech’s assertion (at 22) that this description would somehow cause the POSA to “target” the 8 mg dose cannot be squared with the reference’s unambiguous teaching to the opposite. Alvotech cannot prove obviousness by “plainly mischaracteriz[ing] the reference,” which is “exemplary of hindsight reasoning.” *Sanofi-Aventis U.S., LLC v. Dr. Reddy’s Labs., Inc.*, 933 F.3d 1367, 1379-80 (Fed.

Cir. 2019). “Considered for all its teachings, not selectively,” as precedent requires, *Henny Penny*, 938 F.3d at 1332, the AU Label teaches away because it expressly “discourage[s] ... the path set out in the reference” and leads “in a direction divergent from the path that was taken in the claim.” *AstraZeneca AB v. Mylan Pharm. Inc.*, 19 F.4th 1325, 1337 (Fed. Cir. 2021) (cleaned up). The AU Label explicitly “discourage[s]” (*id.*) use of 8 mg aflibercept because it instructs to provide “adequate treatment” to ameliorate the increased IOP from overdosage and to “contact the Poisons Information Centre.” Ex.1009, 35. And it leads “in a direction divergent from the path that was taken in the claim” (*AstraZeneca*, 19 F.4th at 1337) because the claims require intravitreal administration of 8 mg aflibercept, the same dose that the AU Label advises to call Poison Control if administered.¹ Ex.1009, 35.

¹ Alvotech asserts that Regeneron “relied on this ‘overdose’ data to justify” Eylea HD. Pet. 22. Alvotech’s characterization is inaccurate: Regeneron noted that “isolated cases of unintentional dosing with 8 mg per eye occurred and were also well tolerated,” but it did not “rel[y] on” those data, nor did it suggest that they were a basis for approving Eylea HD—instead, the basis was the clinical trials that used one of the claimed formulations. Ex.1066, 19. Regardless, Regeneron’s statement is not prior art and is irrelevant. The ’036 patent’s inventors took a divergent path

The AU Label’s teaching away “on its own is sufficient to sustain the nonobviousness” of the challenged claims. *AstraZeneca*, 19 F.4th at 1336; *Winner*, 202 F.3d at 1349-50. And it is entirely consistent with the prior art’s teachings that increasing dose and concentration risked inflammation, aggregation, an adverse immune response, and increased viscosity. *Supra* §VI.A.1.a.

Finally, Alvotech’s reliance on *Recor Medical, Inc. v. Medtronic Ireland Manufacturing Unlimited Co.*, 2025 WL 944511 (Fed. Cir. Mar. 27, 2025), only reinforces the teach-away of the AU Label. Pet. 30. Alvotech cites *Recor* in arguing that the AU Label “expressly teaches ‘at least about 8 mg,’” and therefore would have motivated the POSA to treat a patient with a high dose of VEGF antagonist. *Id.* But in *Recor*, the Federal Circuit reiterated that a prior-art reference must be considered “for everything it teaches” and that other teachings in the reference “should not be disregarded.” 2025 WL 944511, at *2. Thus, as much as Alvotech might wish to selectively focus on the “8 mg” overdose in the AU Label and ignore

from the prior art—which clearly taught away from and motivated against using higher-dose and higher-concentration formulations due to concerns over, *e.g.*, increased IOP and aggregation—and “[t]he inventor’s own path itself never leads to a conclusion of obviousness; that is hindsight.” *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1296 (Fed. Cir. 2012).

the accompanying warning to “contact the Poisons Information Centre” if this dose is administered, Ex.1009, 35, the AU Label’s disclosure must be considered “for everything it teaches,” and the clear teach-away from the 8 mg overdose “should not be disregarded.” *Recor*, 2025 WL 944511, at *2.

Vitti does not teach or suggest the claimed dose or concentration. Alvotech also relies on broad ranges of concentrations and doses disclosed in Vitti. Vitti nowhere teaches an actual composition with a concentration greater than 100 mg/ml or a dose greater than 8 mg. Alvotech thus cites (at 20-21) Vitti’s disclosure of a VEGF antagonist concentration of “10±1.5 mg/mL to 100±15.0 mg/mL of VEGF antagonist,” amongst several other ranges, Ex.1007, ¶87; *see id.*, ¶¶27, 94, 127 (similar); and a single isolated disclosure of administering an angiopoietin (Ang-2) inhibitor in combination with “0.05 mg to about 10 mg of a VEGF antagonist.” Pet. 28 (quoting Ex.1007, ¶139); *see* Pet. 21 (citing Ex.1007, ¶¶27, 127, which discuss concentration and volume ranges, as somehow specifically teaching “about 10mg”). These broad ranges fail to render obvious the claimed concentration and dose for multiple reasons.

First, Alvotech’s reliance on Vitti rests entirely on hindsight. ***Every discrete formulation*** disclosed in Vitti contained 2 mg aflibercept at a concentration of 40 mg/ml—the same dose and concentration used in Eylea. *E.g.*, Ex.1007, ¶¶198-201, 227, 243, Table 43. Nowhere in Vitti’s broad disclosure does it suggest using at

least 8 mg and 100 mg/ml of the VEGF antagonist. Rather, Vitti only teaches increasing the dose and concentration of the Ang-2 antibody, which Alvotech simply ignores. *Id.*, ¶¶198-201, Table 43. Likewise, although Alvotech invokes the burden of frequent intravitreal doses, Pet. 20-21, it ignores the solution proposed in Vitti precisely directed at that issue: “methods are provided for reducing the dependence and treatment burden of frequent intravitreal injections,” comprising “sequentially administering ... a pharmaceutical composition comprising an Ang-2 inhibitor in combination with a VEGF antagonist.” Ex.1007, ¶15; *see also id.*, ¶128. Nowhere does Vitti teach to increase the dose and concentration of the VEGF antagonist to meet that goal. And even if Vitti contained such a teaching, Alvotech has not explained why the POSA would have increased the concentration and dose of aflibercept instead of, *e.g.*, using Regeneron’s “mini-trap” fusion protein, *id.*, ¶89 (citing U.S. Patent 7,087,411 (Ex.2020, or “Daly”)), which—with its much smaller size (46 kDa) and “affinity comparable to” aflibercept, and its “optimized characteristics for local/intravitreal delivery”—would have been preferable for achieving high-concentration and high-molar-concentration intravitreal formulations, Ex.2020, 5:1-15, 9:8-26, 16:44-58. *See also Mylan*, 714 F. Supp. 3d at 740 (finding that retinal penetration is “critical for ... clinical use” and is facilitated by “small molecule size,” such that “the smaller 46 kDa ‘mini-trap’ had ‘optimized characteristics for local/intra-vitreous delivery’” and retinal penetration).

Again, Alvotech’s failure to heed the teachings of its cited art is emblematic of hindsight. *Sanofi*, 933 F.3d at 1379-80.

Second, *contra* Alvotech (at 28-29), no range presumption applies. Fundamentally, Alvotech cites no case in which the presumption applied to render obvious the selection of ***active ingredient dose and concentration*** for a pharmaceutical product. Pet. 29 (citing *E.I. DuPont de Nemours & Co. v. Synvina C.V.*, 904 F.3d 996, 1008 (Fed. Cir. 2018) (overlapping ranges applied to pressure and temperature conditions for chemical reaction); *Almirall, LLC v. Amneal Pharm. LLC*, 28 F.4th 265, 272 (Fed. Cir. 2022) (presumption applied to “carbomer thickener ranges”)). As the Federal Circuit has explained, “certain contextual characteristics ... can make the presumption inapplicable.” *Janssen Pharm., Inc. v. Teva Pharm. USA, Inc.*, 141 F.4th 1367, 1376 (Fed. Cir. 2025). “The cases [where the range presumption applied] are overwhelmingly about the makeup of, and/or processes of making, alloys or other compositions.” *Id.* at 1379. As *Janssen* held, the presumption does not apply to a context analogous to the one here: “a choice ... for the related doses in a (psychosis) treatment regimen.” *Id.* The Director should hold likewise here and “apply the normal full obviousness analysis, rather than a truncated version based on the invoked presumption.” *Id.*

Even if the range presumption otherwise applied, two exceptions bar its use here. First, the presumption may be rebutted “by showing that the prior art taught

away from the claimed range.” *DuPont*, 904 F.3d at 1006. As explained *supra* (at 33-37), the prior art here teaches away from increasing the VEGF antagonist dose to 8 mg; thus, any presumption is rebutted.

Second, the presumption does not apply where “the disclosed range is so broad as to encompass a very large number of possible distinct compositions.” *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1306 (Fed. Cir. 2011) (quoting *In re Peterson*, 315 F.3d 1325, 1330 n.1 (Fed. Cir. 2003)). Here, Vitti disclosed a broad dosage range of “0.05 mg to about 10 mg of a VEGF antagonist,” or 50 micrograms to “about” 10,000 micrograms removing the decimal places. Pet. 28; Ex.1007, ¶139. Moreover, that dose range is interrelated with the broad ranges of concentration (“10±1.5 mg/mL to 100±15.0 mg/mL of VEGF antagonist,” amongst others, Ex.1007, ¶87) and volume, where Vitti broadly discloses intravitreal injection volumes of “approximately [up to] 100 µL” or “approximately [up to] 500 µL.” Ex.1007, ¶127. And as explained, Vitti provides no teaching towards *either* the claimed dose or concentration thresholds, and instead merely describes using Eylea’s 2 mg, 40 mg/ml aflibercept composition. Thus, Vitti presents precisely the scenario where the range is “so broad as to encompass a very large number of possible distinct compositions” that requires “nonobvious invention.” *Genetics*, 655 F.3d at 1306 (citation omitted). And Alvotech’s mix-and-match approach (at 29) to arbitrarily select concentrations and volumes in certain of

Vitti's ranges (ignoring other ranges, including the up to 500 μ L volume range, Ex.1007, ¶127) to arrive at embodiments nowhere identified in the reference, while ignoring the countless other embodiments within those ranges, only reinforces that the presumption is inapplicable under *Genetics*.²

Finally, as explained *infra* §VI.A.3, “other pertinent objective indicia” of long-felt need and failure of others support nonobviousness, which further rebut any presumption of obviousness. *DuPont*, 904 F.3d at 1008.

2. The POSA Would Not Have Reasonably Expected To Succeed with High-Dose, High-Concentration Aflibercept

Even assuming a motivation to proceed with the high-concentration, high-dose composition meeting the claimed viscosity requirement (as explained, *supra* §VI.A.1, the prior art motivated against such compositions), the Petition separately fails to establish a reasonable expectation of succeeding with using such compositions to treat angiogenic eye disorders. Across the multitude of Alvotech's references (Pet. 23-27), not one discloses a composition with an 8 mg dose and a 100 mg/ml concentration, much less one used to treat an ophthalmic disorder and meeting the required viscosity. And because Alvotech cannot show a reasonable

² Alvotech improperly employs the same mix-and-match approach with Fiedler (at 67) to derive an 8 mg embodiment from its 30-100 μ L and 1-100 mg/ml ranges.

expectation of success as to any claim, its Petition fails as to each challenged claim.

In re Stepan Co., 868 F.3d 1342, 1345-46 (Fed. Cir. 2017).

a. Treatment

None of Alvotech's cited references teaches either the claimed dose or concentration, and none provides any indication that the required compositions would have succeeded as an intravitreal drug product in treating angiogenic eye disorders. The broad ranges taught in Vitti (Pet. 23-24) and the various other studies Alvotech cites (Pet. 24-25) simply did not involve 8 mg or 100 mg/ml intravitreal products and thus provide no expectation of success.

First, Alvotech asserts that Vitti provides a reasonable expectation of success for "the claimed concentration and dosage ranges," Pet. 24, but as explained *supra* §VI.A.1.b, Vitti describes only broad ranges of dose and concentration, and every specific composition it discloses uses the 2 mg, 40 mg/ml Eylea composition. Moreover, although Alvotech's motivation argument is premised on increasing dosing intervals, *supra* §VI.A.1.b; Pet. 20-21, Vitti nowhere teaches that increasing dose or concentration of the VEGF antagonist would achieve that outcome. To the contrary, Vitti teaches to ***use an additional active ingredient***—an Ang-2 inhibitor, Ex.1007, ¶15—to achieve that objective, which Alvotech simply ignores. Alvotech's reasonable-expectation-of-success argument thus rests on hindsight. *Univ. of Strathclyde v. Clear-Vu Lighting LLC*, 17 F.4th 155, 165 (Fed. Cir. 2021)

(given “reported failures ... and lack of any reliable indicator of success, ... it is only with the benefit of hindsight that a [POSA] would have had a reasonable expectation of success in view of the asserted references”).

Second, Alvotech cites (at 24) the Stewart review concerning aflibercept and ranibizumab, but Stewart likewise does not support a reasonable expectation of success. That a dose increase from 0.5 to 2 mg for aflibercept and ranibizumab was “*suggest[ed]*” to “prolong[] [the] duration of action” without “improv[ing] peak efficacy” does not inform the POSA to simply increase the dose *ad infinitum* to obtain ever greater durability without compromising efficacy or safety. Ex.1039, 1182 (emphasis added). Alvotech ignores that Stewart—in characterizing the results from the ranibizumab studies as “consistent with previously published models which predict that increasing the dose ... has a greater effect on its durability than its efficacy”—cites only to Gaudreault, *id.*, 1182 & n.114, which, as explained above, unambiguously teaches that increasing dose increased inflammation without any benefit, Ex.2014, 727-28 (“absent to moderate” inflammation for 0.5 mg and “moderate to severe” inflammation for 2 mg). The *Mylan* Court addressed Gaudreault in detail, finding that it taught that its dose increase “produced a problematic immune response without providing any advantage in VEGF inhibition.” 714 F. Supp. 3d at 738. Thus, Alvotech’s theory (at 24) that the POSA

would continue increasing dose so the VEGF antagonist would “lay in wait in the eye” lacks any support in the art.

Alvotech’s remaining evidence (at 24-25) fares no better. Ho fatally undermines Alvotech’s reasonable-expectation-of-success theory by finding, *contra* Stewart, that dose increases did not increase durability. Ex.1026, 2190. The CLEAR-IT study in Nguyen did not teach or suggest an 8 mg dose or higher concentrations of aflibercept, and the fact that 0.15 and 4 mg doses had “identical” “safety and tolerability profiles” in a single study teaches nothing about whether a composition with an 8 mg (or higher) dose and 100 mg/ml (or higher) concentration would succeed. Ex.1035, 586. Alvotech’s unelaborated, passing reference to unspecified “other studies” cannot support its theory either; its cited exhibits likewise do not teach or suggest the claimed high-dose, high-concentration compositions. Pet. 25 (citing Ex.1058, 20-21 (non-prior art Eylea regulatory materials); Ex.1030, 14 (“Lehman Presentation” addressing ongoing Eylea clinical studies with doses up to 4 mg, and reporting data only for 1.0 mg)). In asserting that these studies “demonstrated *intravitreal doses* of aflibercept did not pose a risk of systemic toxicity,” *id.*, Alvotech critically omits that none of these studies *involved the claimed doses or concentrations* and thus provide no expectation of success.

Finally, Alvotech again invokes the AU Label’s 8 mg overdoses, Pet. 25 (citing Ex.1009, 35), again ignoring teachings regarding increased IOP and the

warning to call Poison Control upon an overdose of 8 mg, *supra* §VI.A.1.b. Regardless, as Alvotech concedes, the AU Label teaches only a 40 mg/ml concentration of the VEGF antagonist, Pet. 30 (“8 mg [in] ... a volume of 200 microliters”), and thus provides no indication of success for the claimed high-dose, high-concentration compositions.

At bottom, none of Alvotech’s references comes anywhere close to the claimed dose and concentration. “It is only with the benefit of hindsight that a [POSA] would have had a reasonable expectation of success in view of the asserted references,” which is insufficient, *Strathclyde*, 17 F.4th at 165 (quoting *OSI Pharm., LLC v. Apotex Inc.*, 939 F.3d 1375, 1385 (Fed. Cir. 2019)), particularly in view of the ensuing real-world failure of others to develop higher-dose anti-VEGF products, *infra* §VI.A.3. Because Alvotech cannot “show a reasonable expectation of success for [the] specific [VEGF antagonist] dosage” and concentration required, its obviousness argument fails. *Teva Pharm. USA, Inc. v. Corcept Therapeutics, Inc.*, 18 F.4th 1377, 1381 (Fed. Cir. 2021).

b. Viscosity

As none of Alvotech’s cited art teaches the compositions of the claimed methods, it also does not provide any solution to achieve the recited viscosity level. This separately forecloses reasonable expectation of success.

As described above, high viscosity was a particular problem for high-concentration protein formulations and was especially problematic for intravitreal injections. *Supra* §§III.A, VI.A.1.a. Yet Alvotech only musters conclusory reasonable-expectation-of-success assertions based on the **goal** of low viscosity, rather than a **solution** in the prior art to achieve it. Pet. 25-27. That is inadequate.

First, Alvotech observes that Vitti “does not identify any concern about” viscosity, Pet. 25, but that is because ***it does not teach any specific high-dose anti-VEGF formulations, much less discuss their viscosity.*** Vitti’s sole mention of viscosity is in its definition of the generic term “excipient,” defined as “any non-therapeutic agent added to the formulation to provide a desired consistency, viscosity or stabilizing effect.” Ex.1007, ¶96. As discussed above, Vitti describes no specific high-concentration or high-dose formulations of a VEGF antagonist like aflibercept and offers no solution to achieve any particular viscosity, and thus cannot supply a reasonable expectation of success.

Second, Alvotech relies on Larson, which teaches that ***“use of one or more viscosity-lowering water soluble dyes*** permits the preparation of formulations having a viscosity ... less than or about 20 cP, or most preferably less than or about 10 cP, when measured at 25°C.” Ex.1010, ¶¶75, 77 (emphasis added). However, the cited Larson paragraphs do not mention intravitreal injection and do not teach that Larson’s solutions would work for intravitreal injection; rather, they refer only

to “SC [subcutaneous] or IM [intramuscular] injection.” *Id.*, ¶75. Larson’s sole mention of intravitreal injections is its generic listing of Eylea (*id.*, ¶167) alongside **over 700** other biologic products, *id.*, ¶¶88-190. Larson thus offers no teaching that its “water soluble dye” solution would work for an intravitreal injection. Not even Alvotech argues (much less offers evidence) that the POSA would have considered a “water soluble dye” suitable for injection into a patient’s eye.³ Pet. 25-26. Alvotech thus relies on unspecified “other ways” to reduce viscosity, citing Vitti. Pet. 26-27. But as explained, Vitti merely defines the generic term “excipient” to include agents that may affect viscosity, without teaching any particular way to do so—much less with the claimed compositions, which Vitti nowhere discloses. Thus, Larson’s solution for reducing viscosity is concededly inapplicable, and Vitti discloses no solution for reducing viscosity at all.

³ That Larson is directed to subcutaneous and intramuscular (not intravitreal) injections and employs a solution to viscosity-related problems (water-soluble dyes) that neither Larson nor Alvotech asserts is appropriate for intravitreal injections fatally undermines Alvotech’s claim that “a POSA would have been motivated to combine Vitti and the Label with Larson” or “to combine the teachings of Larson with the Label and ... Furfine and Dix.” Pet. 22, 53.

Alvotech relies on Larson’s target viscosity ranges, Pet. 25, 33, but Larson teaches that its preferred ranges depend on “use of one or more viscosity-lowering water soluble dyes,” which Alvotech does not seek to introduce, Ex.1010, ¶77. In contrast, Larson teaches that “in the absence of a viscosity-lowering water soluble dye,” high-concentration protein formulations “may have viscosities greater than 100 cP ... or even greater than 1,000 cP, when measured at 25°C”—well outside the claimed range. *Id.*, ¶75. Larson thus demonstrates an absence of a generic expectation of success to achieve low viscosity, *contra* Pet. 25-26. And even accepting that low viscosity was a desirable goal, “recit[ing] a goal without teaching how the goal is attained” does not provide “a reasonable expectation of success.” *Endo Pharm. Inc. v. Actavis LLC*, 922 F.3d 1365, 1376 (Fed. Cir. 2019).

Alvotech again attempts to invoke the range presumption with Larson’s viscosity range, Pet. 33, but the presumption is inapplicable given that Larson’s viscosity range is entirely untethered from the claimed compositions. Larson does not teach a single structural limitation of the claims, and no case suggests that a numerical range disclosed in isolation can render it obvious in every conceivable circumstance. To the contrary, “the number of differences from the prior art” informs whether the presumption applies, *Janssen*, 141 F.4th at 1376, and the Federal Circuit has explained that “[a] *prima facie* case of obviousness may be made when the only difference from the prior art is a difference in the range or value of a

particular variable.” *In re Kumar*, 418 F.3d 1361, 1366 (Fed. Cir. 2005).⁴ Because Larson does not teach the required dose, concentration, volume, or viscosity of any VEGF antagonist formulation, the range presumption does not apply.

Alvotech also references Furfine and Dix, Pet. 26, but neither teaches any of the claimed compositions, nor do they report viscosity data.⁵ Alvotech quotes Furfine’s disclosure that it provides formulations “particularly suitable for intravitreal injection,” Pet. 26 (quoting Ex.1005, 4:65-67), but Furfine describes no specific embodiment with a concentration of 100 mg/ml or accompanying viscosity data; to the contrary, Furfine’s Examples have a maximum concentration of 50 mg/ml. Ex.1005, Examples 1-8. Alvotech also cites Dix (at 26), but Dix involves intravenous application of aflibercept to treat cancer and nowhere mentions

⁴ The Court in *Janssen* reasoned that the statement in *Kumar* was not a “categorical limit” to the range presumption but explained that differences between the prior art and claims besides the overlapping range nonetheless informed whether the presumption was applicable. 141 F.4th at 1376.

⁵ Alvotech cites Furfine and Dix as establishing a reasonable expectation of success only with respect to the claimed viscosity values, not treatment of angiogenic eye disorders with the claimed high-dose, high-concentration compositions.

intravitreal use or any viscosity values, much less an ophthalmic composition with the recited viscosity. Ex.1006, 1:29-31.

Lacking any prior-art basis to arrive at the required compositions with the claimed viscosity, Alvotech cites its expert's opinions about general viscosity considerations. Pet. 34-35 (citing Ex.1004, ¶¶52-70, 127). But such expert testimony is not a basis to institute PGR, which must be based on "prior art." 37 C.F.R. § 42.204(b)(4); *Qualcomm Inc. v. Apple Inc.*, 24 F.4th 1367, 1376 (Fed. Cir. 2022) ("evidence such as expert testimony and party admissions are not themselves prior art references"); *see also* July 31, 2025 Memorandum to the Board, <https://www.uspto.gov/subscription-center/2025/uspto-issues-memorandum-clarifying-enforcement-rule-104b4-ipr-proceedings> (analogous rule for IPRs). Regardless, the only art cited by Alvotech's expert that Alvotech's Grounds rely upon is Larson, which is deficient as explained above. And Alvotech's inability to identify any references disclosing any specific high-dose, high-concentration intravitreal formulations forecloses its argument that it would have been "routine optimization" to tweak such formulations to achieve "the claimed viscosity range." Pet. 35, 63; *see Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1368 (Fed. Cir. 2007) ("[T]he optimization of a range or other variable within the claims ... flows from the 'normal desire of scientists or artisans to *improve upon what is already generally known.*'" (emphasis added) (citation omitted)).

3. Objective Evidence Supports Nonobviousness

While Alvotech fails to show *prima facie* obviousness, objective evidence of teaching away, long-felt need, and failure of others further supports nonobviousness.

First, in addition to refuting motivation, teaching away also constitutes objective evidence of nonobviousness. *E.g.*, *Monarch Knitting Machinery Corp. v. Sulzer Morat GmbH*, 139 F.3d 877, 885 (Fed. Cir. 1998). As explained *supra* §VI.A.1.b, prior art including the AU Label taught away from the claimed 8 mg dose of aflibercept.

Second, there was a long-felt, “unmet need for a long-acting anti-VEGF that decreases the treatment burden for patients with nAMD,” Ex.2022, 1036, along with a failure of others to meet that need. “Evidence of long-felt need is ‘particularly probative of obviousness when it demonstrates both that a demand existed for the patented invention, and that others tried but failed to satisfy that demand.’” *Millenium*, 862 F.3d at 1369 (citation omitted). That is precisely the case here. There is no dispute that there was a long-felt need to reduce dosing frequency; Alvotech agrees that it was “long known to minimize [intravitreal] injections in the care of patients.” Pet. 1; *e.g.*, Ex.2023 (Dixon 2009), 1577 (“limitations of current therapy include the need for frequent intraocular injections”). Yet notwithstanding this long-felt need to reduce dosing frequency, multiple companies that sought to develop higher-dose VEGF antagonist products to meet that need failed. *Supra*

§II.B. Abicipar was developed at over a threefold higher molar concentration than Eylea, yet despite its “high molar dose,” Ex.2022, 1028, abicipar was withdrawn and never received FDA approval given its high inflammation levels. Ex.2008; *see Pfizer Inc. v. Teva Pharm. USA, Inc.*, 460 F. Supp. 2d 659, 662 (D.N.J. 2006) (“[n]ot getting to market with FDA approval is an appropriate benchmark for failure [of others]”). Likewise, brolucizumab was developed to lessen treatment burden and contained a higher (6 mg) dose than Eylea (2 mg), yet it also resulted in higher intraocular inflammation, Ex.2024, 92; Ex.2012, leading to cases of “irreversible severe vision loss” and abandonment by ophthalmologists, Ex.2013, A7; *see supra* §II.B.⁶

⁶ The ultimate failures of abicipar and brolucizumab occurred after the priority date of the '036 patent. However, such later failures of others serve as objective evidence supporting nonobviousness. *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Pat. Litig.*, 2010 WL 3766530, at *2 (D. Del. Sept. 21, 2010) (“If others continue to fail despite having the patent as prior art, such failures may illustrate just how radically different the patent was from past discoveries. This would be highly relevant to a finding of non-obviousness.”); *see Knoll Pharm. Co. v. Teva Pharm. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004).

In contrast to these failures, Regeneron’s inventors succeeded by developing a composition at a higher VEGF antagonist dose than any anti-VEGF intravitreal product. That composition described in the ’036 patent and encompassed by the claims—8 mg of aflibercept delivered at a 114.3 mg/ml concentration and 70 μ L volume—is now marketed as Eylea HD. Ex.2007, 1; Ex.1001, Example 13, Figs. 19A-19E (stability data for Eylea HD composition); *id.*, Examples 3, 5, 9, Figs. 3A-3C, 5, 9 (viscosity data for formulations up to 170 mg/ml aflibercept). Unlike abicipar and brolucizumab, Eylea HD achieved the same efficacy as Eylea “despite the longer treatment intervals of every 12 or 16 weeks, which allowed for fewer total injections,” and “[j]ust as important, ... the rate of adverse reactions in the 8-mg aflibercept group was infrequent and consistent with the known rate for the 2-mg aflibercept.” Ex.2025 (Park), 5; *see* Ex.2007, 1 (instructing to administer Eylea HD “once every 8 to 16 weeks, +/- 1 week,” after three loading doses).⁷ In contrast to others’ failures, the inventors’ success at developing an anti-VEGF product that achieved not only extended dosing but also efficacy and safety strongly supports

⁷ Vabysmo (faricimab) has also found success in extending dosing, *supra* §II.B, but Genentech’s approach with faricimab followed the approach in Vitti of inhibiting both VEGF and Ang-2, Ex.2026, and uses a lower dose (6 mg) than the 8 mg dose claimed here.

nonobviousness. *Millenium*, 862 F.3d at 1369; *Amgen*, 66 F.4th at 964 (crediting evidence of long-felt need and failure of others where evidence “establish[ed] that many PDE4 inhibitors failed to progress in experimentation and trials or were not sufficiently effective at tolerable doses”).

B. Ground 2: Alvotech Fails To Demonstrate Obviousness over Furfine, Dix, AU Label, Fiedler, and Larson

Alvotech’s Ground 2 combination of Furfine, Dix, AU Label, Fiedler, and Larson overlaps substantially with Ground 1 and does nothing to cure the lack of motivation and reasonable expectation of success in creating a high-dose, high-concentration aflibercept formulation discussed *supra* §VI.A. The POSA would not have been motivated to combine these five asserted references to achieve the high-dose, high-concentration formulations of claim 1, nor would the POSA have any reasonable expectation of success in doing so. The Director should deny institution as to Ground 2.

1. The Prior Art Motivated Against, and Teaches Away from, Using a High Dose of Aflibercept at a High Concentration

As in Ground 1, Alvotech’s myopic focus on discrete prior-art passages in isolation blinks reality. As the prior art as a whole demonstrates, the POSA understood the dangers associated with high-dose, high-concentration anti-VEGF formulations and was motivated against pursuing such a formulation. *Supra* §VI.A.1. Many of Alvotech’s Ground 2 motivation arguments (at 49-53) simply

regurgitate its motivation points from Ground 1 and fail for the same reasons. *Id.* Moreover, the teachings of Furfine, Dix, and Fiedler do not substantiate obviousness.

a. Alvotech’s Recycled Ground 1 Arguments Again Fail To Establish the POSA’s Motivation

Alvotech starts by contending (at 49) that the POSA knew that the “solution” to the “treatment burden” concern “was to increase the VEGF antagonist concentration and thus increase the VEGF antagonist dose.” In support, Alvotech cites only its expert’s opinion regarding the AU Label (*id.* (citing Ex.1003, ¶271)) and cross-references its Ground 1 arguments (*id.*). But as explained, no intravitreal formulations in development at the time met either the “at least about 8 mg” or “at least 100 mg/ml” claim limitations—and the prior art as a whole taught against increasing dose and concentration. *Supra* §VI.A.1. Moreover, Alvotech’s continued reliance on the AU Label fares no better in Ground 2. *Id.*

Alvotech’s remaining motivation arguments—based on Stewart, Ho, Nguyen, AU Label, and Ex.1030, *see* Pet. 49-51—fail to support obviousness. As discussed in detail above, *supra* §VI.A.1:

- (1) Stewart speculated that increasing dose increases durability, Ex.1039, 1182;

(2) Ho debunked Stewart's hypothesis and found no "clinically meaningful difference" in "durability," Ex.1026, 2190;

(3) Nguyen's CLEAR-IT study only compared doses of 0.15 and 4 mg; did not evaluate doses higher than 4 mg; did not disclose the concentration of aflibercept or the injection volume; and did not evaluate whether the 4 mg dose had any benefits over the approved, marketed 2 mg dose, Ex.1035, 581-83, 586;

(4) the AU Label, when considered "for everything it teaches" without "disregard[ing]," *Recor*, 2025 WL 944511, at *2, its instruction to "contact the Poisons Information Centre" upon accidental administration of an 8 mg "overdose," Ex.1009, 35, teaches away from the 8 mg dose; and

(5) a study involving only a "single intravitreal injection" between 0.05 and 4.0 mg and no higher dosages, and reporting data only for the 1.0 mg dose, Ex.1030, 18-19, does not support Alvotech's contention (at 51) that the "POSA knew that the 'maximum tolerated dose' of

aflibercept had not been reached” and would increase dose indefinitely until an 8 mg or higher dose were achieved.

Alvotech’s reliance (at 51) on these references as purportedly showing the safety and efficacy of “high-concentration” VEGF antagonist formulations is further undermined by the fact that these cited passages concern dose, not concentration. *See* Ex.1039, 1182 (comparing 0.5 with 2 mg formulations with no mention of concentration); Ex.1026, 2182, 2190 (same); Ex.1035, 586-87 (comparing 0.15 with 4 mg formulations with no mention of concentration); Ex.1030, 18 (“maximum tolerated dose”); Ex.1009 (discussing 8 mg overdose with no increase in concentration). Such references—which discuss formulations with doses of less than 8 mg and unknown concentrations—could not possibly motivate the POSA to use a formulation with an 8 mg or higher dose and a concentration of 100 mg/ml or higher.

In sum, these references’ teachings as a whole do not motivate—and instead teach away from—the use of the claimed high-dose, high-concentration formulations. *Supra* §VI.A.1.

b. Dix, Fiedler, and Furfine Do Not Establish the POSA’s Motivation To Use a High-Dose, High-Concentration Formulation

As compared to Ground 1, Alvotech swaps Vitti for Dix, Fiedler, and Furfine to argue that the POSA would have been motivated to use high-dose, high-

concentration VEGF antagonist formulations. Pet. 51-53. Crucially, however, none of those references discloses the claimed high-dose, high-concentration formulations nor provides any safety or efficacy data for an anti-VEGF intravitreal formulation at or above 100 mg/ml. Accordingly, Alvotech points to nothing in those references to displace the POSA's understanding of the risks associated with a high-concentration formulation at or above 100 mg/ml. *Supra* §VI.A.1.a.

Moreover, Fiedler, Dix, and Furfine each present additional issues that would motivate the POSA against using the claimed formulations.

Dix: Alvotech's reliance on Dix for obviousness is fatally undermined by the breadth of Dix's disclosure of concentration ranges, as well as its non-disclosure of intravitreal use.

First, Alvotech relies on Dix (at 52, 61) for its disclosure of "a high concentration stable liquid formulation" with "50-100 mg/ml of the fusion protein." Ex.1006, 2:20-24, 10:1-55. But this argument presents nearly identical issues as Mylan's prior failed reliance on a related Dix patent (Dix '226) in the *Mylan* litigation. *Mylan* concerned the '865 patent, which claimed, *inter alia*, a VEGF antagonist formulation suitable for intravitreal use. Here, the '036 patent claims, *inter alia*, a VEGF antagonist formulation (at a significantly higher concentration) that is also administered via intravitreal injection. Whereas both the '865 patent and the '036 patent involve intravitreal administration, neither Dix nor Dix '226

“disclose[s], suggest[s], or contemplate[s] ophthalmic formulations or intravitreal injections.” *Mylan*, 714 F. Supp. 3d at 745. Further, Mylan relied on a broad range of possible concentrations in Dix ’226 (10-50 mg/ml), and only one point within that range overlapped with the claimed concentration (40 mg/ml). *Id.* Here, the Dix range relied on by Alvotech is even broader (50-100 mg/ml) and likewise overlaps with the claimed range at only one specific point (100 mg/ml). Neither Dix nor Dix ’226 provides any “guidance as to whether any formulations in that range would be preferable for intravitreal use.” *Id.* These key findings supported the Court’s holding that Dix ’226 did not render the ’865 patent obvious. *Id.* The same result obtains here with respect to Dix and the ’036 patent.

Additionally, the *Mylan* Court repeatedly held that references containing no teachings of intravitreal use could not support a motivation to use their teachings in an intravitreal formulation. *See id.* at 740 (“As for Fraser, that reference undisputedly provides no teachings regarding intravitreal use of VEGF Trap and thus provides no motivation either.”); *id.* at 743 (finding no obviousness when “neither reference provides any motivation to use aflibercept intravitreally”). The Director should find the same here. Alvotech has not established that intravitreal and non-intravitreal formulations are interchangeable or that the POSA would view the latter as informative of the former; thus, the POSA would not have been

motivated to use non-intravitreal references such as Dix to develop an intravitreal formulation.

Nor does Alvotech's reliance (at 52, 61) on Dix's Example 4-5 disclosures of 100 mg/ml formulations support a motivation to use the claimed formulations. Ex.1006, 10:60-12:10. The POSA would not have expected, based on the purported stability of these "lyophilized" and "reconstituted" formulations, *id.*, that other, high-concentration, liquid formulations would be stable, let alone suitable for intravitreal use. To the contrary, Dix's Examples 1-3—assessing the stability of 50, 75, and 100 mg/ml liquid formulations—found that percent native conformation (an indicator of stability) decreased as concentration increased. *Id.*, 7:40-9:67. Only the 50 mg/ml formulations evidenced at least 98% native conformation. *Id.*; *see Mylan*, 714 F. Supp. 3d at 747 (formulation "stability," including a greater than "98% native conformation, indicated to the POSA that ... 'there's a relatively lower risk of inflammation'" (quoting Ex.2015, 2170:5-21 (Trout))). Moreover, each Example 1-3 formulation had 20% sucrose, disclosed in Dix as a stabilizer. Ex.1006, 7:40-9:67. Accordingly, given (1) Dix's non-disclosure of intravitreal administration; (2) its teaching that increasing concentration beyond 50 mg/ml reduces liquid formulation stability, thereby increasing the risk of inflammation for intravitreal administration; and (3) its liquid formulations' inclusion of amounts of sucrose inappropriate for intravitreal administration, Ex.2015, 1679:13-21 (Graham), Dix would not have

motivated the POSA to use the claimed high-concentration formulations intravitreally.

Finally, Alvotech's reliance (at 51-52, 61) on Dix's claims reciting "[a] stable liquid formulation of comprising 100 mg/mL of [aflibercept] ... [and] 5% sucrose" is unavailing for similar reasons. Ex.1006, claims 1-2. As explained, Dix never discloses intravitreal administration. Even if Dix's claimed formulations are sufficiently stable for intravenous or subcutaneous administration, *id.*, 10:6-39, the POSA would not understand them to be sufficiently stable for intravitreal administration, especially given Dix's instruction that the stability of its liquid formulations decreases as concentration increases from 50 to 75 or 100 mg/ml. *Id.*, 7:40-9:67. Furthermore, while Dix provides stability data for liquid 100 mg/ml formulations containing 20% sucrose and lyophilized and reconstituted 100 mg/ml formulations containing 5% sucrose, Dix contains no such data for liquid 100 mg/ml formulations containing only 5% sucrose, as claims 1-2 recite. *Id.*, 9:20-12:10; *see id.*, 10:29-57 (listing % degradation for formulations with "5-20% sucrose" without specifying a precise sucrose concentration). Absent such data, and given Dix's teaching that, when lyophilization is not employed, more sucrose is needed to stabilize its formulations (20% vs. 5%), *id.*, 7:40-12:40, the POSA would not have been motivated to use Dix's claimed formulations intravitreally—especially given

that Dix provides no viscosity data and that a “stable” formulation is not necessarily a low-viscosity one. *Infra* §VI.B.2.

Fiedler: The *Mylan* litigation is similarly instructive as to Alvotech’s reliance (at 61) on Fiedler. Fiedler discloses no specific high-concentration formulations. Rather, it discloses a broad concentration range (“1 to 100 mg/ml”), which overlaps with the claimed range at only one point (100 mg/ml), and which applies generically to a “VEGF antagonist,” *i.e.*, “an anti-VEGF antibody or an antigen-binding fragment [thereof] or a soluble VEGF receptor fusion protein and more preferably ... ranibizumab or aflibercept.” Ex.1011, ¶¶18-19. Dix ’226 likewise covered a broad concentration range (10-50 mg/ml) and “a broader generic set of VEGF-specific fusion protein antagonist molecules.” *Mylan*, 714 F. Supp. 3d at 732 (cleaned up). The *Mylan* Court held that “[a]lthough Dix disclosed the range of 10-50 mg/ml of a VEGF antagonist, it disclosed no 40 mg/ml formulation [and] did not teach to use 40 mg/ml of the specific protein claimed.” *Id.* at 745. The Director likewise should find that Fiedler’s broad disclosure of 1-100 mg/ml of a generic VEGF antagonist does not disclose formulations with 100 mg/ml or higher of the specific anti-VEGF proteins recited by the challenged claims, especially given Fiedler’s non-disclosure of any specific high-concentration formulations and its instruction that concentration is “most preferably 6 or 10 mg/ml.” Ex.1011, ¶76.

Fiedler thus would not have motivated the POSA to use the claimed high-concentration formulations.

Furfine: Alvotech also relies (at 52-53, 61) on *Furfine*, which, like Fiedler, discloses no specific high-concentration embodiment, instead reciting and claiming only a generic range of 1-100 mg/ml. Ex.1005, 2:4-9, 2:49-54, claim 1. *Furfine*'s specific embodiments have a maximum concentration of “about 80 mg/ml,” *id.*, 2:55-60, and its examples describe formulations with a maximum concentration of only “50 mg/ml,” *id.*, 7:60-10:49. Moreover, Alvotech makes no attempt to argue that *Furfine* discloses the claimed dose of “at least about 8 mg” or the claimed injection volume of “about 100 microliters or less,” much less any accompanying viscosity data. Only with hindsight can Alvotech allege that the POSA would have been motivated by these disclosures to use the claimed high-dose, high-concentration formulations.

“Overlapping Ranges”: Alvotech's reliance (at 61) on the 1-100 mg/ml disclosures of Fiedler and *Furfine*, as well as the 50-100 mg/ml disclosure of Dix, as establishing *prima facie* obviousness is unavailing for the same reasons discussed above with respect to Vitti. *Supra* §VI.A.1.b. Application of the obviousness presumption in this particular inventive context (*i.e.*, the selection of the dose and concentration of the active ingredient in a protein formulation) is inappropriate, *see Janssen*, 141 F.4th at 1379, and Alvotech's cases—*DuPont*, 904 F.3d at 1008, and

Almirall, 28 F.4th at 272, which address claims to chemical reaction conditions and thickener amount ranges, respectively—are inapt. Even if the obviousness presumption applied, it would be rebutted by the prior-art teach-away from high-dose, high-concentration formulations, as well as the “other pertinent objective indicia” discussed above. *DuPont*, 904 F.3d at 1006, 1008; *supra* §VI.A.1.b. Additionally, just like with Vitti’s disclosure of “10±1.5 mg/mL to 100±15.0 mg/mL of VEGF antagonist,” Ex.1007, ¶87, the 1-100 mg/ml range of Furfine and Fiedler and the 50-100 mg/ml range of Dix are “so broad as to encompass a very large number of possible distinct compositions” that requires “nonobvious invention.” *Genetics*, 655 F.3d at 1306 (citation omitted). That the Dix and Fiedler disclosures are not limited to claim 1’s proteins further renders the presumption of obviousness inappropriate. *Supra* §VI.A.1.b; *see Mylan*, 714 F. Supp. 3d at 730-32 (finding that Dix ’226’s disclosure “of ‘10-50 mg/ml of the fusion protein’” could not invoke the presumption because it “is not a small range” and “is not linked to aflibercept specifically, but instead refers to a generic ‘VEGF-specific fusion protein antagonist’”). Alvotech cannot salvage its deficient motivation and reasonable-expectation-of-success showings by relying on any obviousness presumption.

2. The POSA Would Not Have Reasonably Expected To Succeed with High-Dose, High-Concentration Aflibercept

Alvotech’s theory of why the POSA would have reasonably expected success with a high-dose, high-concentration VEGF antagonist formulation largely

duplicates its Ground 1 theory. *See* Pet. 23-27, 53-55. As explained above, the POSA would not have reasonably expected to succeed with the claimed high-dose, high-concentration formulation. *Supra* §VI.A.2.

First, Alvotech argues that “a POSA would have reasonably expected that high-concentration VEGF antagonist formulations (having a corresponding higher-dosage) would safely and effectively treat the same angiogenic eye diseases as low-concentration VEGF antagonist.” Pet. 53. But Alvotech’s only citation for this proposition is a *supra* cite to its identical argument in Ground 1. *Id.* As detailed above, the POSA would not have reasonably expected a high-dose, high-concentration VEGF antagonist formulation to treat angiogenic eye diseases safely and effectively. *Supra* §VI.A.2.a.

Second, Alvotech rehashes its Ground 1 argument that because a four-fold increase in ranibizumab dose from 0.5 to 2 mg “showed similar results in efficacy and no adverse effects, ... a POSA would have had a reasonable expectation that a 4-fold increase in aflibercept dosage would also be safe and effective.” Pet. 53-54. This argument fails for the reasons explained above. *Supra* §VI.A.2.a. The purported success of one particular four-fold dosage increase (0.5 to 2 mg of ranibizumab) does not mean that *any* four-fold dosage increase will succeed without any safety or efficacy tradeoffs. Indeed, references such as Gaudreault conveyed

serious safety concerns (*e.g.*, increased inflammation) associated with VEGF antagonist dose increases. *Id.*

Third, Alvotech argues that “to the extent a POSA would have been concerned about the viscosity of high-concentration formulations,” *Dix*, *Furfine*, and *Larson*⁸ would have assuaged such concerns. Pet. 54-55. As explained, high viscosity was a particular problem for high-concentration protein formulations, especially for intravitreal injections. *Supra* §§III.A, VI.A.1.a. As the *Mylan* Court held, “[a]ntibodies tend to form viscous solutions at high concentration,” and “high viscosity would be especially problematic for intravitreal injections because it leads to very long injection times and even can make the formulation unusable.” 714 F. Supp. 3d at 743 (cleaned up). As explained below and *supra* §VI.A.2.b, Alvotech cannot explain away this viscosity concern by invoking teachings from *Dix*, *Furfine*, and *Larson*.

Dix: Alvotech argues (at 54) that “*Dix* teaches that ‘high concentration’ VEGF antagonist formulations ... can be made into stable liquid formulations.” This argument is both irrelevant and misleading. Alvotech offers no relationship between

⁸ Alvotech does not, however, rely on these references (or *Fiedler*) as supporting a reasonable expectation of success in treating angiogenic eye disorders with the claimed compositions.

viscosity and stability. In any event, Dix discloses intravenous formulations for cancer treatment, not intravitreal formulations, which have different and more demanding viscosity requirements. *See supra* §§III.A, VI.A.1.a. Dix discloses no viscosity data whatsoever. Alvotech has not demonstrated that the POSA would have a reasonable expectation of success in taking Dix’s non-intravitreal formulation and modifying it for intravitreal use.

Furfine: Alvotech argues (at 54) that Furfine’s formulations are “suitable for intravitreal injection,” but fails to acknowledge that Furfine’s specific embodiments have a maximum concentration of “about 80 mg/ml,” Ex.1005, 2:55-60, and its Examples describe formulations with concentrations of 40 and 50 mg/ml, *id.*, 7:60-10:49; *see supra* §VI.A.2.b. Moreover, Furfine reports no viscosity data. Coupled with the prior art’s teaching away from high-concentration formulations, the POSA would not have reasonably expected to succeed in combining Furfine with other references to achieve the claimed “at least 100 mg/ml” concentration with the claimed viscosity.

Larson: As in Ground 1, Alvotech again invokes Larson, which fails to supply a reasonable expectation of success. *Supra* §VI.A.2.b. Alvotech contends that Larson “teaches that the viscosity of high-concentration biologics must be low enough that the biologic can be administered intravitreally through a 18-32 gauge needle.” Pet. 54-55. Alvotech misreads Larson. Larson’s low-viscosity

formulations are directed to non-intravitreal uses, specifically subcutaneous and intramuscular injections. *See, e.g.*, Ex.1010, Abstract (“Concentrated, low-viscosity, low-volume liquid pharmaceutical formulations of proteins have been developed. Such formulations can be rapidly and conveniently administered **by subcutaneous or intramuscular injection**, rather than by lengthy intravenous infusion.”); *id.*, ¶21 (nearly identical); *id.*, ¶74 (stating that “low-viscosity protein solutions” can be “useful for **subcutaneous (SC) and intramuscular (IM) injections**”); *id.*, ¶224 (describing administration “by **intramuscular, intraperitoneal (i.e., into a body cavity), intracerebrospinal, or subcutaneous injection**”) (emphases added). Larson’s only mention of intravitreal administration is an isolated reference to Eylea—among over 700 other listed biological products. *Id.*, ¶167; *supra* §VI.A.2.b.

As explained *supra* §VI.B.1.b, references disclosing non-intravitreal formulations do not inform the POSA what will be suitable for intravitreal use. In addition, as explained above, Larson teaches to reduce viscosity using a “water soluble dye,” but Alvotech makes no effort to demonstrate that such a dye would be suitable for intravitreal administration. *Supra* §VI.A.2.b. Larson therefore would not provide a reasonable expectation of success in achieving the claimed high-dose, high-concentration, low-viscosity formulations. *Id.*

3. Objective Evidence Supports Nonobviousness

Finally, for the same reasons explained *supra* §VI.A.3, objective evidence supports a finding of nonobviousness.

C. Grounds 4-5: Alvotech Fails To Demonstrate Obviousness

In Grounds 4-5, Alvotech asserts that “claims 2 and 3 would have been obvious over the Ground 1 references” (Ground 4) and “over the Ground 2 references” (Ground 5), both “in combination with the Clinical Review.” Pet. 86, 88. These Grounds thus fail for the same reasons as above; as explained, neither the Ground 1 nor Ground 2 references demonstrate the POSA’s understanding that intravitreal injection of higher-concentration aflibercept formulations would have the same clinical effects as lower-concentration formulations—including (as recited by claims 2-3) with respect to maintenance or achievement of “a reduction in central retinal thickness” and “an improvement in best corrected visual acuity.” *See supra* §§VI.A-B.

Alvotech relies on the Clinical Review solely for the disclosure that patients receiving aflibercept would not experience a significant increase in blood pressure. But the cited conclusion was drawn after “IVT administration of doses of up to 4 mg/eye,” and the recommended dosage in the Clinical Review was 2 mg. Ex.1008, 8, 10. Thus, the Clinical Review did not evaluate the safety of administering a higher, 8 mg dose of aflibercept. Moreover, it noted a dose-dependent correlation

between aflibercept concentrations and blood pressure elevations upon systemic administration of aflibercept, suggesting that higher doses (even if administered intravitreally) carry a greater risk of causing a significant increase in blood pressure. *Id.* Thus, Grounds 4-5 fail because Alvotech has not shown that the Clinical Review would have motivated the POSA with a reasonable expectation of success to increase aflibercept dose to achieve the clinical outcomes recited by claims 2-3 while avoiding a significant increase in blood pressure.

D. Ground 3: Alvotech Fails To Demonstrate Lack of Written Description

Ground 3 challenges the adequacy of the '036 patent's written description, the exact same issue already addressed during prosecution. According to Alvotech, the claims are invalid under 35 U.S.C. § 112(a) because the claims cover a "broad genus of formulations" while "the specification discloses only a small number of species," Pet. 77, and "because the[] [claims] do not require a buffer—a component the specification makes clear is required," Pet. 83. Alvotech is wrong on both fronts. First, the specification discloses a representative number of species sufficient to demonstrate the inventors' possession of the full scope of the claims. Second, Alvotech's no-buffer theory is not only legally unfounded but also disregards the knowledge of the POSA concerning self-buffering formulations. Alvotech cannot show a reasonable likelihood that the claims are invalid for lack of written description.

1. The Specification Demonstrates Possession of the Full Scope of the Claims

A patent is adequately described if “the disclosure ... reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date.” *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc). Where a patent claims a genus, written description may be satisfied if “a representative number of species falling within the scope of the genus” is disclosed. *Id.* at 1350. There are no “bright-line rules governing ... the number of species that must be disclosed to describe a genus claim, as this number necessarily changes with each invention, and it changes with progress in a field.” *Id.* at 1351. Overall, “the representative-species inquiry is directed to whether the inventor ‘has truly invented the genus’ as opposed to ‘a research plan, leaving it to others to explore the unknown contours of the claimed genus.’” *Ajinomoto Co. v. ITC*, 932 F.3d 1342, 1359 (Fed. Cir. 2019) (citation omitted).

Alvotech’s primary challenge to the ’036 patent’s written description is that the claims encompass a “massive genus” of formulations but the specification discloses “only a small corner of the claimed genus.” Pet. 76-77. According to Alvotech, “there is no disclosure of a representative number of species in the genus because ... the disclosed species are highly similar to one another ... and do not reflect the full scope of the claims.” Pet. 80. Alvotech is wrong.

The specification discloses a representative number of species. As discussed *supra* §III.A, the patent’s disclosures related to Figures 3B, 3C, 5, and 9 discuss at least 31 formulations with a concentration of 100 mg/ml or higher and a viscosity of less than 15 cP. Ex.1001, 9:46-11:26, 38:47-67, 42:17-22, Figs. 3B, 3C, 5, 9. Those formulations include aflibercept at concentrations between 100 and 155 mg/ml; viscosity reducers (*e.g.*, arginine, lysine, sodium chloride, magnesium chloride) at concentrations between 0 and 200 mM; buffers (*e.g.*, phosphate, histidine) at concentrations such as 10 and 20 mM; thermal stabilizers (*e.g.*, sucrose) at amounts such as 5%; surfactants (*e.g.*, polysorbate 20) at amounts such as 0.03%; and counterions and amino acids (*e.g.*, sodium sulfate, sodium thiocyanate, sodium citrate, glycine, sodium aspartate, sodium glutamate, and combinations thereof) at concentrations such as 40 and 50 mM. *Id.* Alvotech’s characterization of over thirty formulations comprising more than a dozen ingredients and numerous concentrations and amounts thereof as “highly similar to one another” is facially incredible.⁹ Pet. 80.

⁹ Similarly, Alvotech’s complaint (at 76) that “Regeneron’s own specification teaches no more about making high-concentration formulations with the claimed viscosity levels than the prior art” is plainly false. As explained above, *supra* §§VI.A-B, there were *no prior-art disclosures* of high-concentration, low-viscosity

The POSA’s knowledge confirms that these formulations are representative. “[T]he patent specification is written for a [POSA], and such a person comes to the patent with the knowledge of what has come before,” such that “it is unnecessary to spell out every detail of the invention in the specification.” *LizardTech, Inc. v. Earth Res. Mapping, Inc.*, 424 F.3d 1336, 1345 (Fed. Cir. 2005). Here, the ingredients in the ’036 patent’s disclosed formulations—including buffers such as histidine and phosphate, stabilizers such as sucrose, and surfactants such as polysorbate—are “known structures” with which the POSA would have been exceedingly familiar. *Mylan*, 714 F. Supp. 3d at 755 (quoting Ex.2015, 2096:7-2099:18 (Trout)); *see also id.* at 751 (“categories of organic co-solvent, buffer, and stabilizing agent” are “structures [that] were well known in the art” (quoting Ex.2015, 2110:1-5 (Trout)). “For such known classes of structures, [a] patent d[oes] not need to provide an exhaustive description to the POSA.” *Id.* at 752. Indeed, a “patent need not teach, and preferably omits, what is well known in the art.” *McRO, Inc. v. Bandai Namco Games Am. Inc.*, 959 F.3d 1091, 1102 (Fed. Cir. 2020). The POSA would have

intravitreal formulations. The ’036 patent, by contrast, discloses at least 31 such formulations with considerable variety in terms of ingredients—and amounts and concentrations thereof—and thereby extensively teaches “making high-concentration formulations with the claimed viscosity levels.” Pet. 76.

recognized that the specific ingredients in the '036 patent's exemplary formulations are generally representative of the performance of their particular class of known structures—*e.g.*, histidine and phosphate are representative of known buffers generally, sucrose is representative of known stabilizers generally, and polysorbate 20 is representative of known surfactants generally. Accordingly, the POSA “could make predictable changes to the described [formulations]”—*i.e.*, by adjusting the identity and amount of the different components—“to arrive at other types of [formulations]” falling within the scope of the claims. *Ajinomoto*, 932 F.3d at 1360-61. The POSA would understand that the 31 formulations disclosed by the '036 patent are “structurally similar to, and thus representative of,” the class of high-concentration, low-viscosity formulations “coming within the claim[s]” of the '036 patent. *Id.* at 1360. And *contra* Alvotech, over thirty formulations with more than a dozen ingredients, in light of the POSA's extensive knowledge, clearly “provide a POSA with sufficient information about which potential options for formulations will achieve the required viscosity levels and which will not.” Pet. 80.

Alvotech does not seriously contest that the POSA would have been familiar with—and capable of making predictable adjustments to—the ingredients of the disclosed formulations with the teachings of the '036 patent in hand. At best, Alvotech generically asserts that “specific formulation components and percentages matter to achieving the required viscosity levels,” Pet. 79; *see also* Ex.1004, ¶273

(same), and more specifically notes that “all the tested formulations that contain a histidine buffer fall within the claimed viscosity range of 5-15 cP,” whereas “[t]he tested formulations containing a phosphate buffer ... sometimes fall above the claimed range, showing viscosities of up to 17.3 cP,” Pet. 79; *see* Ex.1004, ¶273. That histidine-containing formulations have slightly lower viscosities at very high protein concentrations than phosphate-containing formulations does not render the disclosed formulations non-representative. As discussed *infra* (at 78-80), the POSA would recognize a workable upper concentration limit around 160-170 mg/ml. Indeed, as Alvotech notes (at 79), the '036 patent instructs that, “[a]t higher VEGF Trap concentrations,” *i.e.*, concentrations around 160-170 mg/ml, “the histidine buffer showed an improvement in viscosity (relative to phosphate).” Ex.1001, 42:19-21; *see id.*, Figs. 3A-3C, 5. Accordingly, even if (as Alvotech asserts) histidine is slightly better than phosphate at concentrations approaching the upper extremity of the concentration range encompassed by claim 1, the POSA would recognize that, across the concentration range as a whole, histidine and phosphate behave comparably. The POSA therefore would recognize the disclosed histidine- and phosphate-containing formulations as representative of the claimed formulations more generally.

Given the '036 patent's disclosure of over thirty exemplary formulations, the variety of those formulations in terms of ingredients and amounts, and the POSA's

knowledge about how to predictably adjust the identity and amounts of those ingredients, Alvotech’s attempt (at 81) to analogize the ’036 patent’s disclosure to the specification at issue in *Pernix Ireland Pain DAC v. Alvogen Malta Operations Ltd.*, 323 F. Supp. 3d 566 (D. Del. 2018), falls flat. The written-description deficiency in that case was that “[t]he specification contains a detailed description”—including “test results from [a study performed] on [a disclosed] formulation and characteristics of that formulation, such as its components and its dissolution profile”—“only [for] **a single embodiment** within the broad scope of the claims.” *Id.* at 624-25 (emphasis added); *see also id.* at 626 (“[T]he formulation [must] be described with sufficient specificity to ensure that the inventors have invented the full scope of the formulations recited in the claims and not simply **a single operative embodiment** within that class.” (emphasis added)). A single example simply could not provide any “guidance as to” which additional formulations within the scope of the claims “would satisfy the functional limitations of the claims and which would not.” *Id.* at 625. Here, by contrast, there are 31 formulations with the claimed concentrations and viscosities and with different types and amounts of buffer, surfactant, stabilizer, viscosity-reducing agent, counterions, and amino acids—a far cry from *Pernix*’s single-embodiment disclosure. The ’036 patent’s extensive disclosure of varied, representative species therefore properly “descri[bes] ... the class of formulations that will work.” *Id.* at 626.

For similar reasons, Alvotech’s reliance (at 78-80) on *AbbVie Deutschland GmbH v. Janssen Biotech, Inc.*, 759 F.3d 1285 (Fed. Cir. 2014), is unavailing. In that case, the claims recited all human antibodies “defined by their high affinity and neutralizing activity to human IL-12, a known antigen,” as represented by the antibody’s “ k_{off} rate.” *Id.* at 1292, 1299. The fatal written-description problem was “that the functional requirement of the claims, *i.e.*, the k_{off} rate, is dependent on the structure of the antibody,” but the specification’s “disclosure is limited to a family of closely related, structurally similar antibodies” and therefore could not show possession of “antibodies having widely varying structures.” *Id.* at 1298. In particular, the disclosed species were all incredibly similar, *i.e.*, “they share[d] 90% or more sequence similarity in the variable regions and over 200 of those antibodies differ from [a disclosed antibody] by only one amino acid.” *Id.* at 1300. Disclosing “one type of structurally similar anti-bodies” could not support a “claimed genus cover[ing] structurally diverse antibodies,” especially where some of those non-disclosed species “only share[d] a 50% sequence similarity with the [disclosed] antibodies,” and where “antibodies with 80% sequence similarity to [disclosed species] could bind to completely different antigens.” *Id.* The claims here, by contrast, do not encompass an analogous genus of “structurally diverse” formulations; rather, they recite formulations comprising a limited class of VEGF receptor fusion proteins as well as other, unclaimed ingredients (*e.g.*, buffers,

surfactants), with which the POSA would have been exceedingly familiar. And whereas, in *AbbVie*, the functional limitation (k_{off}) had an unpredictable, complicated relationship to the relevant structure (antibody amino-acid sequence), here, as discussed *supra* (at 73), the POSA easily could “make predictable changes to the described [formulations] to arrive at other types of [formulations]” in light of their knowledge and the ’036 patent’s disclosure of numerous, varied, high-concentration, low-viscosity formulations. *Id.* at 1301.

Alvotech also argues that the claims “recite concentrations of at least 100 mg/mL of VEGF fusion protein, with no stated upper limit,” despite the specification disclosing “*no examples* of VEGF fusion protein concentrations above 155 mg/mL that achieve the required viscosity levels.” Pet. 79; *see also* Ex.1004, ¶275 (“There are no examples of VEGF fusion protein concentrations above 155 mg/mL that achieve the required viscosity levels.”). Alvotech disregards, however, that “‘open-ended claims’” may be upheld “where the upper bound ‘would be limited by what a [POSA] would understand to be workable’ and where the patent’s specification adequately supported that range.” *SB*, 127 F.4th at 916. Such is the case here. The specification of the ’036 patent—*e.g.*, Figures 3C and 5—teaches how, as aflibercept concentration increases beyond 140 mg/ml, formulation viscosity increases at an increasing rate, exceeding the 15 cP limit at concentrations around 160-170 mg/ml. Ex.1001, 9:46-11:26, 38:47-67, Figs. 3C, 5. The POSA therefore would have little

difficulty recognizing that concentrations of 160-170 mg/ml represent the workable upper limit for intravitreally administered formulations. *See SB*, 127 F.4th at 916. Nor would the POSA have had any difficulty recognizing that the inventors possessed low-viscosity formulations with concentrations between 100 mg/ml and that workable upper limit, because the patent discloses numerous example formulations with a concentration of 155 mg/ml and a viscosity of less than 15 cP. Ex.1001, 9:46-10:4, 38:47-54, Fig. 3C. Accordingly, “the patent’s specification adequately support[s] th[e] range” between at least 100 mg/ml and the implicit upper limit of 160-170 mg/ml. *SB*, 127 F.4th at 916.

According to Alvotech itself, the POSA would recognize an implicit upper limit on protein concentration in intravitreally administered formulations. Alvotech asserts that “a POSA knew that 100 μ L was the upper safe volume limit,” and that “while any injection volume between 50 μ L and 100 μ L would have been clinically acceptable, a POSA would have been motivated to use a lower injection volume to lower the risk of adverse clinical events,” with a “50 μ L volume or a volume as close to 50 μ L as possible” preferred by the clinician. Pet. 70-71. Alvotech then reasons that, “[g]iven these parameters, a skilled formulator would have determined the range of possible concentrations for aflibercept in the aqueous pharmaceutical formulation is 80 mg/mL to 160 mg/mL.” Pet. 71. Alvotech thus recognizes that,

for an 8 mg dose,¹⁰ the workable upper concentration limit would be 160 mg/ml. Likewise, Dr. Falconer also seems to recognize an implicit upper limit of “about 160 mg/mL,” above which “the viscosity of both phosphate and histidine-containing formulations falls well above the claimed [viscosity] range.” Ex.1004, ¶274. Because the specification discloses numerous formulations with 155 mg/ml aflibercept and a viscosity of less than 15 cP, Ex.1001, 9:46-10:4, 38:47-54, Fig. 3C,

¹⁰ That claim 1 recites doses of “at least about 8 mg” does not affect the adequacy of claim 1’s written-description support. Claim 1 is limited to formulations with an injectable volume of “about 100 microliters or less,” and as explained, there is an implicit upper concentration limit around 160-170 mg/ml. The POSA would recognize that claim 1 does not encompass—and the specification need not describe—all possible combinations of dosages above 8 mg and volumes below 100 microliters. Rather, the POSA would understand claim 1 to encompass formulations with dosages and volumes that are within the claimed ranges and that result in concentrations above 100 mg/ml but less than 160-170 mg/ml, *e.g.*, an 8 mg dose in a 70 microliter volume, a 9 mg dose in a 60 microliter volume, or a 10 mg dose in a 100 microliter volume. And the specification clearly discloses representative species of such formulations.

formulations with the concentrations encompassed by claim 1 are adequately described.

In sum, the '036 patent discloses over thirty formulations with a large variety of ingredients and amounts. This extensive disclosure, viewed in light of the POSA's knowledge, is no mere "research plan[]" leaving it to others to explore the unknown contours of the claimed genus," but instead shows that "the inventor[s] ha[ve] truly invented the genus" of high-concentration, low-viscosity formulations. *Ajinomoto*, 932 F.3d at 1359 (quotation marks and citation omitted). The claims are adequately described.

2. The Claims Are Not Invalid for Not Reciting a Buffer

In Ground 3, Alvotech also complains that the claims do not recite "a buffer." Pet. 83-86. Alvotech maintains that "the specification makes clear" that a buffer "is required" to achieve the viscosities recited by the '036 patent's claims. Pet. 83. And "[b]ecause the specification supports only formulations with a buffer that achieve the claimed viscosity levels, yet the claims broadly cover any high-concentration VEGF formulation that would meet those levels, the claims are invalid for lack of written description." Pet. 86. Alvotech's no-buffer theory suffers several fatal shortcomings.

To start, Alvotech misunderstands the law. As the Federal Circuit has explained, "[t]here is no rigid requirement that the disclosure contain 'either

examples or an actual reduction to practice.” *Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1308 (Fed. Cir. 2015) (citation omitted). Nor must a patentee “describe in the specification every conceivable and possible future embodiment of his invention.” *Cordis Corp. v. Medtronic AVE, Inc.*, 339 F.3d 1352, 1365 (Fed. Cir. 2003) (citation omitted). Accordingly, that the ’036 patent does not disclose an exemplary formulation without an excipient buffer does not render the claims invalid. Similarly, “[a] claim is not defective when it states fewer than all of the steps that may be performed in practice of an invention.” *Smith & Nephew, Inc. v. Ethicon, Inc.*, 276 F.3d 1304, 1311 (Fed. Cir. 2001). Written description does not require that the ’036 patent’s claims list every component (*e.g.*, a buffer) of the compositions that may be used in the claimed methods. Finally, Alvotech overlooks that the relevant inquiry is whether a “patent has an adequate written description of ***what is claimed***.” *In re Entresto*, 125 F.4th 1090, 1099 (Fed. Cir. 2025) (emphasis added). “Because the [’036] patent does not claim [formulations without an excipient buffer], those [formulations] need not have been described,” even if they are “encompasse[d]” by “the claim scope.” *Id.* at 1095, 1097. That the claims do not recite—and that the specification does not disclose a formulation without—an excipient buffer therefore does not render them invalid for lack of written description.

Alvotech's cited authorities, meanwhile, are inapposite. Alvotech argues at length about how the '036 patent teaches that buffers are essential to achieving the claimed viscosities, culminating with a citation to *Gentry Gallery, Inc. v. Berkline Corp.*, 134 F.3d 1473 (Fed. Cir. 1998). Pet. 83-86. But the Federal Circuit has rejected the notion that *Gentry* "announce[d] a new 'essential element' test mandating an inquiry into what an inventor considers to be essential to his invention and requiring that the claims incorporate those elements." *Cooper Cameron Corp. v. Kvaerner Oilfield Prods., Inc.*, 291 F.3d 1317, 1323 (Fed. Cir. 2002). Nor does *LizardTech* (Pet. 85) support Alvotech's position. There, the specification "clearly describe[d] [only] one embodiment of the thing claimed," and the Court held that "the description of one method for creating a seamless DWT does not entitle the inventor of the ... patent to claim any and all means for achieving that objective." 424 F.3d at 1346. Here, however, the specification discloses 31 varied, representative embodiments, such that the POSA would "understand how to make a [low-viscosity formulation] generically," including one without an excipient buffer, as discussed below. *Id.* at 1345. Alvotech's no-buffer theory is devoid of legal support.

Even were Alvotech correct that the specification must describe formulations without an excipient buffer, the POSA would have understood the inventors to possess such formulations. In protein formulations, buffers help with "maintaining

pH,” Ex.1001, 18:49-53, and the patent provides four exemplary excipient buffers: histidine, phosphate, citrate, and acetate, *id.*, 2:61-3:8, 7:61-66, 18:58-65. The POSA would have recognized, however, that excipient buffers are not the only means of maintaining formulation pH; rather, the POSA would have known that the fusion protein itself (*e.g.*, aflibercept) has buffering capacity.

By the priority date of the '036 patent, the POSA would have been familiar with self-buffering protein formulations, which had long been known in the art. Gokarn, for instance, describes “formulations comprising a pharmaceutical protein, that are buffered by the protein itself, that do not require additional buffering agents to maintain a desired pH, and in which the protein is substantially the only buffering agent”; notes that “fusion proteins” are “[h]ighly preferred”; and identifies “VEGF” as a target for binding. Ex.2021, 3:17-20, 41:6-16, 44:31-34, 45:1-18. Aflibercept is a VEGF receptor fusion protein, and the POSA would understand Gokarn’s teachings as applicable to it. Ex.1001, 3:49-4:5. Aflibercept dimers also contain 28 histidine residues, *id.*, 4:56-5:6 (amino acids 27-457 of SEQ ID NO:2), and the POSA would have known that “the imidazole ring in [histidine’s] structure can accept protons [and] ... thus may act as a buffer ... when [histidine] is present as an amino acid making up a protein structure,” *Formycon*, 2024 WL 3423047, at *16. The POSA also would have understood that “[t]he pKa of histidine in polypeptides ranges around 6.0,” such “that both free histidine and certain proteins (polypeptides)

containing histidine residues could act as buffers within a pH range of roughly 5-7,” *id.*; see Ex.2021, 38:21-22, which is nearly identical to the 5.0-6.8 pH range disclosed for the ’036 patent’s formulations, Ex.1001, 2:41-50, 5:11-23, 5:51-60, 15:3-6, 18:49-53. And the POSA would have appreciated that self-buffering capacity increases with protein concentration, *e.g.*, Ex.2021, 78:1-80:14, Figs. 10-11, 14-16 (describing self-buffering capacity at concentrations up to 90 mg/ml), so the high-concentration formulations of the ’036 patent are particularly well-suited for protein-buffering.

Accordingly, the POSA would have recognized that aflibercept has buffering capacity, such that the concentration of excipient buffer could be reduced—even to 0 mM—by relying on that capacity, especially at the higher concentrations recited by the ’036 patent’s claims. That the specification does not expressly discuss self-buffering formulations is of no moment, because, as before, a “patent need not teach, and preferably omits, what is well known in the art.” *McRO*, 959 F.3d at 1102; *Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357, 1367-68 (Fed. Cir. 2006). Therefore, *contra* Alvotech (at 86), the POSA would have recognized that the inventors possessed formulations that do not include an excipient buffer and that rely on the fusion protein to maintain the formulation’s pH.

VII. Conclusion

For the foregoing reasons, institution should be denied.

Date: December 26, 2025

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CERTIFICATION UNDER 37 C.F.R. § 42.24(d)

In accordance with 37 C.F.R. § 42.24, as amended, the undersigned certifies that this Patent Owner Preliminary Response complies with the applicable type volume limitations of 37 C.F.R. §§ 42.24(a)(ii) and 42.24(b)(1). Exclusive of the portions exempted by 37 C.F.R. § 42.24(a), this Patent Owner Preliminary Response contains 18,663 words as counted by the word processing program used for its preparation (Microsoft Word 2019).

Date: December 26, 2025

/David I. Berl/

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CERTIFICATE OF SERVICE
(37 C.F.R. § 42.6(e))

The undersigned hereby certifies that on December 26, 2025, I caused true and correct copies of the following materials:

- Patent Owner's Preliminary Response
- Patent Owner's Exhibit List
- Exhibits 2015-2036

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