UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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AZURITY PHARMACEUTICALS, INC.,
Petitioner,

v.

HELSINN HEALTHCARE S.A.,
Patent Owner.

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Case IPR2025-00949
Patent US 10,828,297 B2

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# AZURITY PHARMACEUTICALS' REPLY

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## I. INTRODUCTION

Patent owner Helsinn's response requires rewriting the claims to import limitations that do not exist. 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 $NK_1$-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 $NK_1$-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") 18-21. The legal standards have not changed, so the Board should continue to reject these arguments.

Helsinn addresses only independent claims 1-3, 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 nausea focus is neither supported nor relevant

#### 1. Most claims do not require preventing nausea specifically

Helsinn's independent claims require treating "***nausea and vomiting***" expressly (EX1004, 21:45-49) or implicitly via the definition of "***complete response***" (EX1004, 21:50-55), while only claim 3 of the contested claims addresses "***preventing nausea***" separately (EX1004, 21:56-61). POR 17. Thus, for all but one independent claim, Helsinn's nausea-focused arguments are irrelevant because treating CINV is sufficient and the prior art expressly teaches treating both nausea and vomiting.

The specification defines "complete response" as "no emetic episodes, no rescue medication", thus expressly including vomiting as well as nausea. EX1004, 18:10-13. Record evidence confirms that combining 5-$HT_3$- and $NK_1$-receptor antagonists improves the composite endpoints of complete protection and reduced rescue medication. Pet. 20, 47-49, 53; EX1009, ¶¶1333-40, 1373. As Dr. Roeland explained, these are the gold-standard measurements of nausea and vomiting available. EX2091, ¶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.").

### 2. For claim 3, preventing nausea in some subjects suffices

Claim 3 recites "preventing nausea" (EX1002, 21:56), which means no nausea in at least some patients (cf. EX1002, 18:10-15, defining "total control"), something even the prior art accomplished. EX1002, 19:Table 6 (showing "No Nausea" and "Total Control" in more than half the non-netupitant patients for both acute and delayed nausea); POR 10 (showing no nausea for more than half the "Palo alone" and "Aprepitant Regimen" patients). Although Helsinn suggests its claimed triple therapy is better, that argument is a red-herring because the contested claims provide no baseline for comparison—so the baseline could be no treatment. Again, the prior-art triple therapy already provided nausea treatment.

Treating both nausea and vomiting is explicit in treating chemotherapy-induced ***nausea and vomiting*** (CINV), but Helsinn attempts to leverage "preventing nausea" into a requirement for ***improved*** nausea treatment ***compared to standard therapy***. No such requirement appears in the contested claims. Hence, any treatment of nausea suffices, yet even Helsinn concedes that dexamethasone (one of the triple therapy components) treats nausea. EX1067, 117:23-118:2, 119:15-20; see also EX1004, 1:29-30 ("Palonosetron hydrochloride [another prior-art triple-therapy component] has recently emerged as a highly efficacious anti-

nauseant", citing prior art). Thus, absent an express baseline, the nausea prevention in claim 3 is met by any treatment that is more effective than placebo. The inclusion of an effective amount of dexamethasone (when used in combination with the $NK_1$-inhibitor) or palonosetron suffices.

### 3. Statistical significance is a red herring

Helsinn also imports into the contested claims a requirement for statistically-significant efficacy for treatment (POR 17), but the express claim language and the specification contradict this assertion. No contested claim requires statistical significance as compared to standard therapy. Without a comparator, statistical significance is meaningless. EX1004, 8:29-32 ("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***." (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.").

Moreover, because no contested claim provides a baseline for statistical comparison, importing Helsinn's limitation into these claims 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 the contested claims, the baseline must be broad enough to include any comparator, including no treatment or treatment with insufficient dexamethasone without an $NK_1$-inhibitor boost.

**B. The striatum-occupancy element is descriptive**

As the petition explained (Pet. 43-45), the striatum-occupancy element of claims 7, 16, and 22 simply describes the result of using an effective amount on an $NK_1$-inhibitor. Significantly, Helsinn did not point to any additional step in these claims beyond administering netupitant 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 because these claims do not specify a dosage.

**C. Comprising**

Helsinn attacks the combination by arguing other drugs might also be effective against nausea. POR 27-30. Claims 1-3 use the transitional term "comprising" before the treatment steps. EX1004, 21:45-61. Hence, the contested 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 13-15. 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 7-10) 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 13-14. 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 experience 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. 9, as modified in ID 9, 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 13-14, citing EX2091, ¶¶24-26. 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.

### 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 own 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 13-16) 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).

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 3-4, 17-20), but the claims do not require treating nausea separately. Indeed, claim 1 explicitly treats CINV together, while claim 2 implicitly treats CINV together

because a complete response requires no emetic episodes, while claim 3 requires the context of "highly emetogenic cancer therapy", meaning the supposedly independent nausea prevention is ***always*** linked to vomiting. EX1004, 21: 45-61; cf. EX2091, ¶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." EX1004, 1:6-10. Similarly, claims 1 and 2 address both nausea and vomiting with no singular focus on nausea. Moreover, the existing triple therapy (with both dexamethasone and

palonosetron) already treated acute and delayed nausea. E.g., EX1010, 148 ("almost identical" guidelines provided "recommendations for prevention of acute and delayed nausea and vomiting"). Hence, providing new tools to treat CINV patients sufficed as a reason to employ another $NK_1$-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 24. 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, "treating CINV" is the claimed problem. ID, 19 ("multiple solutions to the problem of treating CINV may have been obvious"). Indeed, a POSA would have substituted netupitant as the $NK_1$-inhibitor for the same reason the art substituted palonosetron for ondansetron (the 5-$HT_3$-inhibitor): to use the triple therapy with a new drug targeting the same mechanistic pathway. Pet. 25;

EX1009, ¶¶738-40, 794-96. Helsinn vaguely argues that netupitant and aprepitant were not "equivalent" (POR 25) but does not (and cannot) dispute that netupitant was a known $NK_1$-inhibitor. Helsinn complains that the art lacked studies comparing aprepitant's and netupitant's efficacy (POR 26-27) without showing such studies are a prerequisite for obviousness. In a footnote, Helsinn also argues that netupitant was one of "millions of compounds" (POR 26-27 n.21) 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); see also EX1011, 1362 (singling netupitant out (along with one other $NK_1$-inhibitor, befetupitant) for praise in the context of treating CINV with $NK_1$-inhibitors).

To the extent Helsinn argues (POR 25-27) the petition failed to compare netupitant's properties to other $NK_1$-inhibitors in use, Helsinn is wrong. See, e.g., Pet. 12-13. 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 would reduce pharmaceutical 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 27-30. As an initial matter, claims 1-3 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 both independent claims being directed to both nausea and vomiting. By Helsinn's logic, prior art 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 the art suggested. Indeed, an "inferior solution" can be obvious even when a superior solution is also available. *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 32-34) 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 33 ("[T]he preclinical animal data in Azurity's cited reference (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 $NK_1$-inhibitor in combination with dexamethasone and palonosetron to treat CINV. For claims 1 and 2, no more is required.

For claim 3, Helsinn's own data shows that prior art treatment completely prevented nausea in more than half the patients. EX1004, 19:Table 6 (showing "No Nausea" and "Total Control" in more than half the non-netupitant patients for both acute and delayed nausea); POR 10 (showing no nausea for more than half the "Palo alone" and "Aprepitant Regimen" patients). As even Helsinn concedes, dexamethasone and palonosetron (two components of the triple therapy) treat nausea. EX1067, 117:23-118:2, 119:15-20; EX1004, 1:29-30 ("Palonosetron hydrochloride [another prior-art triple-therapy component] has recently emerged as a highly efficacious anti-nauseant", citing prior art). Hence, the proposed combination would have been expected to work for most patients based on the two triple-therapy components that do not change.

### F. Reasonable expectation of success

Helsinn argues that preclinical animal studies "would not necessarily translate to efficacy in humans". POR 34. As an initial matter, the contested claims are not limited to humans. Moreover, the prior art provides objective evidence that those skilled in the art considered netupitant 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. This 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 $NK_1$-inhibitors do not always work out (POR 37-38), 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 independently as compared to standard therapy. POR 44. Yet, as discussed above (II.A), the contested claims do not 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 44-46), yet fails to show either independent claim requires this comparison. What the data does show is large percentages in both groups being successfully treated for nausea. POR 45-46, citing EX1030, Table 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 46 (original emphasis).

**G. Bös narrowed the $NK_1$-inhibitors to try**

Helsinn argues that the prior-art identified millions of $NK_1$-inhibitors in 2009. POR 26-27 & n.21. Yet Bös highlighted three out of "millions." EX1014,

13:14-23:16 (compounds Ia-Ic), one of which was netupitant. Nor was Bös a fluke: other prior art highlighted two (including netupitant) out of 31. EX1011, 1362. Both references identified netupitant as a preferred candidate. While Helsinn and Dr. Roeland exaggerate the challenge, Bös (as EX1011 objectively confirms) provided ample direction to those seeking an $NK_1$-inhibitor to employ instead of aprepitant.

### H. Helsinn's striatum-receptor occupancy arguments are misplaced

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

Helsinn claims 7, 16, and 22 recite "netupitant occupies at least 70% of said patient's striatum NK1 receptors seventy-two hours after said administration." EX1004, 22:10-13, 41-43, 65-67. Helsinn argues that the reference Azurity uses to address this limitation (Hargreaves, EX1012) does not discuss netupitant. POR 51. This argument is a strawman because the petition used Hargreaves to show that the art used striatum occupancy as a proxy for $NK_1$-inhibitor therapeutic effectiveness. Pet. 17 ("Hargreaves teaches a 75% or greater NK1-receptor occupancy was associated with therapeutic doses that blocked emesis."), citing EX1012, 23 and EX1009, ¶¶116-17.

Helsinn argues that nothing connects Hargreaves to netupitant (POR 50-52), but this misses the point. Hargreaves teaches a proxy for $NK_1$-inhibitor

effectiveness. Pet. 43-45. Because netupitant is an $NK_1$-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 53), 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 53), but it is independent authority supporting Azurity. Helsinn invites Office adjudicative inconsistency without providing any evidence to the contrary. Moreover, as discussed above (II.B), the plain language of this element shows the striatum-receptor element is simply a description of an effective dose.

**2. Helsinn's 72-hour argument is a red herring**

Helsinn argues that "Azurity has provided no analysis regarding why a POSA would have been motivated to choose to focus on receptor occupancy at ninety-six hours rather than other time points…." POR 54. Helsinn has inverted the petition's actual argument and thus misses the point: the 72-hour occupancy level is a ***result*** of the proposed modification, not the reason for the modification. Pet. 43-45. Helsinn does not engage Azurity's showing much less rebut it. For example, Helsinn criticizes Azurity's citation to Helsinn's specification for loss of only 20-30% of $NK_1$-receptor occupancy at 96 hours for lacking a baseline. POR 52-53. Yet if this critique were correct, it would be a defect of Helsinn's written

description for this limitation. Similarly, Helsinn argues "netupitant's half-life does not directly translate to receptor occupancy" (POR 34), but again Azurity's argument does not require knowing the receptor occupancy in advance: the POSA simply seeks an effective triple therapy for treating delayed emesis; hence, 72-hour occupancy is a result of the substitution rather than a reason for it. Netupitant's known extended half-life is simply consistent with this result. Pet. 44; EX1009, ¶1058; *cf.* EX1010, 145-46, Table 3 (palonosetron also treats delayed emesis and has comparable half-life); EX1009, ¶¶1011-12 (POSA similarly motivated to use single-dose palonosetron). Helsinn has rebutted strawman arguments rather than engaging the petition's facial showing.

## V. SECONDARY CONSIDERATIONS

Helsinn argues unexpected results and industry skepticism defeat obviousness for the contested claims. POR 54-55. The arguments for both are based on faulty claim construction and unsupported testimony. Moreover, Helsinn argues nexus without tying its argument to any specific claim. POR 55-56. 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 57 ("standard therapy"). Helsinn asserts results for just two dosages (200 mg and 300 mg of netupitant) in the delayed phase of nausea. *Id*. Yet the contested claims are not limited to these two dosages. Indeed, the specification explicitly contemplates "the netupitant is preferably administered in an amount ranging from about 50 to about 500 mg., from about 200 to about 400 mg." EX1004, 10:19-21.

As discussed above (II.A.3), properly construed, the contested claims cannot be limited to statistically-significant improvement over standard therapy because neither claim recites these limitations and their plain language cannot support such limitations. Yet the closest prior art, the aprepitant-5-$HT_3$ antagonist-dexamethasone treatment worked for CINV; indeed, it was the recognized standard in 2009. Pet. 11-12; EX2091, ¶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 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*** $NK_1$-inhibitor, not from netupitant alone. Pet. 54-56; EX1009, ¶¶153-56, 197-200, 1382-90. 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 $NK_1$ 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 points to Bös for an independent reason 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, which are not in any contested claim) for a result (improved treatment of delayed nausea) that is not in most of the claims. 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 57, citing EX2091, ¶¶243-46. Dr. Roeland's testimony is infected with Helsinn's focus on treating nausea rather than vomiting. EX2091, ¶¶243-46. Once again, the petition relies on Bös to substitute netupitant as the $NK_1$-inhibitor to treat CINV generally. Pet. 12-13; see also EX1011, 1362 (Hoffman singling out netupitant as one of two promising alternatives to aprepitant in treating CINV). 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 $NK_1$-inhibitors to treat nausea is a red herring because it does not correlate to the limitations of the contested claims, 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 1-23 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., *Compositions and methods for treating centrally mediated nausea and vomiting*, U.S. Patent 8,623,826 B2, issued 17 January 2014 |
| 1002 | F. Trento et al., *Compositions and methods for treating centrally mediated nausea and vomiting*, U.S. Patent 9,186,357 B2, issued 17 November 2015 |
| 1003 | F. Trento et al., *Compositions and methods for treating centrally mediated nausea and vomiting*, U.S. Patent 9,943,515 B2, issued 17 April 2018 |
| 1004 | F. Trento et al., *Compositions and methods for treating centrally mediated nausea and vomiting*, 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, *Anti-Emetic Therapy in Cancer Chemotherapy: Current Status*, 101 Basic & Clinical Pharmacology & Toxicology 143-150 (2007) |
| 1011 | T. Hoffmann et al., *Design and synthesis of a novel, achiral class of highly potent and selective, orally active neurokinin-1 receptor* |

| Exhibit | Description |
|---|---|
| | *antagonists*, 16 Bioorganic & Medicinal Chemistry Letters 1362-1365 (2006) |
| 1012 | R. Hargreaves, *Imaging Substance P Receptors ($NK_1$) in the Living Human Brain Using Positron Emission Tomography*, 63(11) J. Clinical Psychiatry 18-24 (2002) |
| 1013 | The Antiemetic Subcommittee of the Multinational Association of Supportive Care in Cancer (MASCC), *Prevention of chemotherapy- and radiotherapy-induced emesis: results of the 2004 Perugia International Antiemetic Consensus Conference*, 17 Annals of Oncology 20-28 (2006) |
| 1014 | M. Bös et al., *4-phenyl-pyridine derivatives*, 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., *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*, 112 Cancer 2080 (2008). |
| 1017 | D. Bonadeo et al., *Soft Capsules Comprising Palonosetron Hydrochloride Having Improved Stability and Bioavailability*, PCT Publication WO 2008/049552 (published 2 May 2008) |
| 1018 | R.J. Gralla et al., *Recommendations for the use of antiemetics: evidence-based, clinical practice guidelines*, 17 Journal of Clinical Oncology 2971 (1999). |
| 1019 | K. Jordan et al., *Guidelines for Antiemetic Treatment of Chemotherapy-Induced Nausea and Vomiting: Past, Present, and Future Recommendations*, 12 The Oncologist 1143-1150 (September 2007) |

| Exhibit | Description |
|---|---|
| 1020 | Curriculum Vitae of Dr. Stephen J. Peroutka |
| 1021 | G.K. Reddy et al., *Novel Neurokinin-1 Antagonists as Antiemetics for the Treatment of Chemotherapy-Induced Emesis*, 3 Support Cancer Therapy 140-42 (2006). |
| 1022 | M.S. Aapro et al., *A phase III, double-blind, randomized trial of palonosetron compared with ondansetron in preventing chemotherapy-induced nausea and vomiting following highly emetogenic chemotherapy*, 17 Annals of Oncology 1441-49 (2006) |
| 1023 | D. Campos et al., *Prevention of cisplatin-induced emesis by the oral neurokinin-1 antagonist, MK-869, in combination with granisetron and dexamethasone or with dexamethasone alone*, 19(6) Journal of Clinical Oncology, 1759 (2001) |
| 1024 | A.E. Chang et al., eds., Oncology: An Evidence-Based Approach (2006) |
| 1025 | S.P. Chawla et al., *Establishing the Dose of the Oral $NK_1$ Antagonist Aprepitant for the Prevention of Chemotherapy-Induced Nausea and Vomiting*, 97 Cancer 2290 (2003). |
| 1026 | S.P. Chawla et al., *Establishing the Dose of the Oral $NK_1$ Antagonist Aprepitant for the Prevention of Chemotherapy-Induced Nausea and Vomiting*, 37th Annual Meeting of the American Society of Clinical Oncology, in 20 Proceedings of ASCO 383a (2001) |
| 1027 | A. De Leon, *Palonosetron (Aloxi): a second-generation 5-HT3 receptor antagonist for chemotherapy-induced nausea and vomiting*, in 19(4) Baylor University Medical Center Proceedings 413 (2006) |

| Exhibit | Description |
|---|---|
| 1028 | R.A. Duffy, *Potential therapeutic targets for neurokinin-1 receptor antagonists*, 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., *Efficacy and tolerability of aprepitant for the prevention of chemotherapy-induced nausea and vomiting in patients with breast cancer after moderately emetogenic chemotherapy*, 23(12) Journal of Clinical Oncology 2822 (2005) |
| 1035 | S.M. Grunberg et al., *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*, 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-zunrisarezonic/ |
| 1037 | P.J. Hesketh et al., *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*, 21(22) Journal of Clinical Oncology 4112 (2003) |
| 1038 | G.S. Paulekuhn et al., *Trends in active pharmaceutical ingredient salt selection based on analysis of the orange book database*, 50(26) Journal of Medicinal Chemistry 6665 (2007) |
| 1039 | S. Poli-Bigelli et al., *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*, 97(12) Cancer 3090 (2003) |
| 1040 | T. Qiu et al., *Antiemetic regimen with aprepitant in the prevention of chemotherapy-induced nausea and vomiting*, 99(33) Medicine e21559 (2020) |
| 1041 | C. Rojas, *The antiemetic 5-HT3 receptor antagonist Palonosetron inhibits substance P-mediated responses in vitro and in vivo*, 335(2) The Journal of Pharmacology and Experimental Therapeutics 362 (2010) |
| 1042 | C. Ruhlmann & J. Herrstedt, *Casopitant: a novel NK1-receptor antagonist in the prevention of chemotherapy-induced nausea and vomiting*, 5 Therapeutics and Clinical Risk Management 375 (2009) |
| 1043 | R. Saito et al., *Roles of substance P and NK1 receptor in the brainstem in the development of emesis*, 91(2) Journal of Pharmacological Sciences 87 (2003) |

| Exhibit | Description |
|---|---|
| 1044 | Ronald D. Schoenwald, Pharmacokinetics in Drug Discovery and Development (2002) |
| 1045 | A.G. Thomas, *Netupitant and palonosetron trigger NK1 receptor internalization in NG108-15 cells*, 232 Experimental Brain Research 2637 (2014) |
| 1046 | K.E. Thummel, *Gut instincts: CYP3A4 and intestinal drug metabolism*, 117(11) Journal of Clinical Investigation 3173 (2007) |
| 1047 | D.S. Wang, *Effect of aprepitant for the prevention of chemotherapy-induced nausea and vomiting in women: a randomized clinical trial*, 4(4) JAMA Network Open e215250 (2021) |
| 1048 | W. Yeo et al., *A randomized study of aprepitant, ondansetron and dexamethasone for chemotherapy-induced nausea and vomiting in Chinese breast cancer patients receiving moderately emetogenic chemotherapy*, 113 Breast Cancer Research and Treatment 529 (2009) |
| 1049 | S.F. Zhou, *Drugs Behave as Substrates, Inhibitors and Inducers of Human Cytochrome P450 3A4*, 9(4) Current Drug Metabolism 310 (2008) |
| 1050 | *Parenteral*, 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, *Developing Early Formulations: Practice and Perspective*, 341 International Journal of Pharmaceutics 1 (2007) |
| 1060 | G. Sanso, *Double capsule for the administration of active principles in multiple therapies*, U.S. Patent 6,350,468 B1 (issued 26 Feb. 2002) |
| 1061 | B. Cromie, *Drug Combinations*, 1(2) Current Medical Research and Opinion 78 (1972) |
| 1062 | Deposition of Eric Roeland, M.D. (11 May 2026) |
| 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 4835 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