

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 IPR2025-00948  
Patent US 9,943,515 B2

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AZURITY PHARMACEUTICALS' OPPOSITION  
TO HELSINN'S DISCRETIONARY-DENIAL REQUEST

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## I. INTRODUCTION

The Director should deny Patent Owner (Helsinn)'s request for discretionary denial of institution. Helsinn does not assert *Fintiv* applies here, because it indisputably does not. Helsinn does not identify any alternative forum for resolving the parties' dispute, because no litigation is co-pending. Helsinn thus relies exclusively on alleged settled expectations based on ex parte examination. But Helsinn's arguments fail because Helsinn undermined the ex parte examination and caused the challenged patent to issue in error. Perhaps this is why Helsinn has studiously avoided litigating the validity of the patent and continues to seek to do so now.

Petitioner Azurity explained at length in its petition, with supporting expert testimony, how Helsinn undermined ex parte examination. Paper 2 (#2, Pet.), 5-8, 57, 60-63. Despite being fully apprised by the petition materials of the prosecution problems ***Helsinn*** created, Helsinn failed to address most of them squarely, misdirected on the few it did address, and then retreated to the false defense that Helsinn is entitled to rely on the validity of the very examination process Helsinn undermined. Of course, Helsinn has no settled expectations in perpetuating examination error Helsinn itself invited. The Executive Power invested in the President by the U.S. Constitution is not so powerless. Absent co-pending litigation, the Executive has no reason to cede its Congressionally-enacted mandate

to correct patentee-induced examination errors in deference to the Judiciary. This is doubly true here, where denying institution would only surrender the Executive’s opportunity to address artificially-high drug prices based on examination error of Helsinn’s own creation. The Director should refer this petition for institution to permit the Office to address and correct material examination error.

## **II. *ADVANCED BIONICS* DOES NOT BAR INSTITUTION**

### **A. Material Examination Error Warrants Referral for Trial**

Referring a petition for institution is warranted where (as here) “the Petitioner appears to show a material error by the Office” because “it is an appropriate use of Office resources to review the potential error.” *Microsoft v. Partec Cluster Competence Center*, IPR2025-00318, #9 (USPTO Dir. 2025). The Office appropriately considers a patentee’s “unfair dealings”—here, materially misrepresenting data as showing unexpected results—when deciding to refer for institution. *Tessell, Inc. v. Nutanix, Inc.*, IPR2025-00322, #14 (USPTO Dir. 2025).

The petition (with supporting exhibits including Dr. Stephen J. Peroutka’s disinterested expert testimony) detailed how Helsinn obtained this patent using misleading, inconsistently presented data that omitted material information. Helsinn failed to address, much less rebut, most material errors that the petition identified. For example, Helsinn did not dispute many Azurity showings that—

contrary to Helsinn’s prosecution statements—prior-art a prepatent showed efficacy for nausea. Nor did Helsinn deny that its data table presented during examination of the patentably-indistinct parent Trento’826 patent materially differed from the table its Rule 132 declarants used (though Helsinn told the Office they were the same) and that the tables omitted data detrimental to Helsinn’s unexpected-results arguments. Nor did Helsinn deny that its specification and prosecution history neither define nor discuss its purportedly unexpected “synergy” that led to allowance. Nor did Helsinn deny that prior-art therapeutics also showed such “synergy”. Nor did Helsinn dispute the lack of nexus between such “synergy” and these claims. Nor did Helsinn deny that its declarants are interested parties—an inventor to these patents and another Helsinn employee.

If Helsinn tries to address its failings in subsequent briefing, such untimely arguments should be disregarded as further examples of Helsinn gamesmanship attempting to deprive Azurity of a chance to respond.<sup>1</sup> Such gamesmanship should

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<sup>1</sup> For example, Helsinn repeatedly, improperly attempts a blanket incorporation of its yet-unfiled preliminary response into its request, citing a superseded FAQ as authorizing such incorporation. PORD, 24 n.10. Helsinn is wrong: the FAQ discourages detailed repetition, and does not authorize sandbagging with new

not be rewarded.

Helsinn wrongly asserts the petition failed to rebut Helsinn's secondary-consideration evidence; actually, Helsinn just ignores Azurity's arguments. As summarized below, Azurity showed Helsinn invited material error during examination. Helsinn's unfair dealings with the Office induced material error leading to these claims' erroneous allowance. Helsinn's continued reliance now on its materially erroneous data and mischaracterizations just highlights Helsinn's ongoing misconduct (and refusal to cure).

### **1. Helsinn Obtained Its Patent Based On Purported Unexpected Results**

The petition explained that the examiner erroneously allowed the involved claims due to his misapprehension that the claimed treatment of nausea and vomiting using netupitant was unexpectedly different from the prior-art treatment using aprepitant. This misapprehension arose because Helsinn represented that netupitant could be administered in a single dose and provided an unexpected efficacy during the acute phase of therapy. Pet., 5-8.

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argument. If the argument is material to discretionary denial, it must be in Helsinn's request—so Azurity can address it—not hidden in a future paper that Azurity cannot rebut.

The examiner considered there to be a strong *prima facie* obviousness case against the claims because the prior art showed an NK<sub>1</sub>-receptor antagonist (e.g., aprepitant) combined with a 5-HT<sub>3</sub>-receptor antagonist (e.g., casopitant, palonosetron) and dexamethasone defined a new standard of care for treating chemotherapy-induced nausea and vomiting. Pet., 5-7; EX1007, 147-150. The examiner also found (1) “[t]he familiarity of working with an NK-1 antagonist and its intended use make obvious the administration of netupitant, as claimed, based on the administration of other NK-1 antagonists, e.g. aprepitant” made it “obvious to administer netupitant on day one of five consecutive days;” (2) the specification’s Table 5 failed “to distinguish over aprepitant, especially since numbers were fairly similar;” (3) the “binding habit of netupitant is an inherent property of netupitant” and the other purported benefits were known in the art; and (4) Helsinn failed to establish unexpected results and that “administration of a single dose...may also be construed as an inherent property of netupitant especially since the prior art teaches administration to patients for treatment of chemotherapy-induced nausea and vomiting.” Pet., 7; EX1007, 215-18; EX1009, ¶40.

Helsinn ultimately amended the independent claims to recite “no further netupitant or pharmaceutically acceptable salt thereof is administered during said five consecutive days, and said single dose of netupitant or pharmaceutically acceptable salt thereof [is] effective to treat said nausea and vomiting for said five

consecutive days.” Pet., 8; EX1007, 324, 326. Helsinn stated “it is unexpected that a single dose of netupitant would be effective against nausea and vomiting during the acute and delayed phases of emesis.” Pet., 7; EX1007, 328-29. Following after-final-rejection prosecution to enter amendments and terminal disclaimers, the examiner allowed the claims without further substantive examination. Pet., 8; EX1009, ¶¶41-49.

This allowance was due to erroneous findings of unexpected results stemming from Helsinn’s misrepresentations. For example, contrary to Helsinn’s prosecution argument, the prior art expected single-dose netupitant would be effective. Pet., 65-66; EX1009, ¶¶1391-1393; §II.A.2 below. Helsinn did not dispute in its Patent Owner Discretionary Denial brief (PODD) that a single dose of netupitant was *expected* to provide therapeutic effect during acute and delayed phases. Section II.A.3 below. Unexpected results also did not exist with netupitant because the prior-art NK<sub>1</sub>-receptor antagonist aprepitant had the necessary properties—much of which Helsinn’s request did not deny. Pet., 55-67; EX1009, ¶¶1329-1400; §§II.A.4-II.A.5 below. Helsinn misrepresented these purported unexpected results to the Office (and to the same examiner) during the parent Trento’826 examination, tainting the Trento’515 patent, which has claims “not patentably distinct” from Trento’826. EX1007, 150-151; Pet., 57. Helsinn’s prosecution response invited material error by altering tables to remove data

unsupportive of its contentions. Pet., 8; EX1009, ¶¶1360-1379.

**2. A Single, One-Time Dose of Netupitant Was Obvious**  
***a. Helsinn Mischaracterized Azurity's Arguments***

Helsinn argued Azurity's references did not disclose the claimed single, one-time dose of netupitant. Paper 7, (PO Disc. Denial brief (#7, PODD)), 19. Actually, the petition explained how the references showed using a single, one-time dose of netupitant to prevent nausea and vomiting during a five-day period following treatment with emetogenic chemotherapy. Pet., 19-21, 37-39; EX1009, ¶¶520-526, 619-625. As Dr. Peroutka summarized:

Herrington confirms its *single dose of aprepitant* administered on day one, where no further NK<sub>1</sub> receptor antagonist is administered during the five day period, is *effective to treat nausea and vomiting for the five consecutive days*.

A POSA would have been motivated to use a single dose of aprepitant as disclosed by Herrington in Herrstedt's triple therapeutic combination for decreased costs, increased convenience, and patient preference for single administration. *See* Section IX.G, above. Thus, it is my opinion that a POSA would have had *good reason to employ the single dose of NK<sub>1</sub> receptor antagonist in the dosing protocol of Herrstedt without dosing on subsequent days*. As discussed above, the POSA would have employed Bös' second generation NK<sub>1</sub> receptor antagonist—netupitant—in Herrstedt's protocol.

EX1009, ¶¶523-524 (cited at Pet., 21); *see also id.*, ¶¶622-623 (cited at Pet., 37-

39). Helsinn did not dispute that these references taught a single dose of NK<sub>1</sub>-receptor antagonist provided “similar effectiveness compared with 3-day” dosages. EX1016, Background; Pet., 20-21, 39; EX1009, ¶¶523, 622.

***b. Helsinn’s Merits Arguments Justify Referral to the Board***

To eke out its discretionary-denial arguments, Helsinn made misdirected, piecemeal attacks against the petition’s merits. PODD, 19-22. Not only does Helsinn mischaracterize the petition as conclusory (as explained below, the petition was fully supported), but Helsinn’s arguments themselves justify referral to the Board to expose their weaknesses on a fully-developed record.

For example, Helsinn characterized the Bös reference as disclosing “a large genus that covers millions of compounds” (PODD, 20) but ignored that Bös *specifically identifies netupitant* as “characterized by valuable therapeutic properties as a highly selective antagonist of the Neurokinin 1.” Pet., 12 (citing EX1014, 14:32-38); *see also* EX1009, ¶¶97-98. Bös also specifically tested netupitant in animal models that demonstrated its administration “completely blocked the emesis induced by the emetogens.” Pet., 13 (citing EX1014, 19:10-20); EX1009, ¶99. Thus, Helsinn’s characterization of Bös’ disclosure of netupitant as merely one compound of millions was misleading and entirely divorced from the focus of the Bös reference. Trial on the merits is vital in this case because it will

confirm Helsinn’s mischaracterizations are indeed mischaracterizations.

Helsinn also falsely stated that the petition failed to explain why a single dose of netupitant would be effective against nausea and vomiting for five consecutive days. PODD, 20-21. But Helsinn did not dispute nor deny Herrstedt is a prior-art reference that describes single-dose administration of aprepitant on day one of a five consecutive day treatment period that was effective to treat nausea and vomiting during five consecutive days. Pet., 20; EX1009, ¶522. Nor did Helsinn dispute that netupitant was known to have a functional half-life of 30 hours (Pet., 20), which was considered “large” by those skilled in the art. EX1009, ¶522. The petition and Dr. Peroutka explained this fact rendered obvious administering netupitant on day one of five consecutive days, where no further netupitant is administered during the consecutive 5-day treatment. *E.g.*, Pet., 19-21; EX1009, ¶¶520-526. Again, the petition provided meritorious arguments, while Helsinn’s mischaracterization shows why trial is appropriate to avoid perpetuating the Office’s error in allowing these claims.

Helsinn also falsely contends the petition failed to explain why a drug effective for emesis would have been effective for treating nausea. PODD, 21. But—as the petition directly addressed—the prior art showed such antiemetic therapy treated *both* nausea and vomiting during acute and delayed phases of emesis. Pet., 17-18, 20-21. For example, the prior art showed “no significant

differences between Arms A [3-day aprepitant] and B [single day-1 dose aprepitant] for emesis, nausea, or the use of break-through antiemetics.” EX1016, Abstract; Pet., 21; EX1009, ¶523. Thus, the petition directly addressed how the prior art showed the drug was effective for treating nausea, contrary to Helsinn’s argument. Again, such mischaracterization *justifies* referral to confirm the real facts.

Helsinn again incorrectly argued the petition “provides no basis for why a POSA would have” “assume[d] that Herrington’s aprepitant results are equally applicable to a drug regimen involving netupitant.” PODD, 21. Actually, the petition showed “aprepitant was merely ‘the first drug’ in this class of selective NK<sub>1</sub> receptor antagonists” and that the prior art “not only discloses netupitant...as a potent and selective NK<sub>1</sub> receptor antagonist, but also recommends use of an effective amount of netupitant”. EX1009, ¶516; Pet., 18-19. Dr. Peroutka identified numerous benefits of netupitant (EX1009, ¶¶516-518) and explained the prior art provided “good reason to replace Herrstedt’s NK<sub>1</sub> receptor antagonist (aprepitant) with the second generation NK<sub>1</sub> receptor antagonist of BöS (netupitant)” (*id.*, ¶518). As Dr. Peroutka explained:

The person having ordinary skill would have expected netupitant to work at least as effectively and in the same manner as aprepitant. Thus, the skilled artisan would have expected—since only a single dose of aprepitant was required for therapeutic effect during the acute and

delayed phases of emesis—that only a single dose of netupitant would also be required during the acute and delayed phases of emesis.

EX1009, ¶1394.

Helsinn’s continuing mischaracterization of the record provides ample reason to refer this case for institution and trial to restore integrity to the Office’s consideration of these claims.

### **3. Helsinn Did Not Dispute: A Single Dose of Netupitant was Expected to Provide Therapeutic Effect During Acute and Delayed Phases**

The petition showed the Office materially erred by accepting Helsinn’s purported unexpected results that a single dose of netupitant was effective “during the acute and delayed phases of emesis” (EX1007, 203) and that netupitant purportedly unexpectedly “also treats emesis during the acute phase” (*id.*). Pet., 66. The petition explained how the prior art showed a single netupitant dose was *expected* to provide therapeutic effect during acute- and delayed-phase emesis. Pet., 65-66; EX1009, ¶¶1395-1397.

Helsinn did not meaningfully dispute the petition’s showing of material error. Instead, Helsinn maintained netupitant had unexpectedly superior properties over aprepitant (PODD, 22). But Helsinn did not deny, for example, that:

The person having ordinary skill would have expected netupitant to work at least as effectively and in the same manner as aprepitant.

Thus, the skilled artisan would have expected—since only a single

dose of aprepitant was required for therapeutic effect during the acute and delayed phases of emesis—that only a single dose of netupitant would also be required during the acute and delayed phases of emesis. EX1009, ¶1394; *see also id.*, ¶¶1391-1393 (explaining that a single dose of netupitant did not provide unexpected results).

Helsinn likewise did not dispute that “a skilled artisan would have expected netupitant to treat emesis during the acute phase as well as delayed phase” because the POSA “would have expected netupitant to work at least as effectively and in the same manner as” aprepitant, which also demonstrated efficacy in treating acute and delayed phases. Pet., 66; EX1009, ¶¶1395-1397.

Thus, the Office materially erred in allowing these claims based on purported unexpected results for single-dose administration and acute-phase treatment, mistakenly relying on Helsinn’s misstatements while the prior art demonstrated otherwise.

#### **4. Helsinn Never Denied Most Mischaracterizations and Fabrications that Underlie Its “Unexpected” Results**

Helsinn’s discretionary-denial request never acknowledges most of the petition’s showings that Helsinn’s “unexpected” results—presented to the examiner during the parent Trento’826 examination—were fictional. Instead, Helsinn misrepresented discrete aspects of the petition to argue (incorrectly) that a few elements of their unexpected results arguments were unaddressed; but Helsinn

is wrong, all were addressed, as explained below.

As the petition showed, any of numerous errors during examination were material and induced erroneous allowance of these claims. Pet., 55-66; EX1009, ¶¶1329-1390. For purposes of discretionary denial, the many arguments Helsinn failed to deny remain un rebutted. Again, Helsinn cannot properly incorporate hypothetical arguments from its unfiled POPR.

***a. No Dispute: Aprepitant Showed Efficacy for Nausea.***

The petition showed a prior-art NK<sub>1</sub>-receptor antagonist—aprepitant—effectively treated nausea, contrary to Helsinn’s representations during examination. Pet., 55-57; EX1001, 2:12-26, 4:37-39, EX1005, 328-39 (arguing *inter alia* that aprepitant was not active against nausea). Helsinn’s request failed to dispute many aspects of the Emend label that showed aprepitant’s efficacy and Helsinn conceded dispositive showings in the petition (see §II.A.5, below). Helsinn never disputed Azurity’s discussion of many other references showing aprepitant effectively treats nausea. Thus, the un rebutted record shows aprepitant was known to treat nausea and Helsinn’s contrary prosecution misrepresentations induced material error.

***i. Emend Label***

Helsinn did not deny the Emend label’s “complete protection” endpoint

requires no significant nausea. Nor did Helsinn dispute a POSA would have understood the Emend label's "complete protection" showed statistical significance and improvement in no significant nausea for subjects receiving aprepitant. Pet., 57-58; EX1009, ¶¶1333-1340, 1371-1373.<sup>2</sup> Nor did Helsinn deny a POSA would have recognized improved nausea treatment (particularly for significant nausea) was represented in the Emend Label Table 1 and Table 2 data, even if not calculated to statistical significance. EX1030; Pet., 57-58; EX1009, ¶1335.

Azurity explained that the Emend label's nausea and significant nausea results showed efficacy, even if statistical significance was not calculated for nausea. Pet., 57-58. For example, Dr. Peroutka, elaborated that "although not calculated for statistical significance, a POSA would have recognized an improvement for treatment of nausea (and in particular for treatment of significant nausea) represented in the Emend Label Table 1 data. *Id.* (e.g., 66% → 73%

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<sup>2</sup> For clarity, note that "complete protection" as discussed in the petition (e.g., Pet., 57-58, 62) differs from "complete response" which Helsinn mentions in its discretionary denial briefing. PODD, 3. "Complete protection" requires *inter alia* no significant nausea; "complete response" does not. *See, e.g.*, Pet., 57; EX1030, 7; EX1001, 16:4-17.

overall in significant nausea).” EX1009, ¶1335 (cited at Pet., 58). Discussing Emend Label Table 2, Dr. Peroutka explained “a POSA would have recognized an even greater improvement for treatment of nausea in this study cohort (and in particular for treatment of significant nausea), even if not calculated for statistical significance. *Id.* (e.g., 64% → 71% overall in significant nausea; 39% → 49% overall in nausea).” EX1009, ¶1336 (cited at Pet., 58). The “POSA therefore reasonably would have expected aprepitant had a beneficial effect on nausea, notwithstanding the lack of calculated statistical significance for those specific parameters.” *Id.*

Helsinn also never disputed a POSA would have recognized aprepitant improved treatment of nausea—particularly significant nausea—during the delayed and overall phases based on the “complete protection” that was calculated to statistical significance. Pet., 57-58; EX1009, ¶¶1333-1340, EX1030, Table 1 (reproduced below, first), Table 2 (reproduced below, second).

ENDPOINTS	Aprepitant Regimen (N = 260) <sup>†</sup> %	Standard Therapy (N = 261) <sup>†</sup> %	p-Value
<b>PRIMARY ENDPOINT</b>			
Complete Response			
Overall <sup>‡</sup>	73	52	<0.001
<b>OTHER PRESPECIFIED ENDPOINTS</b>			
Complete Response			
Acute phase <sup>§</sup>	89	78	<0.001
Delayed phase <sup>  </sup>	75	56	<0.001
Complete Protection			
Overall	63	49	0.001
Acute phase	85	75	NS*
Delayed phase	66	52	<0.001
No Emesis			
Overall	78	55	<0.001
Acute phase	90	79	0.001
Delayed phase	81	59	<0.001
No Nausea			
Overall	48	44	NS**
Delayed phase	51	48	NS**
No Significant Nausea			
Overall	73	66	NS**
Delayed phase	75	69	NS**

<sup>†</sup>N: Number of patients (older than 18 years of age) who received cisplatin, study drug, and had at least one post-treatment efficacy evaluation.  
<sup>‡</sup>Overall: 0 to 120 hours post-cisplatin treatment.  
<sup>§</sup>Acute phase: 0 to 24 hours post-cisplatin treatment.  
<sup>||</sup>Delayed phase: 25 to 120 hours post-cisplatin treatment.  
\*Not statistically significant when adjusted for multiple comparisons.  
\*\*Not statistically significant.  
Visual analogue scale (VAS) score range: 0 mm = no nausea; 100 mm = nausea as bad as it could be.

ENDPOINTS	Aprepitant Regimen (N = 261) <sup>†</sup> %	Standard Therapy (N = 263) <sup>†</sup> %	p-Value
<b>PRIMARY ENDPOINT</b>			
Complete Response			
Overall <sup>‡</sup>	63	43	<0.001
<b>OTHER PRESPECIFIED ENDPOINTS</b>			
Complete Response			
Acute phase <sup>§</sup>	83	68	<0.001
Delayed phase <sup>  </sup>	68	47	<0.001
Complete Protection			
Overall	56	41	<0.001
Acute phase	80	65	<0.001
Delayed phase	61	44	<0.001
No Emesis			
Overall	66	44	<0.001
Acute phase	84	69	<0.001
Delayed phase	72	48	<0.001
No Nausea			
Overall	49	39	NS*
Delayed phase	53	40	NS*
No Significant Nausea			
Overall	71	64	NS**
Delayed phase	73	65	NS**

<sup>†</sup>N: Number of patients (older than 18 years of age) who received cisplatin, study drug, and had at least one post-treatment efficacy evaluation.  
<sup>‡</sup>Overall: 0 to 120 hours post-cisplatin treatment.  
<sup>§</sup>Acute phase: 0 to 24 hours post-cisplatin treatment.

Helsinn did not rebut Dr. Peroutka’s explanation that, from this complete protection parameter, a “POSA would have therefore understood that aprepitant likely had an effect on nausea—most notably with significant nausea” when

considering the “complete protection” parameters. EX1009, ¶¶1333-1336 (cited at Pet., 57-58). When read as a whole, “a POSA would have understood Emend label to show that aprepitant had a beneficial effect on treating both nausea and vomiting.” *Id.*, ¶1340 (cited at Pet., 58).

*ii. Trento’826 Example 5*

Helsinn did not deny its specification shows aprepitant and netupitant have comparable effects on nausea. Pet., 58-59; EX1009, ¶¶1341-51. Helsinn did not—and could not—deny it ***omitted information*** from its specification experiment when summarizing information in its Rule 132 declaration, which falsely stated that certain data was “not reported” when it actually was. *Compare* EX1001 (Trento’826), Table 6, Column 6 (“Palo + Aprep”) *with* EX1005, 346, Column 6; *see also* EX1009, ¶1341 (cited at Pet., 58-59).

Additionally, regarding the specification’s Table 6 “Palo+Aprep” study purportedly showing unexpected benefits of netupitant over aprepitant, Helsinn did not deny the aprepitant-palonosetron study was materially different from the other studies of the table. *See, e.g.*, EX1009, ¶¶1345-48 (participants of the aprepitant study (1) could receive additional chemotherapies (increasing emesis and nausea); (2) did not receive aprepitant in FDA-approved dosing (instead receiving an experimental regimen); and (3) received an experimental regimen of the antiemetic dexamethasone) (cited at Pet., 59). Helsinn provided no apples-to-apples

comparison because, as Dr. Peroutka explained, “[e]ach of the above-described differences precludes making a direct comparison between Grunberg’s results and the specification’s results” to the extent that a POSA could not reasonably rely on any such comparison for unexpected results. *Id.*, ¶¶1349-1350 (cited at Pet., 59).

Helsinn also did not deny its Rule 132 declaration data omitted information from this patent showing aprepitant and netupitant are comparable for treating nausea. Pet., 59; *see also* EX1001, Table 6 (reproduced below):

Efficacy endpoint	Palo alone (n = 136)	Palo + Netu 100 mg (n = 135)	Palo + Netu 200 mg (n = 137)	Palo + Netu 300 mg (n = 135)	Aprepitant Regimen (N = 134)	Palo + Aprep 285 mg (N = 41)**
<b>No Emesis</b>						
Overall	76.5	87.4*	87.6*	91.1*	87.3*	
Acute	89.7	93.3	92.7	98.5*	94.8	
Delayed	80.1	90.4*	91.2*	91.9*	89.6*	
<b>No Rescue</b>						
Overall	95.6	97.8	100	98.5	97.8	
Acute	97.8	99.3	100	100	100	
Delayed	97.1	97.8	100	98.5	97.8	
<b>No Nausea</b>						
Overall	50.7	54.8	62.0	61.5	58.2	32
Acute	75.0	72.6	77.4	80.0	77.6	59
Delayed	53.7	59.3	65.0	68.1*	60.4	41
<b>No Significant Nausea</b>						
Overall	79.4	80.0	86.1	89.6*	85.8	56
Acute	93.4	94.1	94.2	98.5*	94.0	79
Delayed	80.9	81.5	89.8*	90.4*	88.1	59
<b>Total Control</b>						
Overall	50.0	54.8	61.3	59.3	56.0	
Acute	71.3	71.9	76.6	80.0	74.6	
Delayed	52.2	59.3	65.0*	65.9*	58.2	
<b>Complete Protection</b>						
Overall	69.9	76.3	80.3*	83.0*	78.4	51
Acute	87.5	89.6	88.3	97.0*	89.6	76
Delayed	73.5	80.0	87.6*	84.4*	82.1	66

\*p-value < 0.05 compared with palonosetron-alone; aprepitant comparisons p-values calculated by post-hoc analysis  
 \*\*As reported by Grunberg et al., Support Cancer Care (2009) 17: 589-594

EX1009, ¶1344 (cited at Pet., 59). As Dr. Peroutka explained, “a POSA would have understood that the data” of the full table “shows aprepitant has an antinausea effect, that *the effect is comparable to netupitant* even at the highest (300 mg) dose [of netupitant], and that the antinausea effect of aprepitant is better than low dose (100 mg) netupitant.” EX1009, ¶1344 (cited at Pet., 59). Helsinn failed to argue otherwise or dispute Dr. Peroutka’s explanation of the data.

*iii. Campos & Post-Critical Data*

Helsinn did not deny that the Campos reference (prior art not listed on the face of the patent) showed aprepitant was known to provide beneficial effects for nausea during the acute phase for CINV—contrary to Helsinn’s asserted unexpected results. EX1023, Abstract, 1763 & Table 4; Pet., 60; EX1009, ¶1352. Nor did Helsinn dispute that median nausea scores were lower with Campos’ aprepitant-based triple therapy in the delayed phase of treatment. Pet., 60; EX1023, 1763-1764; EX1009, ¶1353. Thus, a POSA would have known aprepitant provided a beneficial effect for treating nausea—contrary to what Helsinn told the Office. This included therapeutic efficacy for preventing acute-phase nausea of CINV. Pet., 60; EX1009, ¶1354. Further post-critical date data confirms this understanding—*none of which* Helsinn disputes. Pet., 60; EX1009, ¶¶1355-59.

Accordingly, the Office materially erred in allowing these claims based on Helsinn’s unsupported assertion of unexpected results that never actually existed.

Helsinn invited this error during examination and should not be rewarded for it now.

***b. No Dispute: Misrepresented and Omitted Data During Examination***

The petition showed Helsinn’s secondary-considerations case before the Office was rife with misrepresentations and omissions, including material differences between Helsinn’s arguments during examination and its Rule 132 declaration. Helsinn failed to dispute that material data was missing. PODD, 18-23. As explained below, Helsinn’s material omissions induced an unsupported finding of unexpected results, resulting in erroneous allowance of these claims.

***i. Differences Between the Rule 132 Declaration and Helsinn’s Arguments***

Helsinn did not—and could not—dispute that its response data differed materially from the Rule 132 declarants’ representations. Pet., 60-61. Helsinn misled the Office during examination of the patentably-indistinct parent Trento’826 patent by presenting a different table but stating the table was “taken from the 132 Declaration of Giorgia Rossi and Claudio Pietra filed concurrently herewith.” EX1005, 330. The table Helsinn presented during examination falsely implied netupitant-palonosetron combinations were more effective than other drug combinations—including aprepitant combinations. Pet., 61; EX1009, ¶¶1362-

1363. Compare EX1005 (file history of '462 application), 331 (Response to the USPTO) (below)

TABLE 2								
Efficacy Endpoint	1 Palo + Netu (HEC) <sup>a</sup>	2 Ondan + Aprep (HEC) <sup>a</sup>	3 Palo + Netu (MEC) <sup>b</sup>	4 Ondan + Aprep (MEC) <sup>c</sup>	5 Palo + Aprep (HEC) <sup>d</sup>	6 Palo + Aprep (MEC) <sup>e</sup>	7 Ondan + Aprep (MEC) <sup>f</sup>	8 Palo + Aprep (HEC) <sup>g</sup>
No Nausea								
Overall (0-120h)	61.5	58.2	50.3	ns	ns	32 <sup>ncs</sup>	30.6 <sup>ns</sup>	59.9 <sup>ncs</sup>
Acute (0-24h)	80.0	77.6	ns	ns	ns			
Delayed (25-120h)	68.1*	60.4	ns	ns	ns			
No Significant Nausea								
Overall (0-120h)	89.6*	85.8	74.6*	ns	ns	56 <sup>ncs</sup>	66.1 <sup>ns</sup>	91 <sup>ncs</sup>
Acute (0-24h)	98.5*	94.0	ns	ns	ns			
Delayed (25-120h)	90.4*	88.1	ns	ns	ns			

with EX1005 (file history of '462 application), 346 (Rule 132 Declaration Table 2) (below).

**TABLE 2**

Efficacy Endpoint	1 Palo + Netu (HEC) <sup>a</sup>	2 Ondan + Aprep (HEC) <sup>a</sup>	3 Palo + Netu (MEC) <sup>b</sup>	4 Ondan + Aprep (MEC) <sup>c</sup>	4a Ondan + Aprep (HEC) <sup>c1</sup>	5 Palo + Aprep (HEC) <sup>d</sup>	6 Palo + Aprep (MEC) <sup>e</sup>	7 Ondan + Aprep (MEC) <sup>f</sup>	8 Palo + Aprep (HEC) <sup>g</sup>
Percentage of Patients with No Nausea									
Overall (0-120h)	61.5	58.2	50.3	33	48,49	nr	32 <sup>ncs</sup>	30.6 <sup>ncs</sup>	59.9 <sup>ncs</sup>
Acute (0-24h)	80.0	77.6	70.4	nr	nr,nr	nr	nr	nr	nr
Delayed (25-120h)	68.1*	60.4	53.3	nr	51,53	nr	nr	nr	nr
Percentage of Patients with No Significant Nausea									
Overall (0-120h)	89.6*	85.8	74.6*	61	73,71	88.5	56 <sup>ncs</sup>	66.1 <sup>ncs</sup>	91 <sup>ncs</sup>
Acute (0-24h)	98.5*	94.0	87.3	nr	nr,nr	nr	nr	nr	nr
Delayed (25-120h)	90.4*	88.1	76.9	nr	75,73	nr	nr	nr	nr

\*Statistically Significant (p < 0.05)  
 nr Data Not Reported  
 ncs Non-Comparative Study; statistical significance not evaluated

The annotated red highlights indicate cells where data differed from the declaration; the yellow highlights indicate removal of “not reported” values—which sometimes were simply deleted, but other times were falsely labeled “not significant.” EX1009, ¶¶1362-1363. These differences were material and induced the finding of unexpected results, as Dr. Peroutka explained:

Based on my experience, the actual data does not support the examiner’s change in position. I can only surmise the examiner mistakenly attributed to the declaration what was actually described in the Office action response, and thus *erred by believing there were unexpected and surprising results that did not exist.*

EX1009, ¶1364 (cited at Pet., 61). The omissions were also egregious—for example, “Column 4a” of the Rule 132 declaration was *entirely deleted* from the

version in Helsinn’s response.

*ii. Lacking Underlying Data of Internal Studies*

Helsinn did not dispute that it never provided the Office with the underlying procedures and details of its internal studies—upon which it relied for unexpected results. As Dr. Peroutka explained, a POSA would not have relied on Helsinn’s internal studies to recognize “unexpected” results without seeing that information. Pet., 61; EX1009, ¶¶1365-1366 (“[T]here is insufficient data provided to allow a POSA to scrutinize and compare the studies. In my opinion, a POSA would not have compared the internal Helsinn netupitant studies without having an opportunity to review the (missing) underlying data.”). Helsinn’s discretionary-denial briefing fails to rebut this material examination error.

*iii. Excluded Yeo Data*

Helsinn did not deny that its data presented during the parent Trento’826 examination falsely stated that aprepitant’s efficacy for treating nausea was “not reported” in a prior-art reference, while the reference itself (Yeo) showed aprepitant had a comparable—or even *improved*—antinausea effect. Pet., 62; EX1009, ¶¶1367-1370. Dr. Peroutka supplied the Yeo data Helsinn had omitted in annotated Table 2, below:

TABLE 2

	1	2	3	4	4a	5	6	7	8
Efficacy Endpoint	Palo + Netu (HEC) <sup>2</sup>	Ondan + Aprep (HEC) <sup>a</sup>	Palo + Netu (MEC) <sup>b</sup>	Ondan + Aprep (MEC) <sup>c</sup>	Ondan + Aprep (HEC) <sup>2</sup>	Palo + Aprep (HEC) <sup>d</sup>	Palo + Aprep (MEC) <sup>e</sup>	Ondan + Aprep (MEC) <sup>f</sup>	Palo + Aprep (HEC) <sup>g</sup>
Percentage of Patients with No Nausea									
Overall (0-120h)	61.5	58.2	50.3	33	48,49	nr	32 <sup>ncs</sup>	30.6	59.9 <sup>ncs</sup>
Acute (0-24h)	80.0	77.6	70.4	nr	nr,nr	nr	nr	nr 62.3	nr
Delayed (25-120h)	68.1*	60.4	53.3	nr	51,53	nr	nr	nr 47.3	nr
Percentage of Patients with No Significant Nausea									
Overall (0-120h)	89.6*	85.8	74.6*	61	73,71	88.5	56 <sup>ncs</sup>	66.1	91 <sup>ncs</sup>
Acute (0-24h)	98.5*	94.0	87.3	nr	nr,nr	nr	nr	nr 88.5	nr
Delayed (25-120h)	90.4*	88.1	76.9	nr	75,73	nr	nr	nr 74.1	nr

\*Statistically Significant (p < 0.05)  
nr Data Not Reported  
ncs Non-Comparative Study; statistical significance not evaluated

EX1009, ¶1369 (cited at Pet., 62). Nor did Helsinn dispute Dr. Peroutka’s explanation that:

Comparing the aprepitant and ondansetron MEC data with the netupitant and palonosetron MEC data, the results are *substantially similar*, especially with prevention of significant nausea. Indeed, during the acute phase, there was a slight *improvement* in the aprepitant study as compared Helsinn’s internal netupitant study.

It is my opinion that the data withheld from the examiner’s consideration further confirms that there were no unexpected results for the combination of netupitant and palonosetron. A POSA would have understood that the ondansetron studies only included the 5-HT<sub>3</sub> receptor antagonist in effective quantities during the acute phase (EX1048 (Yeo), Abstract) (half-life of (Herrstedt), Table 3)) and would have recognized that in this time period the netupitant study yielded equivalent results to the aprepitant study, particularly for

prevention of significant nausea. A POSA would have considered any improvement with the netupitant dosing to be moderate at best—not unexpectedly beneficial or surprising.

EX1009, ¶¶1369-1370 (cited at Pet., 62).

*iv. Excluded and Unaddressed Emend Label Data*

Helsinn did not deny its Rule 132 declaration and Office-action response failed to include the “complete protection” data from prior-art Emend labels. Pet., 62; EX1009, ¶¶1371-1373. Nor did Helsinn dispute the Emend labels’ “complete protection” required subjects to have no significant nausea. EX1030, 4; EX1009, ¶¶1372 (cited at Pet., 62). Nor did Helsinn deny the Emend label showed aprepitant provides statistically-significant improvement for overall “complete protection.” *Id.* Nor did Helsinn deny the label illustrated improvement for nausea parameters, though not calculated for statistical significance. *Id.*; EX1009, ¶1373.

In sum, Helsinn did not deny the information omitted from its declaration concerning the Emend label was material. As Dr. Peroutka explained, contrary to Helsinn’s representations during examination, “a POSA would have understood the Emend label to show a benefit against nausea—and in particular against significant nausea—when treating HEC with an aprepitant antiemetic drug combination.” EX1009, ¶1373.

*v. Mischaracterized Grunberg Comparison*

Helsinn did not deny the Grunberg study purportedly showing “palo+aprep” in both the specification (Table 6) and the Trento’826 Rule 132 declaration (column 6) is an apples-to-oranges comparison and the arguments presented during examination omitted details showing the material differences. Pet., 63; EX1009, ¶¶1374-1379. Although Helsinn presented Grunberg as though it were directly comparable to Helsinn’s internal studies, Helsinn’s request for discretionary denial did not deny they materially differ. For example, in Grunberg, participants could receive additional emetogenic chemotherapy, causing additional emesis and nausea (EX1009, ¶1375 (cited at Pet., 63)), the aprepitant dose was a single large dose rather than the FDA-approved dose (*id.*, ¶1376), and only a single prophylactic dose of dexamethasone was administered versus the other study groups receiving it four consecutive days (*id.*, ¶1377). Dr. Peroutka explained—and Helsinn did not rebut—that “[e]ach of these differences precludes making a direct comparison between Grunberg’s results and the specification’s results because such a flawed comparison would overstate the antiemetic effect of netupitant in the combination as compared to aprepitant in the combination.”

Hence, the Office materially erred in allowing these claims based on Helsinn’s material misrepresentations and omissions. Helsinn must not continue to profit from it.

***c. No Dispute: Synergy Neither Defined Nor Shown with Specificity***

Helsinn failed to dispute that the specification neither defined nor discussed “synergy” for either the claims or the “unexpected” results. Pet., 63-64; EX1009, ¶1381. Helsinn did not rebut that its own data showed no unexpected differences between aprepitant and netupitant when combined with palonosetron to treat emetogenic chemotherapies. Pet., 64. Nor did Helsinn dispute that, if synergy existed, the data showed such effect also occurred with the prior-art palonosetron-aprepitant combination. *Id.*; EX1009, ¶¶1382-1385 (cited at Pet., 64). As Dr. Peroutka explained, even assuming *arguendo* Helsinn’s data before the Office was accurate, EX1009, ¶1386 (cited at Pet., 64):

the data at most indicates there is a benefit of combining palonosetron with aprepitant *or* netupitant because the underlying values for nausea show substantial similarity. A POSA would not have understood these data to show ‘an unanticipated statistically significant effect’ specifically with the combination of netupitant and palonosetron.

***d. No Dispute: Lack of Nexus***

Helsinn did not dispute the lack of nexus between the alleged synergy and the claimed effect. Azurity explained—and Helsinn did not dispute—that any benefit observed with netupitant-palonosetron was substantially the same as the aprepitant-palonosetron benefit, and that the data at best indicates a benefit from combining palonosetron with *any* NK<sub>1</sub>-receptor antagonist, including aprepitant.

Pet., 65; EX1009, ¶¶1387-1388. Nor did Helsinn deny that most claims do not specify a dose, yet some aprepitant-palonosetron combinations *outperform* netupitant-palonosetron combinations. Pet., 65; EX1009, ¶1389.

Helsinn did not dispute the petition’s showing of no nexus between the alleged synergy and the *claimed* effect. Nor did Helsinn dispute Dr. Peroutka’s explanation that “the alleged unexpected benefit from in vitro Substance P inhibition *fails to have sufficient bearing on the claimed treatment of nausea*” because, e.g., Substance P inhibition “was a target for multiple therapeutic effects, including mood disorders and pain,” and in vivo testing demonstrated no unexpected benefit for nausea. Pet., 65; EX1009, ¶1390.

*e. No Dispute: Rule 132 Declaration From Interested Parties*

Helsinn did not dispute that the Office relied on purported unexpected results from a Rule 132 declaration from Helsinn’s Giorgia Rossi and Claudio Pietra to allow the claims in the patentably-indistinct Trento’826 parent patent. Pet., 65; EX1005, 341-350. Giorgia Rossi is an inventor of the patent, and Claudio Pietra was a Helsinn employee. EX1009, ¶20. Thus, the Office’s reliance on this declaration erroneously accorded dispositive weight to the testimony of interested witnesses when allowing these claims.

The Office materially erred in allowing these claims relying on self-serving

and erroneous testimony. Helsinn must not be rewarded for its misrepresentations.

## **5. Helsinn's Omissions and Misleading Data were Material and Induced Erroneous Allowance**

As shown above (§II.A.4), Helsinn did not dispute or deny the vast majority of Azurity's contentions. As shown below, the petition (and corresponding exhibits) explained how material errors during examination induced these claims' allowance, and Helsinn's mischaracterizing discretionary-denial request did not show otherwise.

### *a. Aprepitant Shows Efficacy for Nausea*

As the petition showed, a POSA knew prior-art aprepitant showed efficacy for preventing nausea—contrary to Helsinn's purportedly unexpected results. Pet., 55-60; EX1009, ¶¶1330-1359. As Dr. Peroutka testified, “contrary to Helsinn's representations to the USPTO, experimental data shows that a POSA would have understood aprepitant to be effective at treating nausea.” EX1009, ¶1332 (cited at Pet., 56-57). The POSA also would have understood a single-time dose of the NK1-receptor antagonist would provide the claimed therapeutic effect.

Sections II.A.2II.A.3 above.

### *i. Emend Label*

The petition showed—and Helsinn's discretionary-denial briefing did not meaningfully dispute—that when evaluated holistically the Emend label proved a

POSA knew art aprepitant prevented chemotherapy-induced nausea. EX1009 (Peroutka Decl.), ¶¶1333-40; Pet., 57-58; §II.A.4.a.i, above. Material examination error resulted from failure to consider the label as a whole.

The petition directly addressed the applicability of improvement in values demonstrating treatment of nausea and significant nausea, even if not calculated to statistical significance, as Dr. Peroutka explained:

[A]lthough not calculated for statistical significance, a POSA would have recognized an improvement for treatment of nausea (and in particular for treatment of significant nausea) represented in the Emend Label Table 1 data. *Id.* (e.g., 66% → 73% overall in significant nausea). A POSA would have therefore understood that aprepitant likely had an effect on nausea—most notably with significant nausea (having VAS > 25 mm). This was true during the delayed phase as well as overall (which includes acute and delayed phases).

Pet., 57-58; EX1009, ¶1335 (cited at Pet., 57-58). The petition and Dr. Peroutka also explained “a POSA would have recognized an even greater improvement for treatment of nausea in [the aprepitant] study cohort (and in particular for treatment of significant nausea),” versus standard therapy, “even if not calculated for statistical significance. *Id.* (e.g., 64% → 71% overall in significant nausea; 39% → 49% overall in nausea).” EX1009, ¶1336 (citing EX1030); Pet., 58.

Although statistical significance was not calculated for stand-alone nausea

parameters, the label’s “‘complete protection’ value includes a lack of significant nausea” by definition and illustrated statistically-significant nausea reduction following aprepitant treatment. Pet., 58-59; EX1009, ¶¶1333-1334. Helsinn did not rebut Azurity’s explanation of this complete protection parameter. The label showed “substantial improvement of complete protection for overall, acute phase, and delayed phase parameters” following treatment with aprepitant. Pet., 57-58; EX1009, ¶¶1334; EX1030, 7 & Table 1 (first below), Table 2 (second below).

ENDPOINTS	Aprepitant Regimen (N = 260) <sup>†</sup> %	Standard Therapy (N = 261) <sup>†</sup> %	p-Value
<b>PRIMARY ENDPOINT</b>			
Complete Response			
Overall <sup>‡</sup>	73	52	<0.001
<b>OTHER PRESPECIFIED ENDPOINTS</b>			
Complete Response			
Acute phase <sup>§</sup>	89	78	<0.001
Delayed phase <sup>  </sup>	75	56	<0.001
Complete Protection			
Overall	63	49	0.001
Acute phase	85	75	NS*
Delayed phase	66	52	<0.001
No Emesis			
Overall	78	55	<0.001
Acute phase	90	79	0.001
Delayed phase	81	59	<0.001
No Nausea			
Overall	48	44	NS**
Delayed phase	51	48	NS**
No Significant Nausea			
Overall	73	66	NS**
Delayed phase	75	69	NS**
<sup>†</sup> N: Number of patients (older than 18 years of age) who received cisplatin, study drug, and had at least one post-treatment efficacy evaluation. <sup>‡</sup> Overall: 0 to 120 hours post-cisplatin treatment. <sup>§</sup> Acute phase: 0 to 24 hours post-cisplatin treatment. <sup>  </sup> Delayed phase: 25 to 120 hours post-cisplatin treatment. *Not statistically significant when adjusted for multiple comparisons. **Not statistically significant. Visual analogue scale (VAS) score range: 0 mm = no nausea; 100 mm = nausea as bad as it could be.			

ENDPOINTS	Aprepitant Regimen (N = 261) <sup>†</sup> %	Standard Therapy (N = 263) <sup>†</sup> %	p-Value
<b>PRIMARY ENDPOINT</b>			
Complete Response			
Overall <sup>‡</sup>	63	43	<0.001
<b>OTHER PRESPECIFIED ENDPOINTS</b>			
Complete Response			
Acute phase <sup>§</sup>	83	68	<0.001
Delayed phase <sup>¶</sup>	68	47	<0.001
<b>Complete Protection</b>			
Overall	56	41	<0.001
Acute phase	80	65	<0.001
Delayed phase	61	44	<0.001
No Emesis			
Overall	66	44	<0.001
Acute phase	84	69	<0.001
Delayed phase	72	48	<0.001
No Nausea			
Overall	49	39	NS*
Delayed phase	53	40	NS*
No Significant Nausea			
Overall	71	64	NS**
Delayed phase	73	65	NS**

<sup>†</sup>N: Number of patients (older than 18 years of age) who received cisplatin, study drug, and had at least one post-treatment efficacy evaluation.  
<sup>‡</sup>Overall: 0 to 120 hours post-cisplatin treatment.  
<sup>§</sup>Acute phase: 0 to 24 hours post-cisplatin treatment.

Dr. Peroutka explained:

In other words, when evaluating whether a patient achieved “*complete protection*,” the Emend label requires (1) *no* emetic episodes; (2) *no* rescue therapy; **and** (3) *no significant nausea*. Table 1 of the Emend label shows results of the first of two studies described in the label. It indicates substantial improvement of *complete protection* for overall, acute phase, and delayed phase parameters, and identifies the delayed phase and overall parameters were also statistically significant.

EX1009, ¶1334 (emphasis original) (cited at Pet., 57-58).

Helsinn’s cherry-picked reading of the Emend label induced material Office error by baselessly asserting aprepitant failed to treat nausea but netupitant unexpectedly did. Helsinn’s discretionary-denial briefing fails to rebut the petition’s showing that Helsinn was wrong.

*ii. Trento'826 Example 5*

Helsinn induced material Office error when it removed data showing aprepitant's efficacy on nausea from a data set presented during examination of the patentably-indistinct Trento'826 parent patent. Pet., 58-59. The specification itself showed aprepitant's effect on nausea is comparable to netupitant's. EX1001 (Trento'826), 16:62-19:43, Table 6.

First, Helsinn selectively edited data presented during examination, removing “acute” and “delayed” efficacy endpoints, falsely labeling them as “not reported”. EX1009, ¶1341 (cited at Pet., 58-59); §II.A.4.b, above (annotating differences between tables). Helsinn did not deny this fact. PODD, 18-22.

Second, as explained above (§II.A.4.a.ii), the data Helsinn provided during examination gave an apples-to-oranges comparison—material differences that Helsinn did not identify for the Office or otherwise address. Pet., 59; EX1009, ¶¶1345-48. As Dr. Peroutka explained, “Each of the above-described differences precludes making a direct comparison between Grunberg's results and the specification's results” to the extent that a POSA could not reasonably rely on any such comparison for unexpected results. *Id.*, ¶¶1349-1350 (cited at Pet., 59).

Third, as explained above (§II.A.4.a.ii), Helsinn omitted from its presentation during examination material information from the specification itself that illustrated aprepitant's *comparable* effect on treating nausea. Pet., 58-59. Data

in the specification's Table 6 showed aprepitant's efficacy, but Helsinn's prosecution arguments did not provided the full comparison. *Id.*; EX1001, Table 6 (reproduced in §II.A.4.a.ii, EX1009, ¶1344 (Dr. Peroutka annotations). As Dr. Peroutka explained:

This data shows the aprepitant dose (blue) had similar antinausea effect to the 200 mg dose of netupitant (purple). Notably, the aprepitant dose had *greater antinausea effect* as compared to the 100 mg dose of netupitant (red). Thus, a POSA would have understood that the data shows aprepitant has an antinausea effect, that the effect is comparable to netupitant even at the highest (300 mg) dose, and that the antinausea effect of aprepitant is better than low dose (100 mg) netupitant.

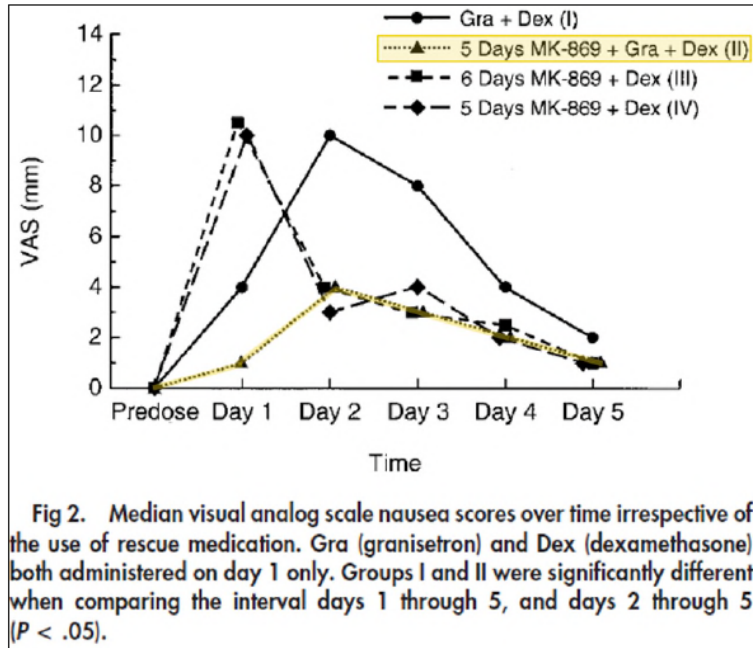
EX1009, ¶1344 (emphasis original) (cited at Pet., 59).

Helsinn's cherry-picked data and edited entries thus induced material error by falsely supporting unexpected results. Pet., 58-59; EX1009, ¶1341.

### *iii. Campos*

Helsinn wrongly alleged aprepitant lacked efficacy for nausea during the acute phase of treatment while prior art showed otherwise. Pet., 60; e.g., EX1001 (Trento'826), 2:12-15. The Campos reference showed that aprepitant provided efficacy for nausea during the acute phase of treatment. "Campos explains that the triple therapy (5-HT<sub>3</sub> receptor antagonist, dexamethasone, plus aprepitant) provided 'nausea ratings [that] were significantly lower' in 'the first 24 hours rank

analysis’ compared to 5-HT<sub>3</sub> receptor antagonist plus dexamethasone.” EX1009, ¶1353 (quoting EX1023 (Campos), 1763) (cited at Pet., 60) & EX1023, Fig. 2 (reproduced below).



As Dr. Peroutka explained, “contrary to Helsinn’s representations to the Office, aprepitant was known in the prior art to provide beneficial effect to nausea, including specifically providing therapeutic effect to prevent nausea during the acute phase for CINV.” EX1009, ¶1354 (cited at Pet., 60). Helsinn’s misrepresentation of prior art during the Trento’826 examination thus induced material error by falsely supporting unexpected results.

*iv. Post-Critical Publications*

Material error also exists because the Office did not have post-critical date publications confirming aprepitant’s efficacy for treating nausea. These post-

critical date publications confirm “aprepitant provides therapeutic efficacy for nausea, contrary to Patent Owner’s contentions otherwise.” EX1009, ¶1355; Pet., 60. *See, e.g.* EX1047, 8 (Wang concluding its study shows aprepitant “***had an important role in improving protection against nausea.***”); EX1040 (meta-analysis of over fifty trials showing aprepitant “significantly improved the proportion of patients who have no nausea event during the overall...and delayed phases”); EX1030 (Emend label showing beneficial effect on nausea). EX1009, ¶¶1356-1358 (cited at Pet., 60). Post-critical date publications are not prior art, of course, but show Helsinn’s studies and arguments could not have been correct.

*v. At Most, Difference in Degree—Not Kind*

Error further exists because the Office failed to recognize that—even if improvement occurred treating nausea when substituting netupitant for aprepitant in the antiemetic triple therapy, any difference was immaterial. As Dr. Peroutka explained, a POSA reviewing even Helsinn’s cherry-picked data presented during examination would have understood “that the difference is not significant and not material—put differently, there is at most a difference of degree rather than a difference in kind.” EX1009, ¶1359 (annotating the Helsinn’s prosecution table, below); Pet., 60.

	1	2	3	4	4a	5	6	7	8
Efficacy Endpoint	Palo + Netu (HEC) <sup>a</sup>	Ondan + Aprep (HEC) <sup>a</sup>	Palo + Netu (MEC) <sup>b</sup>	Ondan + Aprep (MEC) <sup>c</sup>	Ondan + Aprep (HEC) <sup>c1</sup>	Palo + Aprep (HEC) <sup>d</sup>	Palo + Aprep (MEC) <sup>e</sup>	Ondan + Aprep (MEC) <sup>f</sup>	Palo + Aprep (HEC) <sup>e</sup>
Percentage of Patients with No Nausea									
Overall (0-120h)	61.5	58.2	50.3	33	48,49	nr	32 <sup>ncs</sup>	30.6	59.9 <sup>ncs</sup>
Acute (0-24h)	80.0	77.6	70.4	nr	nr, nr	nr	nr	nr	nr
Delayed (25-120h)	68.1*	68.4	53.3	nr	51, 53	nr	nr	nr	nr
Percentage of Patients with No Significant Nausea									
Overall (0-120h)	89.6*	85.8	74.6*	61	73, 71	88.5	56 <sup>ncs</sup>	66.1	91 <sup>ncs</sup>
Acute (0-24h)	98.5*	94.0	87.3	nr	nr, nr	nr	nr	nr	nr
Delayed (25-120h)	90.4*	88.1	76.9	nr	75, 73	nr	nr	nr	nr
*Statistically Significant (p < 0.05)									
<sup>nr</sup> Data Not Reported									
<sup>ncs</sup> Non-Comparative Study; statistical significance not evaluated									

The Office materially errs by granting a patent based on unexpected results where there is only a difference in degree rather than a difference in kind. *Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1306 (Fed. Cir. 2015). Thus, even accepting Helsinn’s prosecution data as true, it at most shows only a difference in degree, so allowance was erroneous.

Hence, the Office materially erred in allowing these claims based on a purported unexpected improvement of netupitant over prior-art aprepitant that did not actually fact exist. Helsinn induced this error and should not profit from it.

***b. Helsinn Materially Misrepresented Data During Examination***

As the petition explained, Helsinn misrepresented and omitted material information during examination, inducing erroneous allowance of these claims.

Pet., 60-63. Helsinn neither rebutted nor denied most Azurity arguments identifying these misrepresentations and omissions. §II.A.4, above.

*i. Differences Between Rule 132 Declaration and Helsinn's Examination Argument*

Differences between Helsinn's Rule 132 declaration and its arguments in the parent Trento'826 examination induced material Office error leading to allowance of the involved patentably-indistinct claims. As discussed above (§II.A.4.b.i), Helsinn overcame prior-art rejections by arguing unexpected results from substituting netupitant for prior-art aprepitant, but concealed from the Office material contrary data that illustrated aprepitant provided substantial effect on nausea. Pet., 61; EX1009, ¶1361. Comparing the tables from the declaration and Helsinn's response (reproduced above, §II.A.4.b.i) shows how the differences created a false impression that netupitant-palonosetron had a greater effect than other drug combinations. EX1009, ¶¶1362-1363; Pet., 61. *Compare* EX1005 (file history of '462 application), 331 (Response to the USPTO) *with* EX1005 (file history of '462 application), 346 (Rule 132 Declaration). Dr. Peroutka's red annotations indicated cells where data differed from the declaration; the yellow highlights indicated removal of "not reported" values—which were sometimes simply deleted, but were other times labeled "not significant." EX1009, ¶¶1362-1363 (cited Pet., 61).

Helsinn never addressed these material alterations to the data. For example, Helsinn did not explain or address why the table it put in front of the examiner in an Office action response had *completely deleted a column* (“4a”) than the Rule 132 declaration version. This column related to aprepitant’s antinausea effect disclosed by the Emend label. §II.A.4.a.i, above. As Dr. Peroutka explained, these alterations were material. EX1009, ¶1364 (cited at Pet., 61).

Helsinn should not benefit from its misleading actions.

*ii. Helsinn’s Data Was Lacking*

Azurity identified specific instances where Helsinn’s data presented to the USPTO was insufficient. Pet., 61-63. In response, Helsinn ignored Azurity’s contentions. The petition detailed many other material omissions during examination that Helsinn left unaddressed, and the data presented during examination could not “reasonably be relied upon to show any unexpected results.” Pet., 60-63; EX1009, ¶¶1365-1379.

Material flaws with the data in Helsinn’s argument of unexpected results included: (1) withholding underlying data of Helsinn’s purported comparative studies; (2) omitting data showing aprepitant’s efficacy for treating acute and delayed nausea comparable to netupitant’s; and (3) misrepresenting substantively different scientific studies as comparable.

First, the table Helsinn presented during examination purporting to show

unexpected benefits of palonosetron with netupitant were premised on internal Helsinn studies (columns 1-3), but Helsinn never provided the Office with the underlying details of the studies to determine whether they were comparable to other studies in the table. Pet., 61. Dr. Peroutka explained that “there is insufficient data provided to allow a POSA to scrutinize and compare the studies. In my opinion, without having an opportunity to review the (missing) underlying data.” EX1009, ¶¶1365-1366 (cited at Pet., 61). Helsinn invited Office error with its unsupported assertions about its studies and failure to produce information necessary to show the studies were legitimate comparisons. EX1009, ¶¶1365-1366 (cited at Pet., 61).

Second, as shown above (§II.A.4.b.iii), the table Helsinn presented during examination omitted data showing comparable—and even *improved*—nausea treatment with aprepitant versus netupitant. Pet., 62; EX1009, ¶¶1367-1370; *see also* EX1009, ¶1369 (describing Yeo’s data showing treatment of nausea and the above annotations); Pet., 62. As Dr. Peroutka explained, a “POSA would have understood that the ondansetron studies only included the 5-HT3 receptor antagonist in effective quantities during the acute phase” due to the half-life of ondansetron, in contrast with the known prolonged half-life of palonosetron (having a nearly-order-of-magnitude higher half-life). *Id.*, ¶1370. “A POSA would have considered any improvement with the netupitant dosing to be moderate at

best—not unexpectedly beneficial or surprising.” *Id.*

Third, as shown above (§II.A.4.b.v), Helsinn did not deny the Grunberg study (column 6) presented an apples-to-oranges comparison, and thus its inclusion in the table Helsinn provided during examination was a misrepresentation. Pet., 63. Grunberg’s study differed in important ways that made direct comparison inappropriate. Pet., 63; EX1009, ¶¶1375-1377. As Dr. Peroutka explained:

Each of these differences precludes making a direct comparison between Grunberg’s results and the specification’s results because such a flawed comparison would overstate the antiemetic effect of netupitant in the combination as compared to aprepitant in the combination. In view of the differences between the studies described above, the POSA would not have compared Grunberg’s study with the Helsinn internal MEC study, and therefore it is my opinion that such a comparison cannot reasonably be relied upon to show any unexpected results.

EX1009, ¶¶1378-1379 (cited at Pet., 63-64).

Hence, the Office materially erred in allowing these claims based on purported unexpected results supported only by Helsinn misrepresentations and omissions of material information. Again, Helsinn must not benefit from its misconduct toward the Office and the public.

**c. No Unexpected Synergy Between Netupitant-Palonosetron Versus Aprepitant-Palonosetron**

As shown above (§II.A.4.c), no unexpected synergy exists between netupitant-palonosetron versus prior-art aprepitant-palonosetron. Pet., 63-64. Even taking the Rule 132 declaration table at face value, Dr. Peroutka explained that a POSA would have understood the data to “show the combination of palonosetron with *any* NK1 receptor antagonist had a beneficial effect on nausea” and “such effect is just as applicable to the *known combination* of palonosetron and aprepitant” described in the prior art. EX1009, ¶¶1382 (cited at Pet., 64). See, for example, the combination of palonosetron and either netupitant or aprepitant for use with highly emetogenic chemotherapy (HEC):

Efficacy Endpoint	1 Palo + Netu (HEC) <sup>a</sup>	2 Ondan + Aprep (HEC) <sup>a</sup>	3 Palo + Netu (MEC) <sup>b</sup>	4 Ondan + Aprep (MEC) <sup>c</sup>	4a Ondan + Aprep (HEC) <sup>c2</sup>	5 Palo + Aprep (HEC) <sup>d</sup>	6 Palo + Aprep (MEC) <sup>e</sup>	7 Ondan + Aprep (MEC) <sup>f</sup>	8 Palo + Aprep (HEC) <sup>g</sup>
Percentage of Patients with No Nausea									
Overall (0-120h)	61.5	58.2	50.3	33	48,49	nr	32 <sup>ncs</sup>	30.6	59.9 <sup>ncs</sup>
Acute (0-24h)	80.0	77.6	70.4	nr	nr,nr	nr	nr	nr	nr
Delayed (25-120h)	68.1*	60.4	53.3	nr	51,53	nr	nr	nr	nr
Percentage of Patients with No Significant Nausea									
Overall (0-120h)	89.6*	85.8	74.6*	61	73,71	88.5	56 <sup>ncs</sup>	66.1	91 <sup>ncs</sup>
Acute (0-24h)	98.5*	94.0	87.3	nr	nr,nr	nr	nr	nr	nr
Delayed (25-120h)	90.4*	88.1	76.9	nr	75,73	nr	nr	nr	nr

\*Statistically Significant (p < 0.05)  
<sup>nr</sup> Data Not Reported  
<sup>ncs</sup> Non-Comparative Study; statistical significance not evaluated

EX1009, ¶¶1383 (cited at Pet., 64), where “nr” means “Data Not Reported” in the underlying study.

So even accepted at face value (it should not be), the table merely showed “palonosetron improved the significant nausea and nausea side effects of highly emetogenic chemotherapy *with both NK<sub>1</sub> receptor antagonists*—aprepitant and netupitant.” EX1009, ¶¶1383 (cited at Pet., 64). As Dr. Peroutka explained, a POSA would have found “no surprising or unexpected benefit of the netupitant and palonosetron combination” that Helsinn relied on for purported unexpected results. *Id.* An expected result is the opposite of an unexpected result. *In re Skoll*, 523 F.2d 1392, 1397 (CCPA 1975); Pet., 55.

At most, palonosetron combined with *any* NK<sub>1</sub>-receptor antagonist confers intrinsic benefit as compared to other *5-HT<sub>3</sub>*-receptor antagonists (e.g., ondansetron), but no unexpected and surprising synergy specific to the palonosetron-netupitant combination appears in the record.

**TABLE 2**

Efficacy Endpoint	1 Palo + Netu (HEC) <sup>a</sup>	2 Ondan + Aprep (HEC) <sup>a</sup>	3 Palo + Netu (MEC) <sup>b</sup>	4 Ondan + Aprep (MEC) <sup>c</sup>	4a Ondan + Aprep (HEC) <sup>c2</sup>	5 Palo + Aprep (HEC) <sup>d</sup>	6 Palo + Aprep (MEC) <sup>e</sup>	7 Ondan + Aprep (MEC) <sup>f</sup>	8 Palo + Aprep (HEC) <sup>g</sup>
Percentage of Patients with No Nausea									
Overall (0-120h)	61.5	58.2	50.3	33	48,49	nr	32 <sup>ns</sup>	30.6	59.9 <sup>ns</sup>
Acute (0-24h)	80.0	77.6	70.4	nr	nr,nr	nr	nr	nr	nr
Delayed (25-120h)	68.1*	60.4	53.3	nr	51,53	nr	nr	nr	nr
Percentage of Patients with No Significant Nausea									
Overall (0-120h)	89.6*	85.8	74.6*	61	73,71	88.5	56 <sup>ns</sup>	66.1	91 <sup>ns</sup>
Acute (0-24h)	98.5*	94.0	87.3	nr	nr,nr	nr	nr	nr	nr
Delayed (25-120h)	90.4*	88.1	76.9	nr	75,73	nr	nr	nr	nr

\*Statistically Significant (p < 0.05)  
<sup>nr</sup> Data Not Reported  
<sup>ns</sup> Non-Comparative Study; statistical significance not evaluated

EX1009, ¶1385 (cited at Pet., 64). Dr. Peroutka explained:

As can be seen from this table, palonosetron in combination with either aprepitant or netupitant showed equivalent results for percentage of patients with no significant nausea overall (89.6% (netupitant), 88.5% (aprepitant), 91% (aprepitant)). Similarly, palonosetron in combination with either NK<sub>1</sub> receptor antagonist showed equivalent results for percentage of patients with no nausea overall (61.5% (netupitant), 59.9% (aprepitant)). Any other differences between the studies were in my opinion marginal and insufficient to show unexpected or surprising results.

EX1009, ¶¶1385-1386 (cited at Pet., 64).

Hence, the Office materially erred in allowing these claims based on purported unexpected results when the data did not support such a finding. Indeed,

the results were expected in view of comparable results for the aprepitant-palonosetron combination. The Office materially errs when it grants a patent based on unexpected results where only a difference in degree rather than a difference in kind is shown in the record. *Allergan*, 796 F.3d at 1306.

*d. Alleged Synergy and Claimed Effect Lack Nexus*

The petition demonstrated a lack of nexus between Helsinn’s purported synergistic effects and the claims. Pet., 65; EX1009, ¶¶1387-1390. Dr. Peroutka also discussed the lack of “any evidence of synergy in a way that corresponds to the challenged claims.” EX1009, ¶1387 (cited at Pet., 65).

Helsinn failed to grapple with any of the petition arguments illustrating Helsinn’s inability to show unexpected synergy between netupitant and palonosetron. Pet., 65. As the petition explained, (1) any synergy between netupitant and palonosetron was *expected* because such synergy was also observed with other NK<sub>1</sub>-receptor antagonists; (2) the purported synergy lacked nexus with the full scope of the claimed subject matter; and (3) the Helsinn’s *in vitro* tests could not be relied upon as a stand-in for nausea, as Dr. Peroutka explained.

First, if anything, the data showed a benefit from combining palonosetron with *any* NK<sub>1</sub>-receptor antagonist, which is beyond the scope of Helsinn’s claims (and includes prior-art combinations). Pet., 65; EX1009, ¶1388; §II.A.4.d above. A POSA would have understood any synergistic effect between palonosetron and an

NK<sub>1</sub>-receptor antagonist was not limited to netupitant—it included *inter alia* prior-art aprepitant. Pet., 64; EX1009, ¶¶1382-1385.

Second, the independent claims do not require a specific dose—and because aprepitant combinations were purportedly *superior* to low-dose netupitant combinations—at most, any nexus must be specifically limited to higher netupitant doses. Thus, the purported unexpected results were not commensurate with the claims’ scope. Pet., 65; EX1009, ¶1389.

Third, the proxy *in vitro* Substance P (SP) response in NC108-15 cells did not directly show an effect on patient nausea. Pet., 65. SP was a known target of multiple therapeutic effects, including mood disorders and pain. EX1009, ¶1390 (cited at Pet., 65). In fact, *in vivo* testing specifically evaluating nausea showed *no* unexpected benefit the netupitant-palonosetron combination for nausea. *Id.* Thus, Helsinn’s purported “synergy” for Substance P inhibition fails to have bearing on the claimed treatment of patient nausea. *Id.*

Thus, the Office materially erred in allowing these claims based on fictional unexpected improvement of netupitant over prior-art aprepitant. Helsinn created this error and must not benefit from it.

Each of Helsinn’s many material misrepresentations is sufficient in itself to warrant referral for institution and trial. Referral is warranted where, as here, “the Petitioner appears to show a material error by the Office” because “it is an

appropriate use of Office resources to review the potential error.” *Partec*, IPR2025-00318, #9. Indeed, considering a patentee’s unfair dealings—here, misrepresenting material data purporting to show surprising results—is an appropriate use of Board resources. *Tessell*, IPR2025-00322, #14.

## **B. Denial Under §325(d) is Unwarranted**

### **1. Azurity Did Not Present the Same or Substantially the Same Prior Art and Arguments**

Helsinn did not dispute that the primary ground reference, Herrstedt, was never presented during examination. PODD, 15-17. Although the secondary references Bös and Herrington were available during examination, Helsinn admitted the Office never applied them and, in any case, the examiner failed to note that they identify netupitant specifically out as a particularly good species. *Id.*, 16-17 & n.6. Helsinn’s arguments failed to establish the grounds references and arguments are the same or cumulative to the art and arguments presented during examination.

Moreover, even if the references were similar, a different reason to combine can justify a referral for institution and trial. *Oticon Medical v. Cochlear Ltd.*, IPR2019-00975, #15, 16 (2019) (precedential). Here, the examiner stated during the patent Trento’826 examination that the prior-art Reddy reference was “not anticipatory insofar as netupitant is not a preferred species” but stated motivation nonetheless existed because “it would have been obvious to select netupitant given

its plain enumeration in the prior art reference.” EX1005, 284-285; Pet., 6-7 (discussing the same); EX1009, ¶¶29-30. However, the petition showed that not only was netupitant a known NK<sub>1</sub>-receptor antagonist, but it was an *improved* NK<sub>1</sub> antagonist. Pet., 15, 31 (Bös); EX1009, ¶¶596-602 (Bös). Because the petition uses new references to provide new reasons to combine, the new references are not cumulative to what the Office considered during examination.

## **2. Material Error Exists**

Azurity does not concede that prong 1 of *Advanced Bionics v. MED-EL Elektromedizinische Geräte*, IPR2019-01469, #6 (2020) (precedential), has been met. Nonetheless, as detailed above (§II.A), significant and material error by the Office occurred during examination, induced by Helsinn’s own unfair dealings with the Office. Thus, even if, *arguendo*, *Advanced Bionics* prong 1 has been met, Azurity has shown that reasonable minds cannot disagree: the Office erred in a manner material to the patentability of these claims by allowing said claims. Accordingly, 35 U.S.C. 325(d) does not apply and the petition should be referred for institution and trial on the merits.

### **III. HELSINN HAS NO LEGITIMATELY SETTLED EXPECTATIONS**

#### **A. Age Is Not Dispositive**

Helsinn assumes mere age is sufficient for settled expectations. PODD, 1 (“[T]he ’515 patent has been in force for more than seven years, which creates

strong settled expectations....”), 8 (“Helsinn’s settled expectation...is dispositive”). Discretion is not so simple-minded. For example, the Office has recognized the efficacy of reviewing older patents when related younger patents also warrant review. *Embodiment, Inc. v. LifeNet Health*, IPR2025-00248, #13 (USPTO Dir. 2025) (“[O]ne of the challenged patents has not been in force for a significant period of time (issued in 2022) and the other patent is a parent of the first. Accordingly, Patent Owner has not developed strong settled expectations that favor discretionary denial as to the first patent, and it is an efficient use of Board resources to address the related patent.”); *Padagis US v. Neurelis, Inc.*, IPR2025-00464, #12 (USPTO Dir. 2025) (same, where patents share the same Office error). Here Helsinn’s 10,828,297 patent (in IPR2025-00949) issued in late 2020 from the same primary examiner and is child of the patent in this IPR. EX1004. As fruit from the same poisoned tree, both Helsinn’s involved and ’297 patents can most efficiently be reviewed together as an appropriate use of Board resources.

### **B. Material Error Voids Settled Expectations**

The Office has repeatedly held that material examination error voids even long-settled expectations. *E.g.*, *Anthony Inc. v. ControlTec, LLC*, IPR2025-00559, #12 (USPTO Dir. 2025) (“Although the challenged patents have been in force for approximately eighteen and seventeen years, Petitioner appears to show a material error by the Office, and it is an appropriate use of Office resources to review the

potential error.”); *see also Taiwan Semiconductor Manufacturing v. Marlin Semiconductor*, IPR2025-00847, #11 (USPTO Dir. 2025) (“Although the challenged patent has been in force for fifteen years, Petitioner appears to show a material error by the Office, and it is an appropriate use of Office resources to review the potential error.”); *Activision Blizzard v. Milestone Entertainment*, IPR2025-00708, #13 (USPTO Dir. 2025) (examination error outweighs “strong settled expectations”); *Eunsung Global v. HydraFacial LLC*, IPR2025-00445, #14 (USPTO Dir. 2025) (“Petitioner persuasively demonstrates that the patent examiner overlooked certain teachings ... that appear to disclose the allowable features of the claims[, so d]iscretionary denial is not appropriate....”); *Partec*, IPR2025-00318, #9 (same); *see also Padagis*, IPR2025-00464, #12 (“[T]he patent examiner’s conclusion directly contradicts the Board’s determination and raises concerns of material error such that review of the challenged patents is an appropriate use of Office resources.”), *citing Advanced Bionics*.

Significantly, as explained in §II above, Helsinn’s brief failed to address most of the material errors Helsinn invited during examination, much less rebut the plain import of the prosecution history and Dr. Peroutka’s testimony explaining the significance of Helsinn’s misleading statements and the examiner’s error. Congress created IPRs to permit error correction. The Executive branch should not be baited into punting its own correction process to the Judiciary. Each examination error

Helsinn failed to address is a concession that Helsinn has no legitimately settled expectation.

### **C. Helsinn’s Shotgun Arguments Are Unsupported or Misplaced**

Most of Helsinn’s settled-expectation arguments are unsupported or misplaced.<sup>3</sup> For example, Helsinn relies on a single prior instance of litigation, but admits that it settled, and pointedly omits the terms of the settlement. *PODD*, 11-12 n.3. Helsinn provides no evidence of a favorable outcome; for all we know, Helsinn paid Gland to go away rather than face a defense that would render this patent invalid or unenforceable—an entirely reasonable fear as the petition showed. Similarly, Helsinn relies (*id.*, 10-11) on its routine product development (without providing any supporting details such as amounts spent or market share) for AKYNZEO®—a product that Helsinn has not shown is coextensive with all the claims (it is not, at least because it does not include dexamethasone). *Compare* EX1003, 22:23-44 with EX2005, 1. Just as during examination, Helsinn today advances arguments with facial appeal but no actual support.

Finally, Helsinn argues that Azurity was aware of this patent because

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<sup>3</sup> Helsinn should not be permitted to bolster its arguments later, when Azurity can no longer respond.

Azurity (or a company it acquired) worked with aprepitant—a drug Helsinn elsewhere insists is irrelevant—but Helsinn only provides evidence showing awareness “as early as June 2023”—meaning any “settled expectation” regarding Azurity was less than two-years old when the petition was filed. Helsinn also argues for settled expectations against anyone “practicing in the cancer space”—a field so broad and diverse as to require petitioner omniscience to support such a categorical rule.

Helsinn appears to be seeking a blanket exception for Hatch-Waxman cases that would sweep in anyone practicing in a pharmaceutical “space” trying to challenge weak follow-on patents; yet, a new policy favoring pharmaceutical profits for foreign beneficiaries over lower prices for American patients is starkly inconsistent with this Administration’s settled expectations. Exec. Order 14,297, 90 Fed. Reg. 20749 (May 15, 2025) (“The United States has less than five percent of the world’s population and yet funds around three quarters of global pharmaceutical profits.”). Despite Helsinn’s policy ploy, USPTO remains the Executive’s primary lever for correcting USPTO-based errors in USPTO-granted patents that drive up costs for American patients. Helsinn fails to justify its effort to convince the Executive to surrender its power and defer to the Judiciary.

#### **IV. NO OTHER APPROPRIATE FORUM EXISTS**

“[T]he parties are not currently engaged in a parallel proceeding involving

the challenged patents. \* \* \* As a result, there is currently no concern of inconsistent outcomes and duplication of efforts resulting from two proceedings operating in parallel.” *Amgen v. Bristol-Myers Squibb*, IPR2025-00601, #9 (USPTO Dir. 2025). Helsinn has not even indicated that it will soon assert this patent against Azurity. Hence, *Fintiv* concerns are a poor fit for this case. Without such litigation, Azurity faces enormous risk developing a price-lowering therapy for American cancer patients while languishing in legal limbo. Helsinn has not asserted another forum is currently available, much less one that would be better. Given this Administration’s commitment to lowering prices for American patients rather than protecting profits for foreign actors, Helsinn’s arguments are ironic at best. Exec. Order 14,297, 90 Fed. Reg. 20749 (May 15, 2025) (“The United States has for too long turned its back on Americans, who unwittingly sponsor both drug manufacturers and other countries.”); 35 U.S.C. 316(b) (requiring consideration of “the effect [of PTAB rules] on the economy”).

Helsinn has no settled expectations favoring reexamination over IPR. Its patent grant was conditioned on all provisions of Title 35, U.S. Code. 35 U.S.C. 261 (“Subject to the provisions of this title, patents shall have the attributes of personal property.”); *Oil States Energy v. Greene’s Energy*, 584 U.S. 325, 337 (2018) (“Patent claims are granted subject to the qualification that the PTO has the authority to reexamine—and perhaps cancel—a patent claim in an inter partes

review.” (simplified)). Moreover, IPR empowers the Executive with tools lacking during examination and reexamination, including independent expert testimony and cross examination of witnesses. This case is a paradigmatic example where an ex parte proceeding would needlessly hobble the Executive’s exercise of its error correction power. As explained in great detail in the petition and summarized again above, see §II above, this case turns in large measure on examiner error caused by Helsinn. Indeed, the examiner accepted argument and evidence that was materially misleading—understandably, given the lack of independent expert testimony and cross examination of Helsinn’s interested witnesses. Returning this patent to (re)examination will simply recreate the circumstances under which Helsinn caused the original error.

Azurity could also, presumably, seek declaratory judgment, but this fact again belies any “settled expectation” Helsinn purports to have in its patent-property interest. Helsinn has not (and could not without hypocrisy) suggest another forum for unsettling its expectations. Moreover, it would be extremely incongruous for Helsinn to suggest punting this controversy to the Judiciary, when the error arose in and is best addressed in the Executive branch agency responsible for patents and “the integrity of the patent system,” 35 U.S.C. 316(b), the U.S. Patent and Trademark Office. Administrative Patent Judges are required to “be persons of competent legal knowledge and scientific ability,” 35 U.S.C. 6(a), while

an Article III judge might or might not have comparable abilities without extensive support from subject-matter experts in patent law and the underlying technology. A jury certainly would not have such skill and, in any case, would not be available if this patent were otherwise tried in ANDA litigation. In this context, it is astonishing for Helsinn to imply that the Director should cede Executive-branch power to a different branch to cure a problem dating back to an earlier Administration, when Helsinn filed its misleading response and Rule 132 declaration.

Finally, if Helsinn files an ANDA suit against Azurity—after Azurity has already made the enormous investment necessary to bring a lower-cost option to American cancer patients—in that suit, Azurity would be able to challenge the validity of these claims, again unsettling any expectation Helsinn purports to have. Yet Helsinn has not stipulated that it will not sue Azurity on this patent. Once again, Helsinn’s assertion of settled expectations is incongruous. Without such a stipulation, Helsinn has no plausible basis to claim any expectation that these claims’ unpatentability is “settled”.

In sum, Helsinn attained allowance by alleging unexpected results based on material misrepresentations, not by distinguishing prior art. No alternative forum exists in an Article III court currently, and any forum for challenging validity that might eventually arise would necessarily undercut any presumption of settled

expectations. No better forum exists to hold Helsinn to account for its prosecution conduct.

## **V.CONCLUSION**

Claims 1-23 are unpatentable. Azurity respectfully requests that the Director refer this petition for institution so the Office can address material examination error.

Respectfully submitted,

Dated: 4 September 2025

*/Richard Torczon/*

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

**VI. 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
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