

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AZURITY PHARMACEUTICALS, INC.,
Petitioner,

v.

HELSINN HEALTHCARE S.A.,
Patent Owner.

Case IPR2025-00945
Patent US 8,623,826 B2

AZURITY PHARMACEUTICALS' REPLY

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I. INTRODUCTION

Patent owner Helsinn's response requires rewriting the claims to import limitations that are not there and to ignore limitations that are. The petition provided a facial case of obviousness under 35 U.S.C. §103 and demonstrated why Helsinn's test results fell short of demonstrating difference-in-kind results sufficient to undermine the facial case. Helsinn simply substituted a newer NK₁-antagonist (netupitant) into a standard triple therapy (aprepitant-palonosetron-dexamethasone) for nausea and vomiting. Helsinn's response reimagines the claims to require improved antinausea results over existing treatment, yet Helsinn lacks support for its implicit construction. Helsinn does not, and cannot, show that the proposed combination was expected not to treat nausea at all. Moreover, any purported "synergy" from the proposed combination arises from using prior-art palonosetron with an NK₁-antagonist, not from using netupitant specifically.

Helsinn also relies on flawed legal theories of obviousness that the Board already rejected in the institution decision. Paper 12 ("ID") 24-35. The legal standards have not changed, so the Board should continue to reject Helsinn's arguments.

Helsinn addresses only independent claims 1 and 19, while offering no separate argument for the dependent claims, which consequently fall with their respective independent claims. *Gardner v. TEC Systems*, 725 F.2d 1338, 1350

(Fed. Cir. 1984) (en banc).

II. CLAIM CONSTRUCTION

A. Helsinn's both-and construction is neither supported nor relevant

Helsinn argues claims 1 and 19 require treating *both* nausea and vomiting. POR 16. This argument makes no difference because the prior art expressly treats both. Helsinn suggests its claimed triple therapy is better, but that is a red-herring because claim 19 provides no baseline for comparison—so the baseline could be no treatment—while claim 1's baseline is a strawman that *by definition* is ineffective.

1. No baseline for improvement

Helsinn argues the claims require treating *both* nausea *and* vomiting. POR 16. Treating both is explicit in treating chemotherapy-induced *nausea and vomiting* (CINV). Helsinn, however, attempts to leverage its preamble in claims 1 and 19 into a requirement for *improved* treatment of nausea as compared to standard therapy. No such requirement appears in claims 1 and 19. Indeed, claim 19 lacks any baseline for comparison. EX1001, 23:7-15. Hence, any treatment of nausea suffices, yet even Helsinn concedes that dexamethasone (one of the triple therapy components) treats nausea. EX2088, ¶59; EX1067, 117:23-118:2, 119:15-20; see also EX1001, 1:39-41 (“Palonosetron hydrochloride [another prior-art triple-therapy component] has recently emerged as a highly

efficacious anti-nauseant”, citing prior art).

For claim 1, Helsinn argues that the last element provides a baseline for triple therapy “to treat both nausea and vomiting to a greater extent” than dual therapy (palonosetron and dexamethasone). POR 24-25. Yet this comparator hides a trick: remember that an NK₁-inhibitor **doubles** the effectiveness of dexamethasone. Pet. 15; EX1009, ¶115; EX1010, 47. Yet claim 1 requires using an otherwise **ineffective** amount of dexamethasone. EX1001, 21:50-54. Even Helsinn’s expert, Dr. Roeland, concedes that dexamethasone itself treats nausea. EX2088, ¶59 (“significantly superior to placebo”); EX1067, 121:4-16; EX1013, 24; cf. EX1037, 4113, comparing aprepitant/reduced dexamethasone with placebo/full dexamethasone. Hence, claim 1 fudges the comparator by comparing an **explicitly ineffective** amount of dexamethasone with the same amount of dexamethasone that has NK₁-inhibitor-**doubled** effectiveness: of course, the comparator will be ineffective by definition; however, using an NK₁-inhibitor restores its effectiveness. Thus, properly understood, claim 1’s “improvement” requirement is met simply by restoring dexamethasone’s effectiveness against nausea from an ineffective half-dose back to a full-dose via NK₁-inhibitor enhancement. Netupitant, an NK₁-inhibitor, would be expected to do this.

Because claim 19 provides no baseline, and claim 1 embraces an explicitly ineffective treatment as its baseline, the claim requirement to treat nausea is met by

any treatment that is more effective than an ineffective treatment. The inclusion of an effective amount of dexamethasone (when used in combination with the NK₁-inhibitor) is sufficient.

2. Claim 1 recites “both” not “each of”

Moreover, Azurity does not concede that treating “both nausea and vomiting” to a greater extent means treating *each of* nausea and vomiting to a greater extent. Helsinn’s both-and drafting explicitly joins nausea and vomiting together for the greater-extent comparison. Helsinn could have used a narrower each-of construction, but did not, and does not provide an intrinsic basis for its narrower reading of this plain language. Thus, a net improvement for these parameters together meets claim 1. Record evidence confirms that combining 5-HT₃- and NK₁-receptor antagonists improves the composite endpoints of complete protection and reduced rescue medication. Pet. 60-61, 65; EX1009, ¶¶1333-40, 1373. As Helsinn’s Dr. Roeland explained, these are the gold-standard measurements of nausea and vomiting available. EX2088, ¶¶46-47 (“[S]ponsors developing drugs for the prevention of CINV almost exclusively used the primary efficacy endpoint of ‘complete response’ – defined as no vomiting and no use of rescue antiemetic medication – when conducting clinical trials for a drug’s efficacy against CINV, and ultimately, its approval by the FDA with a CINV indication.”). The claims are thus unpatentable.

3. Therapeutically effective amount

Helsinn also provides a construction of “therapeutically effective amount” that simply repeats Helsinn’s both-and construction (POR 21), which thus fails for the same reasons discussed above.

B. Statistical significance

Helsinn also imports into claims 1 and 19 a requirement for statistically-significant efficacy for treatment (POR 18), but the express claim language and the specification contradict this assertion. Neither claim requires statistical significance as compared to “standard therapy”; claim 1 merely requires effectiveness “to a greater extent” than ineffective treatment, while claim 19 provides no comparison for statistical significance.

Helsinn tries to interpolate a particular baseline requirement from the specification (POR 20, citing EX1001, 8:31-34), but the cited specification portion does not specify the baseline Helsinn manufactures for the claims:

When a measurable result or effect is expressed or identified herein, it will be understood that the result or effect is evaluated based upon its statistical significance relative to *a baseline*.

EX1001, 8:28-31 (emphasis added). Significantly, this purported definition does not specify a particular “baseline” and the word “baseline” is not used again in the specification. Of course, specific embodiments may not be read into the claims.

Phillips v. AWH Corp., 415 F.3d 1303, 1323 (Fed. Cir. 2005) (en banc)

("[A]lthough the specification often describes very specific embodiments of the invention, we have repeatedly warned against confining the claims to those embodiments.").

As noted above (II.A.1), neither claim 1 nor claim 19 provide a legitimate baseline for statistical comparison, so importing this requirement into claims 1 and 19 would render them indefinite. *Geneva Pharmaceuticals v. GlaxoSmithKline*, 349 F.3d 1373, 1384 (Fed. Cir. 2003) (rejecting indefinite construction). Thus, it would be inappropriate to import into the claims a requirement for statistical significance. Alternatively, even if statistical significance were imported into claims 1 and 19, the baseline must be broad enough to include any comparator, including no treatment (as in claim 19) and explicitly ineffective treatment (as in claim 1).

C. Claim 1's striatum-occupancy element is descriptive

As the petition explained (Pet. 32), claim 1's striatum-occupancy element simply describes the result of using an effective amount on an NK₁-inhibitor. Helsinn purports to construe claim 1's striatum-occupancy element (POR 22-24), but baselessly attacks the petition's merits instead. Significantly, Helsinn did not point to any additional step in claim 1 beyond administration that would achieve the claimed effect. Even if Helsinn belatedly argues (in its surreply) that it determined dosages that are effective, this argument would fail for at least two

reasons. First, claim 1 does not specify a dosage. Second, dependent claims (that Helsinn fails to address in its response) require specific dosages, including dosages for which Helsinn has provided no striatum-occupancy results.

For example, claim 6 provides a very broad range of netupitant doses:

The method of claim 1, wherein said therapeutically effective amount of netupitant comprises from about 200 to about 400 mg of netupitant or a pharmaceutically acceptable salt thereof.

EX1001, 22:15-18. As a dependent claim of claim 1, claim 6 includes the striatum-occupancy element to the extent it is limiting. 35 U.S.C. §112 (“A claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers.”). Yet, although claim 6’s range goes as low as 200 mg of netupitant, the specification does not provide support for at least 70% striatum-receptor occupancy at 72 hours at 200 mg. EX1001, 16:Example 4 (disclosing higher striatum-occupancy results for 300 mg and 450 mg doses, but not for 100 mg, and not mentioning 200 mg), Fig. 5 (showing occupancy below 70% at T=72 for the striatum, but over 70% at T=72 for 300 mg and 450 mg). The 200 mg dose lacks support for the striatum-occupancy element unless the element is simply descriptive of any effective dose.

Moreover, nothing in Helsinn’s argument overcomes the grammatical significance of Helsinn’s choice of “which” to start the clause, making clause descriptive rather than limiting. Pet. 9-10; *cf. Minton v. National Association of*

Securities Dealers, 336 F.3d 1373, 1381 (Fed. Cir. 2003) (“A whereby clause in a method claim is not given weight when it simply expresses the intended result of a process step positively recited.”). Nor does Helsinn rebut Hargreaves use of striatum-receptor occupancy simply as a measurable marker of NK₁-inhibitor effectiveness. Pet. 35, EX1009, ¶¶258-59; EX1012, 22-23. In the NK₁-inhibitor context, effectiveness and striatum-receptor occupancy coincide because receptor occupancy indicates the inhibitor is interacting with the brain receptors at a sufficient level. EX1009, ¶86 (“The ’826 patent confirms that the expected therapeutically effective doses of netupitant (e.g., 300 mg, 450 mg) occupy NK₁ receptors in the striatum, and that for any sufficiently large dose of netupitant, the natural result of administering such obvious doses is NK₁ receptor antagonism greater than 70% after 72 (and after 96) hours.”).

The plain-language “which” clause, coupled with the lack of any additional steps beyond administration to achieve the result, and the unsupported broad dosages in the dependent claims confirm that the striatum-occupancy element is not limiting; rather, it simply describes the result for any effective NK₁-inhibitor dose.

D. Comprising

Helsinn attacks the combination by arguing other drugs might also be effective against nausea. POR 31-34. Claims 1 and 19 use the transitional term

“comprising” before the treatment steps. EX1001, 21:40, 23:11. Hence, these claims are open to additional steps, including treatment with additional drugs. *Eye Therapies v. Slayback Pharma*, 141 F.4th 1264, 1269 (Fed. Cir. 2025) (“Generally, the term ‘comprising’ is an open-ended transitional term that allows for additional steps.”).

III. LEVEL OF SKILL

Helsinn repeats its failed argument that a POSA must be an oncologist, which is based on an improper standard for a POSA. POR 12-14. Moreover, Helsinn drops its original expert (POR 4 n.3) and substitutes a new expert (Dr. Roeland), who was too new to the field to meet Helsinn’s own definition of a POSA.

A. Helsinn uses the wrong standard

The Board observed (ID 11-12) that the prior art and patent provide the best measure of the level of skill, and provisionally held that the POSA need not be an oncologist. Helsinn persists in requiring the POSA to be an oncologist. POR 12-13. Yet, the Federal Circuit has cautioned against assuming that designers and end-users have the same skills. *DyStar Textilfarben v. C.H. Patrick Co.*, 464 F.3d 1356, 1362-63 (Fed. Cir. 2006) (historically, dyers and dye formulators were the same, but this is no longer true). Oncologists are end-users because they are performing the treatment. POR 13 (“[C]linical skill in *supportive cancer care* is necessary”).

Significantly, Helsinn made no attempt to show either that *all* oncologists or that *only* oncologists have the requisite skills to design a drug combination. Indeed, Helsinn has not shown that any of the drugs or combinations under discussion were created exclusively by oncologists. Note that Azurity's more realistic definition begins with pharmacology, but includes oncology as a possible area of expertise. Pet. 8, as modified in ID 11, which exclude statistics and medical policy/decision making, and cites *Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001), while using the prior art as evidence of the skill level.

Helsinn relies on Dr. Roeland for its factual assertion that three years of supportive cancer care experience is required. POR 13, citing EX2088, ¶¶24-29. Yet Dr. Roeland provides no foundation for his understanding of the legal standard for a POSA (EX1067, 101:19-103:2), and repeatedly emphasized his own lack of legal knowledge about relevant legal standards. EX1067, e.g., 81:6-7, 103:3-106:25. Dr. Roeland provides no basis beyond his own conclusory statements for requiring such experience, which are thus entitled to little or no weight. *TQ Delta v. Cisco Sys.*, 942 F.3d 1352, 1358 (Fed. Cir. 2019) ("Conclusory expert testimony does not qualify as substantial evidence."). In sum, the level of skill in the art provided in the petition, as amended in the institution decision, remains the most consistent with what the prior art shows drug-therapy designers actually doing, while Helsinn's narrower definition lacks support and is inconsistent with the prior

art. In any case, the outcome is the same under either standard. EX2088, ¶28.

B. Dr. Peroutka is better qualified to discuss how a POSA would approach designing drug therapies in 2009

By virtue of his long experience studying drugs for the relevant pathways and receptors, Dr. Peroutka has ample education (M.D. and Ph.D.), knowledge, and experience to testify on how a POSA would have approached designing a combination prior to 2009 because he was actually working on designing therapeutic treatments at the relevant time. EX1009, ¶¶2-7. Specifically, he worked developing therapies for neurological pathways (*id.*, ¶4), including those involved in this proceeding (*id.*, ¶5). Moreover, he has practical experience in oncology as well as pharmacology. EX2086, 13:14-14:15.

Further undermining Helsinn's attempts to redefine the POSA, Dr. Roeland acknowledged that he became a medical oncologist only in 2013 or 2014, several years after the 2009 priority date, and could only identify his medical internship as pre-critical date experience in oncology. EX1067, 83:5-7, 84:17-22 (certified as a medical oncologist in 2013 or 2014), 85:23-86:7 (listing pre-certification experience). Helsinn's rigid approach to redefining the POSA (POR 12) would thus exclude its own expert. Moreover, Dr. Roeland admitted that even now he lacks relevant experience in biochemistry, pharmacology, or statistics. EX1067, 80:25-81:14, see also *id.* at 130:23-131:5 (not understanding what constitutes a "majority" of patients).

Moreover, Dr. Roeland's entire career as a medical oncologist (since 2013 or 2014) has coincided with his extensive collaborations with Helsinn. EX1067, 83:5-7, 84:10-22 (certified as a medical oncologist in 2013 or 2014), 29:14-38:20 (discussing Helsinn collaborations from 2013 through a 2026 paper). This necessarily colors his testimony. *Nilssen v. Osram Sylvania, Inc.*, 504 F.3d 1223, 1230 (Fed. Cir. 2007) (personal, professional, and financial relationship of declarant to patentee is material); *Refac International v. Lotus Development*, 81 F.3d 1576, 1581-82 (Fed. Cir. 1996) (inside knowledge of inventors and invention is material). Indeed, Dr. Roeland's dependence on Helsinn is underscored by his admission that while he spent around 50 hours preparing for his deposition, he only spent around 20 hours preparing his four lengthy declarations. EX1067, 14:6-18, 148:5-12. While Dr. Roeland has post-critical date experience in treating patients and conducting other designers' studies, he is not himself a designer of drug therapies. Thus, if anything, he is less qualified than Dr. Peroutka to explain how a POSA would have approached designing a new drug combination in 2009. *DyStar*, 464 F.3d at 1362-63 (reversing jury POSA finding focused on user rather than designer).

IV. FACIAL OBVIOUSNESS

A. Nausea as a separate event does not help Helsinn

Whether nausea is a separate event from vomiting is irrelevant to

obviousness because the standard of care was to treat them together (CINV, RINV, PONV), which is what the proposed combination does. Helsinn teases out nausea as a separate consideration to advance its dubious claim construction (POR 6-8), but the claims do not require treating nausea separately. Indeed, claims 1 and 19 explicitly treat CINV together. Cf. EX2088, ¶32 (acknowledging the pathways overlap). Helsinn repeatedly asserts that nausea was not being treated in the aprepitant-based triple therapy, but this is a red herring because Helsinn consistently blurs the baseline to ignore the effect of dexamethasone. E.g., POR 7 (arguing triple therapy was ineffective for nausea, but not identifying the baseline for comparison). Helsinn's arguments fail because they do not account for the actual scope of its claims.

B. Nausea was not the only problem confronting the POSA

Helsinn reimagines the problem to be solved as treating nausea rather than treating CINV. E.g., POR 2 ("Azurity ignored the problem of chemotherapy-induced nausea[.]"). Obviousness is not limited to the inventor's problem. *KSR Int'l v. Teleflex Inc.*, 550 U.S. 398, 420 (2007) ("any need or problem known in the field"). Regardless, Helsinn itself defined the field broadly as "the use of centrally acting NK antagonists to treat nausea and vomiting, particular[ly] nausea and vomiting induced by highly emetogenic chemotherapy, and ... the treatment of such nausea and vomiting over multiple consecutive days." EX1001, 1:18-22.

Similarly, claims 1 and 19 expressly address CINV with no singular focus on nausea. Hence, because the existing triple therapy (with both dexamethasone and palonosetron) already treated nausea, providing new tools to treat CINV patients sufficed as a reason to employ another NK₁-inhibitor even without a singular focus on nausea. *See* EX1013, 20 (“vomiting and nausea continue to be significant side effects of cancer therapy”); EX1067, 119:21-120:1 (“I’d also like to point out that as we are taking care of patients, we’re going to continually try to improve that experience, that just because we have a tool now, we’re hoping that we continue to improve it so that, when any of us get cancer, that experience can be improved.”).

C. Netupitant was an obvious choice for substitution

Helsinn argues that a POSA would not “have looked to swap aprepitant for netupitant given the problem of nausea” or any other known problem. POR 29. To the extent Helsinn limits the problem to nausea rather than CINV, it improperly blinkers the POSA as explained in the previous section. As the Board has always understood, “the problem [is] treating CINV[.]” ID, 25. Indeed, a POSA would have substituted netupitant as the NK₁-inhibitor for the same reason the art substituted palonosetron for ondansetron (the 5-HT₃-inhibitor): to “enhance[] the efficacy of [the existing] combination with new, improved drugs targeting the same mechanistic pathways.” Pet. 50. Helsinn vaguely argues that netupitant and aprepitant were not “equivalent” (POR 29-30) but does not (and cannot) dispute

that netupitant was a known NK₁-inhibitor. Helsinn complains that the art lacked studies comparing aprepitant's and netupitant's efficacy (POR 30) without showing such studies are a prerequisite for obviousness. Helsinn complains that netupitant was exploratory, but ignores Hoffmann's singling netupitant out (along with one other NK₁-inhibitor, befetupitant) for praise in the context of treating CINV with NK₁-inhibitors. EX1011, 1362; ID 26-27. In a footnote, Helsinn also argues that netupitant was one of "millions of compounds" (POR 31 n.20) disclosed in Bös (EX1014), but ignores that netupitant was one of only three compounds for which Bös provided in vitro and in vivo test results. EX1014, 13:14-23:16 (compounds Ia-Ic).

To the extent Helsinn argues (POR 30) the petition failed to compare netupitant's properties to other NK₁-inhibitors in use, Helsinn is wrong. See, e.g., Pet. 40. A POSA does not require FDA approval before attempting an otherwise promising substitution. *Bayer Pharma AG v. Watson Labs., Inc.*, 874 F.3d 1316, 1324, 1326 (Fed. Cir. 2017) ("[A] lack of FDA approval cannot negate an otherwise apparent motivation to formulate a product."). Helsinn's proposed legal standard for pharmaceuticals would reduce obviousness to a chicken-and-egg paradox.

D. Alternative approaches do not make netupitant nonobvious

Helsinn argues that a POSA must exhaust all other "promising" possibilities.

POR 31-32. As an initial matter, claims 1 and 19 use the “comprising” transition and are open to the inclusion of other “promising” treatments for other pathways. Moreover, Helsinn once again improperly limits all reasons for substitution to “solv[ing] the problem for nausea” despite claims 1 and 19 being directed to both nausea and vomiting. By Helsinn’s logic, Hoffmann’s praise for netupitant in the context of treating CINV (EX1011, 1362; ID 26-27) was a futile gesture because a POSA would never have paid attention given all the other alternatives. Fortunately, neither the law nor the art are so blinkered. *Cytiva Bioprocess R&D AB v. JSR Corp.*, 122 F.4th 876, 884 (Fed. Cir. 2024) (“To require a separate justification for starting with Domain C, when that starting point is already taught in the prior art, would lead to the erroneous ‘constricted analysis’ that *KSR* criticized.”). That a POSA could also pursue a quadruple (or more) therapy with all the additional costs and risk does not detract from the simple substitution that Hoffmann suggested. See ID 25 (“Indeed, an inferior solution can be obvious even when a superior solution is also available.”), *citing In re Mouttet*, 686 F.3d 1322, 1334 (Fed. Cir. 2012).

E. Better outcome is not the standard

Helsinn similarly invites error by requiring that substituting netupitant for aprepitant would result in better clinical outcomes (POR 35) but, again, this is not the law. *Bayer*, 874 F.3d at 1328 (“[O]bviousness does not require that the

motivation be the *best* option, only that it be a *suitable* option from which the prior art did not teach away.” (original emphasis) (cleaned up)). Moreover, Helsinn again focuses on whether netupitant would improve clinical *nausea* outcomes. POR 37 (“[T]he preclinical animal data in Azurity’s cited references (Hoffmann and Bös) is limited to netupitant’s effect on emesis.”). Once, again, a POSA would have reason to substitute netupitant for aprepitant simply expecting it to act suitably as an NK₁-inhibitor in combination with dexamethasone and palonosetron to treat CINV. For claims 1 and 19, no more is required.

F. Reasonable expectation of success

Helsinn argues that preclinical animal studies “would not necessarily translate to efficacy in humans”. POR 38. As an initial matter, claim 19 requires a human subject, but claim 1 does not. Moreover, Hoffmann provides objective evidence that those skilled in the art considered netupitant (and befetupitant) sufficiently promising as “optimized” successors to aprepitant, specifically in the context of treating CINV (as well as mood disorders) with less toxicity. EX1011, 1362-63. Hoffmann’s prior-art assessment is more reliable than Helsinn’s litigation-driven speculations using the wrong legal standards.

Helsinn relies on the example of casopitant as evidence that NK₁-inhibitors do not always work out (POR 42), but this example proves the opposite. Although it ultimately failed to meet regulatory requirements, GlaxoSmithKline reasonably

expected it to succeed. Moreover, GSK did not say casopitant failed to treat CINV and PONV; rather, it stopped development “based on the company’s assessment that significant further safety data would be required to support the registration of casopitant on a worldwide basis, which would take a considerable time to produce.” EX2077, 2. Thus, Helsinn has shown that GSK pursued casopitant as a treatment for CINV, expecting it to work, then ceased development for business reasons related to regulatory requirements. Reasonable expectation of success does not require certainty either in law or in the drug-development business. *Hoffmann-La Roche Inc. v. Apotex, Inc.*, 748 F.3d 1326, 1331 (Fed. Cir. 2014) (“Conclusive proof of efficacy is not necessary to show obviousness. All that is required is a reasonable expectation of success.”).

Helsinn also relies on its claim construction requiring statistically-significant improvement in nausea treatment specifically as compared to standard therapy. POR 42-49. Yet, as discussed above (II.A & B), neither claim 1 nor claim 19 require such improvement, nor is it even relevant to the petition’s reason to substitute. For example, Helsinn makes much of a purported lack of statistical significance between an aprepitant-containing therapy and standard therapy (POR 47-49), yet fails to show either claim requires this comparison. What the data does show is large percentages in both groups being successfully treated for nausea. POR 48, citing EX1030, Tables 1 & 2; EX1067, 125:9-131:19 (discussing the

percentages of CINV patients with nausea successfully treated using the aprepitant triple therapy); EX1066 (Dr. Roeland's markings showing numbers of patients with no nausea or no significant nausea treated using standard therapy). As Helsinn concedes, "these tables show a **numerical** improvement in nausea parameters". POR 49 (original emphasis).

G. Hoffmann and Bös narrowed the NK₁-inhibitors to try

Helsinn argues that the prior-art NK₁-inhibitors were not "finite, small, or easily traversed" in 2009. POR 53. Yet Hoffmann highlighted two out of 31. EX1011, 1362. Bös highlighted three out of "millions." EX1014, 13:14-23:16 (compounds Ia-Ic). Both identified netupitant as a preferred candidate. While Helsinn and Dr. Roeland exaggerate the challenge, Hoffmann and Bös provide ample direction to those seeking an NK₁-inhibitor to employ instead of aprepitant.

H. Helsinn's claim 1-specific arguments are misplaced

1. Therapeutic effectiveness meets the striatum-receptor element, which is descriptive and inherent

Helsinn notes that claim 1 requires administering "a therapeutically effective amount" of netupitant "**which** ... crosses the blood brain barrier and occupies at least 70% of neurokinin-1 (NK1) receptors in the striatum *seventy-two hours* after said administration." POR 57 (original emphasis). Helsinn argues that the reference Azurity uses to address this limitation (Hargreaves, EX1012) does not discuss netupitant. POR 58. This argument is a strawman because the petition used

Hargreaves to show that the art used striatum occupancy as a proxy for NK₁-inhibitor therapeutic effectiveness. Pet. 32 (“Hargreaves associates NK₁-receptor occupancy greater than 75% with therapeutic effectiveness.”), citing EX1012, Abstract, 23, Fig. 6B; EX1009, ¶¶248-49.

Helsinn argues that nothing connects Hargreaves to netupitant (POR59), but this misses the point. Hargreaves teaches a proxy for NK₁-inhibitor effectiveness. Because netupitant is an NK₁-inhibitor, an effective amount of netupitant must meet Hargreaves receptor-occupancy threshold. Rather than address this syllogism, Helsinn disputes a strawman that the petition does not assert—whether Hargreaves tested netupitant. While not dispositive, as Helsinn concedes (POR 59), the examiner also found the striatum-receptor element to be an inherent property. Helsinn’s failure to dispute the examiner’s finding might not be an admission (POR 60), but it is independent authority supporting Azurity. Helsinn invites Office adjudicative inconsistency without providing any evidence to the contrary. Moreover, as discussed above (II.C), the plain language of this element shows the striatum-receptor element is simply a description of an effective dose.

2. Claim 1’s comparator is a red herring

Helsinn argues that the prior art does not compare netupitant-palonosetron-dexamethasone against a standard regimen of palonosetron-dexamethasone. POR 61. Neither does claim 1. As explained above (II.A.1), properly construed,

claim 1 compares netupitant-palonosetron-dexamethasone against an explicitly ineffective palonosetron-dexamethasone regimen. EX1001, 21:50-54 (“a first dose of dexamethasone which is ineffective against chemotherapy induced nausea and vomiting (CINV) when administered alone, but effective against CINV when administered in combination with said netupitant”); EX2088, ¶257. This limitation is thus circular: the triple therapy is more effective than a dual therapy that would only be effective when the NK₁-inhibitor is added. As previously discussed, the NK₁-inhibitor effectively doubles the effectiveness of the otherwise ineffective dose of dexamethasone in the comparator. Pet. 15; EX1009, ¶115; EX1010, 47. Because Helsinn never acknowledges this circularity in its claim, it asserts claim requirements that do not exist. Claim 1 only requires a triple therapy that is more effective than an explicitly ineffective regimen.

V. SECONDARY CONSIDERATIONS

Helsinn argues unexpected results and industry skepticism defeat obviousness for claims 1 and 19. POR 65. The arguments for both are based on faulty claim construction and unsupported testimony. Helsinn bears the burden of production on its secondary-consideration arguments. *Galderma Labs. v. Tolmar, Inc.*, 737 F.3d 731, 738 (Fed. Cir. 2013); *McClain v. Ortmayer*, 141 U.S. 419, 429 (1891) (requiring “conclusive evidence”).

A. Helsinn's results are not unexpected

Unexpected results must be based on comparison with the closest prior art and must represent a difference in kind rather than a difference of degree.

Galderama, 737 F.3d at 739. Moreover, an unexpected benefit is insufficient when the prior art provides an independent reason for the modification. *Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286, 1293 (Fed. Cir. 2013) (“Whether or not that combination also solved problems associated with the afternoon trough, we find the motivation to make the combination was real.”). In addition to applying an incorrect legal standard, Helsinn’s argument once again hinges on a faulty claim construction that imports unclaimed statistical significance against an unclaimed baseline. POR 65 (“standard therapy”). Helsinn also asserts results for just two doses (200 mg and 300 mg of netupitant) in the delayed phase of nausea. *Id.* Yet the claims cover a broader range of doses (e.g., claims 6 and 20 (“about 200 mg to about 400 mg)) and only claim 19 (of the argued claims) recites the delayed phase, and then only in the alternative.

As discussed above (II.A.1 & B), properly construed, claims 1 and 19 cannot be limited to statistically-significant improvement over standard therapy because neither claim recites these limitations and their plain language cannot support such limitations. Instead, claim 1 just requires improvement over an explicitly ineffective treatment, while claim 19’s baseline could be no treatment. Yet the

closest prior art, the aprepitant-palonosetron-dexamethasone treatment worked for CINV; indeed, it was the recognized standard in 2009. Pet. 11, citing EX1013, 22; EX2088, ¶62 (“gold standard”). While Helsinn points to percentage improvements (at best a difference of degree) from the substitution of netupitant for aprepitant, Helsinn makes no attempt to show a difference in kind and thus fails to meet its burden of production.

Similarly, Helsinn argues that its inventors hypothesized a synergy between netupitant and palonosetron. POR 11; EX2088, ¶264 (Dr. Roeland relying on the same speculation). Inventor speculation is not proof. Helsinn fails to address, much less rebut, the petition’s showing that any purported synergy resulting in improved nausea treatment arises from using *palonosetron* with *any* NK₁-inhibitor, not from netupitant alone. Pet. 20-21, 27, 67-68, citing EX1009, ¶¶153-56, 197-200, 1382-90. Again, Helsinn fails to meet its burden. Indeed, Dr. Roeland never cited—and in deposition confirmed that he did not even consider—the exhibits (EX1041, EX1045) showing that any synergy arises from palonosetron’s unexpected effect on NK₁ receptors. EX1067, 149:10-152:21 (confirming he only considered the exhibits listed in his Appendix A), 154:22-155:4 (confirming all his rebuttal to Dr. Peroutka’s testimony is in his declaration).

Moreover, Helsinn insists that the petition does not rely on improved nausea treatment as its reason to substitute netupitant for aprepitant. E.g., POR 2 (“Azurity

ignored the problem of chemotherapy-induced nausea[.]”). Instead, the petition does point to Hoffmann and Bös as independent reasons to make the substitution. Pet. 12-13. Because the reason to substitute exists independently of Helsinn’s purported unexpected result, that result (even if real) does not detract from the petition’s obviousness showing. *Allergan*, 726 F.3d at 1293.

Finally, unexpected results must be commensurate with the scope of the claims. *E.I. DuPont de Nemours & Co. v. Synvina CV*, 904 F.3d 996, 1012 (Fed. Cir. 2018). Yet Helsinn provides only two data points (200 mg and 300 mg out of a claimed range of at least about 200 mg to about 400 mg) for a result (improved treatment of delayed nausea) that is either unclaimed (claim 1) or optional (claim 19). Hence, Helsinn has fallen well short of its burden to produce conclusive evidence commensurate with the scope of its claims.

B. The prior art refutes Helsinn’s asserted skepticism

Helsinn asserts skepticism in the prior art based solely on Dr. Roeland’s testimony. POR 66, citing EX2088, ¶¶261-64. Dr. Roeland’s testimony is infected with Helsinn’s focus on treating nausea rather than vomiting. EX2088, ¶¶261-64. Once again, the petition relies on Hoffmann and Bös to substitute netupitant as the NK₁-inhibitor to treat CINV generally. Pet. 12-13. Hoffmann specifically singles out netupitant as one of two promising alternatives to aprepitant in treating CINV. EX1011, 1362. Despite Helsinn’s attempt to change the focus, “generic industry

skepticism cannot, standing alone, preclude a finding of motivation to combine.” *Auris Health v. Intuitive Surgical*, 32 F.4th 1154, 1159 (Fed. Cir. 2022). Here, Dr. Roeland’s testimony that the prior art was skeptical about using NK₁-inhibitors to treat nausea is a red herring because it does not correlate to the limitations of claims 1 and 19, nor is it relevant to the reason the petition provided to substitute netupitant for aprepitant. In sum, Dr. Roeland’s skepticism for one reason would not have dissuaded a POSA from this substitution for a different reason.

VI. CONCLUSION

Claims 1-25 are unpatentable and should be canceled.

Respectfully submitted,

Dated: 3 June 2026

/Richard Torczon/
Richard Torczon, Reg. No. 34,448
Counsel for Azurity Pharmaceuticals, Inc.

VII. EXHIBIT LIST - §42.63(e)

Exhibit	Description
1001	F. Trento et al., <i>Compositions and methods for treating centrally mediated nausea and vomiting</i> , U.S. Patent 8,623,826 B2, issued 17 January 2014
1002	F. Trento et al., <i>Compositions and methods for treating centrally mediated nausea and vomiting</i> , U.S. Patent 9,186,357 B2, issued 17 November 2015
1003	F. Trento et al., <i>Compositions and methods for treating centrally mediated nausea and vomiting</i> , U.S. Patent 9,943,515 B2, issued 17 April 2018
1004	F. Trento et al., <i>Compositions and methods for treating centrally mediated nausea and vomiting</i> , U.S. Patent 10,828,297 B2, issued 10 November 2020
1005	Prosecution history for U.S. Appl. 13/077,462, filed 31 March 2011
1006	Prosecution history for U.S. Appl. 14/069,927, filed 01 November 2013
1007	Prosecution history for U.S. Appl. 15/003,327, filed 19 May 2016
1008	Prosecution history for U.S. Appl. 15/923,050, filed 16 March 2018
1009	Declaration of Stephen J. Peroutka, M.D., Ph.D.
1010	J. Herrstedt & P. Dombernowsky, <i>Anti-Emetic Therapy in Cancer Chemotherapy: Current Status</i> , 101 Basic & Clinical Pharmacology & Toxicology 143-150 (2007)
1011	T. Hoffmann et al., <i>Design and synthesis of a novel, achiral class of highly potent and selective, orally active neurokinin-1 receptor</i>

Exhibit	Description
	<i>antagonists</i> , 16 Bioorganic & Medicinal Chemistry Letters 1362-1365 (2006)
1012	R. Hargreaves, <i>Imaging Substance P Receptors (NK₁) in the Living Human Brain Using Positron Emission Tomography</i> , 63(11) J. Clinical Psychiatry 18-24 (2002)
1013	The Antiemetic Subcommittee of the Multinational Association of Supportive Care in Cancer (MASCC), <i>Prevention of chemotherapy- and radiotherapy-induced emesis: results of the 2004 Perugia International Antiemetic Consensus Conference</i> , 17 Annals of Oncology 20-28 (2006)
1014	M. Bös et al., <i>4-phenyl-pyridine derivatives</i> , U.S. Patent 6,297,375 B1 (issued 2 Oct. 2001)
1015	Eisai, Inc., ALOXI (palonosetron HCl) Capsules, package insert (Aug. 2008)
1016	J.D. Herrington et al., <i>Randomized, Placebo-controlled, Pilot Study Evaluating Aprepitant Single Dose Plus Palonosetron and Dexamethasone for the Prevention of Acute and Delayed Chemotherapy-induced Nausea and Vomiting</i> , 112 Cancer 2080 (2008).
1017	D. Bonadeo et al., <i>Soft Capsules Comprising Palonosetron Hydrochloride Having Improved Stability and Bioavailability</i> , PCT Publication WO 2008/049552 (published 2 May 2008)
1018	R.J. Gralla et al., <i>Recommendations for the use of antiemetics: evidence-based, clinical practice guidelines</i> , 17 Journal of Clinical Oncology 2971 (1999).
1019	K. Jordan et al., <i>Guidelines for Antiemetic Treatment of Chemotherapy-Induced Nausea and Vomiting: Past, Present, and Future Recommendations</i> , 12 The Oncologist 1143-1150 (September 2007)

Exhibit	Description
1020	Curriculum Vitae of Dr. Stephen J. Peroutka
1021	G.K. Reddy et al., <i>Novel Neurokinin-1 Antagonists as Antiemetics for the Treatment of Chemotherapy-Induced Emesis</i> , 3 Support Cancer Therapy 140-42 (2006).
1022	M.S. Aapro et al., <i>A phase III, double-blind, randomized trial of palonosetron compared with ondansetron in preventing chemotherapy-induced nausea and vomiting following highly emetogenic chemotherapy</i> , 17 Annals of Oncology 1441-49 (2006)
1023	D. Campos et al., <i>Prevention of cisplatin-induced emesis by the oral neurokinin-1 antagonist, MK-869, in combination with granisetron and dexamethasone or with dexamethasone alone</i> , 19(6) Journal of Clinical Oncology, 1759 (2001)
1024	A.E. Chang et al., eds., <i>Oncology: An Evidence-Based Approach</i> (2006)
1025	S.P. Chawla et al., <i>Establishing the Dose of the Oral NK₁ Antagonist Aprepitant for the Prevention of Chemotherapy-Induced Nausea and Vomiting</i> , 97 Cancer 2290 (2003).
1026	S.P. Chawla et al., <i>Establishing the Dose of the Oral NK₁ Antagonist Aprepitant for the Prevention of Chemotherapy-Induced Nausea and Vomiting</i> , 37th Annual Meeting of the American Society of Clinical Oncology, in 20 Proceedings of ASCO 383a (2001)
1027	A. De Leon, <i>Palonosetron (Aloxi): a second-generation 5-HT₃ receptor antagonist for chemotherapy-induced nausea and vomiting</i> , in 19(4) Baylor University Medical Center Proceedings 413 (2006)

Exhibit	Description
1028	R.A. Duffy, <i>Potential therapeutic targets for neurokinin-1 receptor antagonists</i> , 9(1) Expert opinion on emerging drugs, 9 (2004)
1029	Press Release, Eisai Co., FDA Approves ALOXI [®] (Palonosetron HCl) Capsules for Prevention of Acute Chemotherapy-induced Nausea and Vomiting (Aug. 24, 2008)
1030	Merck & Co., EMEND, package insert (2008)
1031	DailyMed, EMEND (aprepitant) Capsule, https://web.archive.org/web/20090202144735/http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=7355 (archived Feb. 2, 2009)
1032	U.S. Food and Drug Administration, General Considerations for the Clinical Evaluation of Drugs (1978)
1033	U.S. Food and Drug Administration, Q3A Impurities in New Drug Substances (2008)
1034	D.G. Warr et al., <i>Efficacy and tolerability of aprepitant for the prevention of chemotherapy-induced nausea and vomiting in patients with breast cancer after moderately emetogenic chemotherapy</i> , 23(12) Journal of Clinical Oncology 2822 (2005)
1035	S.M. Grunberg et al., <i>Effectiveness of a single-day three-drug regimen of dexamethasone, palonosetron, and aprepitant for the prevention of acute and delayed nausea and vomiting caused by moderately emetogenic chemotherapy</i> , 17 Supportive Care in Cancer 589 (2009)
1036	Press Release, GSK provides update on regulatory filings for Zunrisa/Rezonic (Sep. 27, 2009), downloaded from https://www.gsk.com/en-gb/media/press-releases/gsk-provides-update-

Exhibit	Description
	on-regulatory-filings-for-zunrisarezonice/
1037	P.J. Hesketh et al., <i>The Oral Neurokinin-1 Antagonist Aprepitant for the Prevention of Chemotherapy-Induced Nausea and Vomiting: A Multinational, Randomized, Double-Blind, Placebo-Controlled Trial in Patients Receiving High-Dose Cisplatin—The Aprepitant Protocol 052 Study Group</i> , 21(22) <i>Journal of Clinical Oncology</i> 4112 (2003)
1038	G.S. Paulekuhn et al., <i>Trends in active pharmaceutical ingredient salt selection based on analysis of the orange book database</i> , 50(26) <i>Journal of Medicinal Chemistry</i> 6665 (2007)
1039	S. Poli-Bigelli et al., <i>Addition of the neurokinin 1 receptor antagonist aprepitant to standard antiemetic therapy improves control of chemotherapy-induced nausea and vomiting: Results from a randomized, double-blind, placebo-controlled trial in Latin America</i> , 97(12) <i>Cancer</i> 3090 (2003)
1040	T. Qiu et al., <i>Antiemetic regimen with aprepitant in the prevention of chemotherapy-induced nausea and vomiting</i> , 99(33) <i>Medicine</i> e21559 (2020)
1041	C. Rojas, <i>The antiemetic 5-HT₃ receptor antagonist Palonosetron inhibits substance P-mediated responses in vitro and in vivo</i> , 335(2) <i>The Journal of Pharmacology and Experimental Therapeutics</i> 362 (2010)
1042	C. Ruhlmann & J. Herrstedt, <i>Casopitant: a novel NK1-receptor antagonist in the prevention of chemotherapy-induced nausea and vomiting</i> , 5 <i>Therapeutics and Clinical Risk Management</i> 375 (2009)
1043	R. Saito et al., <i>Roles of substance P and NK1 receptor in the brainstem in the development of emesis</i> , 91(2) <i>Journal of Pharmacological Sciences</i> 87 (2003)

Exhibit	Description
1044	Ronald D. Schoenwald, Pharmacokinetics in Drug Discovery and Development (2002)
1045	A.G. Thomas, <i>Netupitant and palonosetron trigger NK1 receptor internalization in NG108-15 cells</i> , 232 Experimental Brain Research 2637 (2014)
1046	K.E. Thummel, <i>Gut instincts: CYP3A4 and intestinal drug metabolism</i> , 117(11) Journal of Clinical Investigation 3173 (2007)
1047	D.S. Wang, <i>Effect of aprepitant for the prevention of chemotherapy-induced nausea and vomiting in women: a randomized clinical trial</i> , 4(4) JAMA Network Open e215250 (2021)
1048	W. Yeo et al., <i>A randomized study of aprepitant, ondansetron and dexamethasone for chemotherapy-induced nausea and vomiting in Chinese breast cancer patients receiving moderately emetogenic chemotherapy</i> , 113 Breast Cancer Research and Treatment 529 (2009)
1049	S.F. Zhou, <i>Drugs Behave as Substrates, Inhibitors and Inducers of Human Cytochrome P450 3A4</i> , 9(4) Current Drug Metabolism 310 (2008)
1050	<i>Parenteral</i> , Merriam-Webster, https://www.merriam-webster.com/dictionary/parenterally
1051	NK1 receptor antagonist by Roche, Advances in Drug Discovery (Feb. 23, 2006), https://web.archive.org/web/20080215091703/http://leaddiscovery.blogspot.com/2006/02/nk1-receptor-antagonist-by-roche.html (archived Feb. 15, 2008)

Exhibit	Description
1052	RxList, ALOXI (palonosetron HCl) Capsules, https://web.archive.org/web/20080924091503/http://www.rxlist.com:80/script/main/hp.asp (archived Oct. 24, 2008)
1053	DailyMed excerpts relating to ALOXI (palonosetron HCl) Capsules, downloaded from https://dailymed.nlm.nih.gov/dailymed/index.cfm , https://dailymed.nlm.nih.gov/dailymed/dailymed-announcements-details.cfm?date=2015-10-08 , https://dailymed.nlm.nih.gov/dailymed/archives/index.cfm?query=palonosetron&date=10%2F30%2F2008 , & https://dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archiveid=9092
1054	DailyMed excerpts relating to Aloxi (palonosetron HCl) Capsules, as archived at https://web.archive.org/web/20081112024512/http://dailymed.nlm.nih.gov/dailymed/about.cfm (archived Nov. 12, 2008), https://web.archive.org/web/20090117151926/http://dailymed.nlm.nih.gov/dailymed/drugList.cfm?startswith=P (archived Jan. 17, 2009), and https://web.archive.org/web/20090521131758/http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=8295 (archived May 21, 2009)
1055	PCT Publication WO 2011/061622, filed 18 November 2010
1056	Provisional Patent Appl. 61/382,709, filed 14 September 2010
1057	Provisional Patent Appl. 61/262,470, filed 18 November 2009
1058	Drugs@FDA: FDA-Approved Drugs, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=022233

Exhibit	Description
1059	P. Li & L. Zhao, <i>Developing Early Formulations: Practice and Perspective</i> , 341 International Journal of Pharmaceutics 1 (2007)
1060	G. Sanso, <i>Double capsule for the administration of active principles in multiple therapies</i> , U.S. Patent 6,350,468 B1 (issued 26 Feb. 2002)
1061	B. Cromie, <i>Drug Combinations</i> , 1(2) Current Medical Research and Opinion 78 (1972)
1062	RESERVED
1063	RESERVED
1064	RESERVED
1065	RESERVED
1066	Page 64 of EX2088 with Dr. Roeland's markings from his deposition
1067	Deposition of Eric Roeland, M.D. (11 May 2026)

VIII. CERTIFICATIONS

A. Rule 42.6(e)(4) Certificate of Service

I certify that today this paper was served electronically on Helsinn's counsel at PH-Azurity-Helsinn-IPR@paulhastings.com. See #4 (PO Mand. Not.).

B. Rule 42.24(d) Certification of Word Count

I certify that this paper complies with the type-volume limitation of Rule 42.24, with a word count of 5363 words.

C. Declaration

All statements in this certificate of service made of my own knowledge are true and all statements made on information and belief are believed to be true. I acknowledge that willful false statements and the like are punishable by fine or imprisonment, or both (18 U.S.C. 1001) and may jeopardize the validity of this proceeding.

Dated: June 3, 2026

/ Yawen Wang /

Yawen Wang