UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AZURITY PHARMACEUTICALS, INC.,
Petitioner,

v.

HELSINN HEALTHCARE S.A.,
Patent Owner.

Case IPR2025-00946
Patent US 9,186,357 B2

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, 53-60. 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 aprepitant showed efficacy for nausea. Nor did Helsinn deny that its data table presented during examination of its 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.[1] Such gamesmanship should

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[1] 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. PODD, 22 n.11. Helsinn is wrong: the FAQ discourages detailed repetition, but 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 how the examiner erroneously allowed the Trento'826 claims relying on Helsinn's assertion that its claimed netupitant-palonosetron combination was unexpectedly better than the prior-art aprepitant-palonosetron combination, because the former exhibited "synergy" and treated nausea, whereas the latter did not. Pet., 5-7. The same examiner considered the challenged Trento'357 claims to be "not patentably distinct" and allowed the

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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.

application with no reasons for allowing the claims. Pet, 50; EX1009, ¶¶33-35; EX1006, 235, 331.

The same examiner in the Trento'826 examination considered there to be a strong *prima facie* obviousness case against those patentably-indistinct claims because prior art showed an NK_1-receptor antagonist (e.g., aprepitant) combined with a 5-HT_3 antagonist (e.g., casopitant, palonosetron) and dexamethasone defined a new standard of care for treating chemotherapy-induced nausea and vomiting. Pet., 5-7; EX1005, 284. Prior art also identified netupitant as another NK_1-receptor antagonist under development for the same use. Pet., 5-7, 58; EX1005, 284. Helsinn asserted its unexpected results for netupitant-palonosetron overcame the *prima facie* case, and the examiner ultimately relented based on Helsinn's assertion. Pet., 6-7. Helsinn's "unexpected" results were the ***sole*** basis for allowing the patentably-indistinct Trento'826 claims. Pet., 7-8. The discretionary-denial request confirms Helsinn's reliance on its asserted unexpected results from the Trento'826 examination for the patentability of the Trento'357 claims. PODD, 2-3 (Helsinn alleging unexpected results "which the Office referenced in its Notice of Allowance for the parent '826 patent" "is directly relevant to challenged claims of the '357 patent"), 6-8 (repeating those purported unexpected results as applicable to the '357 patent).

The petition shows, however, that Helsinn's "unexpected" results were

fictional because the prior-art aprepitant-palonosetron combination also had these properties. Pet., 48-60; EX1009, ¶¶1329-1390. As the petition detailed, Helsinn's prosecution response materially altered data tables to remove data unsupportive of its contentions, inducing allowance based on a fiction. Pet., 7; EX1009, ¶¶1360-1379.

2. Helsinn Never Denied Most Mischaracterizations and Fabrications that Underlie Its "Unexpected" Results

Helsinn's discretionary-denial request never even acknowledges most of the petition's showings that Helsinn's "unexpected" results 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. See §II.A.3 below.

As the petition showed, any of numerous errors during examination were material and induced erroneous allowance of these claims. Pet., 48-59; EX1009, ¶¶1329-1390. For purposes of discretionary denial, the many arguments Helsinn failed to deny remain unrebutted. As noted above, Helsinn cannot properly incorporate arguments from its unfiled POPR. See n.1 above.

a. No Dispute: Aprepitant Showed Efficacy for Nausea.

The petition showed a prior-art NK_1-receptor antagonist—aprepitant—

effectively treated nausea, contrary to Helsinn's representations during examination. Pet., 48-49; EX1001, 2:12-26, 4:37-39, EX1005, 328-39 (arguing *inter alia* that aprepitant was not active against nausea). While Helsinn cursorily dismisses Azurity's discussion of the Emend label (Paper 8, PO Disc. Denial brief (#8, PODD), 23-25), its rebuttal failed to dispute many aspects of the Emend label that showed aprepitant's efficacy and—insofar as Helsinn did respond—it conceded dispositive showings in the petition (see §II.A.3, below). Helsinn never disputed Azurity's discussion of many other references showing aprepitant effectively treats nausea. Thus, the unrebutted 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., 50-51; EX1009, ¶¶1333-1340, 1371-1373.[2] 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., 50-51; EX1009, ¶1335.

Instead, Helsinn falsely asserted Azurity does not "address the p-value column for the 'nausea' and 'significant nausea' data in the tables from the Emend label." PODD, 25. Actually, Azurity directly addressed that statistical significance (determined via p-value) was not calculated for nausea. Pet., 50-51. For example, Dr. Peroutka, explained 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% overall in significant nausea)." EX1009, ¶1335 (cited at Pet., 51). Discussing Emend Label Table 2, Dr. Peroutka explained "a

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[2] For clarity, note that "complete protection" as discussed in the petition (*e.g.*, Pet., 50-51, 55) 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., 50; EX1030, 7; EX1001, 16:4-17.

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., 51). 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. PODD, 25 (merely attempting to distinguish "complete protection" from parameters "specifically directed to nausea" alone); Pet., 50-51; EX1009, ¶¶1333-1340, EX1030, Table 1 (reproduced below, first), Table 2 (reproduced below, second).

ENDPOINTS	Aprepitant Regimen (N = 260)† %	Standard Therapy (N = 261)† %	p-Value
PRIMARY ENDPOINT			
Complete Response			
Overall‡	73	52	<0.001
OTHER PRESPECIFIED ENDPOINTS			
Complete Response			
Acute phase§	89	78	<0.001
Delayed phase‖	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**

†N: Number of patients (older than 18 years of age) who received cisplatin, study drug, and had at least one post-treatment efficacy evaluation.
‡Overall: 0 to 120 hours post-cisplatin treatment.
§Acute phase: 0 to 24 hours post-cisplatin treatment.
‖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)† %	Standard Therapy (N = 263)† %	p-Value
PRIMARY ENDPOINT			
Complete Response			
Overall‡	63	43	<0.001
OTHER PRESPECIFIED ENDPOINTS			
Complete Response			
Acute phase§	83	68	<0.001
Delayed phase‖	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**

†N: Number of patients (older than 18 years of age) who received cisplatin, study drug, and had at least one post-treatment efficacy evaluation.
‡Overall: 0 to 120 hours post-cisplatin treatment.
§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., 50-51). 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., 51).

ii. Trento'826 Example 5

Helsinn did not deny its specification shows aprepitant and netupitant have comparable effects on nausea. Pet., 51-52; 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 (and PODD, 26), Column 6; *see also* EX1009, ¶1341 (cited at Pet., 52).

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., 52). 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., 52).

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., 52; *see also* EX1001, Table 6 (reproduced below):

TABLE 6

SUMMARY OF SECONDARY EFFICACY RESULTS: PERCENT OF PATIENTS, MFAS POPULATION

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)**
No Emesis						
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*	
No Rescue						
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	
No Nausea						
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
No Significant Nausea						
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
Total Control						
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	
Complete Protection						
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., 52). 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., 52). 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., 53; 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., 53; 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., 53; EX1009, ¶1354. Further post-critical date data confirms this understanding—***none of which*** Helsinn disputes. Pet., 53; 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 cursorily argued its data was not lacking but failed to dispute numerous issues with its data identified in the petition; instead, Helsinn blames the Office for not requesting Helsinn's material-but-missing data. PODD, 25-26. 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., 54. Helsinn misled the Office while prosecuting the patentably-indistinct parent Trento'826 claims 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., 54; EX1009, ¶¶1362-1363. *Compare* EX1005 (file history of ’462 application), 331 (Response to the USPTO) (below)

TABLE 2

	1	2	3	4	5	6	7	8
Efficacy Endpoint	Palo + Netu (HEC)[a]	Ondan + Aprep (HEC)[a]	Palo + Netu (MEC)[b]	Ondan + Aprep (MEC)[c]	Palo + Aprep (HEC)[d]	Palo + Aprep (MEC)[e]	Ondan + Aprep (MEC)[f]	Palo + Aprep (HEC)[g]
No Nausea								
Overall (0-120h)	61.5	58.2	50.3	ns	ns	32[nsc]	30.6[ns]	59.9[ncs]
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[ncs]	66.1[ns]	91[ncs]
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)[a]	2 Ondan + Aprep (HEC)[a]	3 Palo + Netu (MEC)[b]	4 Ondan + Aprep (MEC)[c]	4a Ondan + Aprep (HEC)[c1]	5 Palo + Aprep (HEC)[d]	6 Palo + Aprep (MEC)[e]	7 Ondan + Aprep (MEC)[f]	8 Palo + Aprep (HEC)[g]
Percentage of Patients with No Nausea									
Overall (0-120h)	61.5	58.2	50.3	33	48,49	nr	32[ncs]	30.6	59.9[ncs]
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[ncs]	66.1	91[ncs]
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., 54). 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. Instead, Helsinn argued that the Office "could have asked" for this material-but-omitted data. PODD, 25-26. Unfortunately, the examiner did not ask. As Dr. Peroutka explained, a POSA would not have relied on Helsinn's internal studies to recognize "unexpected" results without seeing that information. Pet., 54; 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 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., 55; EX1009, ¶¶1367-1370. Dr. Peroutka supplied the Yeo data Helsinn had omitted in

annotated Table 2, below:

TABLE 2

Efficacy Endpoint	1 Palo + Netu (HEC)[a]	2 Ondan + Aprep (HEC)[a]	3 Palo + Netu (MEC)[b]	4 Ondan + Aprep (MEC)[c]	4a Ondan + Aprep (HEC)[c1]	5 Palo + Aprep (HEC)[d]	6 Palo + Aprep (MEC)[e]	7 Ondan + Aprep (MEC)[f]	8 Palo + Aprep (HEC)[g]
Percentage of Patients with No Nausea									
Overall (0-120h)	61.5	58.2	50.3	33	48,49	nr	32[ncs]	30.6	59.9[ncs]
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[ncs]	66.1	91[ncs]
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., 55). 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_3 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., 55).

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. PODD, 22-26; Pet., 55; 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., 55). 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 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., 56; EX1009, ¶¶1374-1379. Although Helsinn presented Grunberg as though it were directly comparable to Helsinn's internal studies, Helsinn's discretionary-denial request 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., 56)), 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 falsely stated Azurity failed to dispute palonosetron-netupitant synergy. PODD, 28; rebutted in §§II.A.3.c-d. Actually, Helsinn failed to dispute that the specification neither defined nor discussed "synergy" for either the claims or the "unexpected" results. Pet., 57-58; EX1009, ¶1381; PODD, 28 (recognizing but not addressing this issue).

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., 57. 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., 57). As Dr. Peroutka explained, even assuming *arguendo* Helsinn's data before the Office was accurate, EX1009, ¶1386 (cited at Pet., 58):

> 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 meaningfully 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_1-receptor antagonist, including aprepitant. Pet., 58; 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., 58; EX1009, ¶1389.

Helsinn did not directly dispute the petition's showing of no nexus between the alleged synergy and the ***claimed*** effect. To the extent Helsinn relies on its footnote repeating the Office's statement in the Trento'826 notice of allowance that "evidence of synergy" related to "the claimed method" (PODD, 27 n.13), Helsinn still failed to address Azurity's explanation that this statement was materially erroneous. Pet., 58; EX1009, ¶¶1387-1390. Helsinn did not 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., 58; EX1009, ¶1390.

e. No Dispute: Rule 132 Declaration From Interested Parties

Helsinn admitted the Office relied on purported unexpected results from a Rule 132 declaration from Giorgia Rossi and Claudio Pietra to allow the claims. Pet., 7; PODD, 9; EX1005, 341-350. Helsinn did not dispute that Giorgia Rossi is an inventor of the patent. Pet., 7; PODD, 9. Helsinn also did not dispute that Claudio Pietra was a Helsinn employee. Pet., 7; PODD, 9. 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.

3. Helsinn's Omissions and Misleading Data were Material and Induced Erroneous Allowance

As shown above (§II.A.2), 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., 48-53; 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., 49-50). Instead of rebutting the petition's numerous showings, Helsinn continued to flood the record with mischaracterizations, alleging discrete failures to address aspects of prior art the petition actually addressed. For example, Helsinn argues Azurity did not address the p-value of "nausea" and "significant nausea" in the Emend label (PODD, 22-23), but Helsinn is wrong (Pet., 50-51) as detailed below.

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., 50-51; §II.A.2.a.i, above. Material examination error resulted from failure to consider the label as a whole.

Helsinn falsely asserted the petition did not "address the p-value column for the 'nausea' and 'significant nausea' data in the tables from the Emend® label." Helsinn relied on an indication that the label showed no "statistically significant" decrease of nausea. PODD, 25-26. First, Helsinn's focus on statistical significance

in its PODD is narrower than its arguments during examination, where it more broadly argued the label failed "to demonstrate a reduction in nausea or significant nausea." EX1005, 329.[3] Helsinn argued statistical significance was not calculated (EX1005, 330), but the petition directly addressed this point, 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., 51; EX1009, ¶1335 (cited at Pet., 51). 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

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[3] Indeed, Helsinn's own internal studies discussed during examination lacked statistical significance for many efficacy endpoints. *See* EX1005, 346 (numerous Helsinn Study entries lacking a "statistically significant" asterisk); EX1001, Table 6 (similar).

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., 51. Thus, Helsinn's assertion about the p-value is false.

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., 50-51; EX1009, ¶1333-1334. Helsinn noted but did not rebut Azurity's explanation of this complete protection parameter. PODD, 25. The label showed "substantial improvement of complete protection for overall, acute phase, and delayed phase parameters" following treatment with aprepitant. Pet., 50-51; EX1009, ¶¶1334; EX1030, 7 & Table 1 (first below), Table 2 (second below).

ENDPOINTS	Aprepitant Regimen (N = 260)† %	Standard Therapy (N = 261)† %	p-Value
PRIMARY ENDPOINT			
Complete Response			
Overall‡	73	52	<0.001
OTHER PRESPECIFIED ENDPOINTS			
Complete Response			
Acute phase§	89	78	<0.001
Delayed phase‖	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**

†N: Number of patients (older than 18 years of age) who received cisplatin, study drug, and had at least one post-treatment efficacy evaluation.
‡Overall: 0 to 120 hours post-cisplatin treatment.
§Acute phase: 0 to 24 hours post-cisplatin treatment.
‖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)† %	Standard Therapy (N = 263)† %	p-Value
PRIMARY ENDPOINT			
Complete Response			
Overall‡	63	43	<0.001
OTHER PRESPECIFIED ENDPOINTS			
Complete Response			
Acute phase§	83	68	<0.001
Delayed phase‖	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**

†N: Number of patients (older than 18 years of age) who received cisplatin, study drug, and had at least one post-treatment efficacy evaluation.
‡Overall: 0 to 120 hours post-cisplatin treatment.
§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., 50-51).

Helsinn admitted it presented data from an older Emend label (EX2016) during examination. PODD, 23 n.12; EX2016. The more-contemporaneous prior-art Emend label Azurity filed (EX1030) showed substantial decreases in nausea. Helsinn noted that Azurity cited a 2008 version of the Emend label, but did not argue that citation was prejudicial. PODD, 23 n.12. Indeed, Helsinn failed to identify any substantive differences between the documents and did not argue (nor could it) that the 2008 label is not prior art. *Id.* Helsinn provided no reason why its Trento'826 prosecution arguments—made in 2013—relied on a decade-old label, as opposed to an updated 2008 Emend label. EX1005, 329-330, 338 (May 17, 2013); PODD, 23-24.[4]

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[4] If Helsinn is suggesting the 2008 label was materially even more inconsistent

Although Helsinn cites the prior-art Herrington reference for prior non-disclosure of nausea control (PODD, 25), Herrington merely notes the label contrasts with Herrington's data showing aprepitant efficacy in preventing nausea. EX1016, 2086 ("The control of nausea was achieved in similar fashion between the 2 aprepitant arms. However, there was a trend toward better significant nausea prevention on Days 4-5 with the 3-day Arm A versus the single dose. In the 3-day arm, 88.5% versus 69.2% did not have significant nausea….").

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 the Trento'826 examination. Pet., 51-52. The specification itself showed aprepitant's effect on nausea is comparable to netupitant's. EX1001 (Trento'826), 16:62-19:43, Table 6.

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with its arguments than the 2003 label it did submit, Helsinn only highlights its practice of hiding unfavorable information from the Office.

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., 51-52); §II.A.2.b, above (annotating differences between tables). Helsinn did not deny this fact. PODD, 22-26.

Second, as explained above (§II.A.2.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., 52; 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., 52).

Third, as explained above (§II.A.2.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., 51-52. 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.2.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., 52).

Helsinn's cherry-picked data and edited entries thus induced material error by falsely supporting unexpected results. Pet., 51-52; EX1009, ¶1341.

iii. Campos

Helsinn wrongly alleged aprepitant lacked efficacy for nausea during the acute phase of treatment while prior art showed otherwise. Pet., 53; 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_3 receptor antagonist, dexamethasone, plus aprepitant) provided 'nausea ratings [that] were significantly lower' in 'the first 24 hours rank analysis' compared to 5-HT_3 receptor antagonist plus dexamethasone." EX1009, ¶1353 (quoting EX1023 (Campos), 1763) (cited at Pet., 53) & EX1023, Fig. 2 (reproduced below).

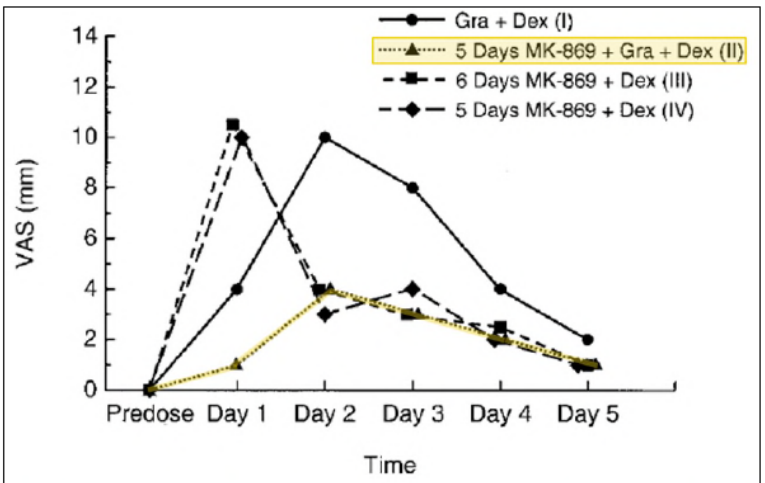

Fig 2. Median visual analog scale nausea scores over time irrespective of the use of rescue medication. Gra (granisetron) and Dex (dexamethasone) both administered on day 1 only. Groups I and II were significantly different when comparing the interval days 1 through 5, and days 2 through 5 ($P < .05$).

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., 53). 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., 53. *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., 53). 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., 53.

TABLE 2

Efficacy Endpoint	1 Palo + Netu (HEC)[a]	2 Ondan + Aprep (HEC)[a]	3 Palo + Netu (MEC)[b]	4 Ondan + Aprep (MEC)[c]	4a Ondan + Aprep (HEC)[c1]	5 Palo + Aprep (HEC)[d]	6 Palo + Aprep (MEC)[e]	7 Ondan + Aprep (MEC)[f]	8 Palo + Aprep (HEC)[g]
Percentage of Patients with No Nausea									
Overall (0-120h)	61.5	58.2	50.3	33	48,49	nr	32[ncs]	30.6	59.9[ncs]
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[ncs]	66.1	91[ncs]
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 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., 53-57. Helsinn neither rebutted nor denied most Azurity arguments identifying these misrepresentations and omissions. §II.A.2, above. Instead, Helsinn yet again mischaracterized the record, alleging the information it provided during examination was not lacking (PODD, 25-26). As shown below, this is false.

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

Differences between Helsinn's Rule 132 declaration and its arguments during the Trento'836 examination induced material Office error leading to allowance these patentably-indistinct Trento'357 claims. As discussed above (§II.A.2.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., 53-54; EX1009, ¶1361. Comparing the tables from the declaration and Helsinn's response (reproduced above, §II.A.2.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., 54. *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., 54).

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.2.a.i, above. As Dr. Peroutka explained, these alterations were material. EX1009, ¶1364 (cited at Pet., 54).

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., 54-57. In response, Helsinn ignored most of Azurity's contentions, focusing instead on just one, arguing that Helsinn "would have" provided pertinent data from its internal studies during examination if it had been asked. PODD, 26. Even if this argument were appropriate (it is not), 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., 54-57; 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., 54. 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., 54). In its discretionary-denial briefing, Helsinn argued that it "would have" provided this information during examination if the Office had asked. PODD, 26. Nonetheless, 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., 54).

Second, as shown above (§II.A.2.b.iii), the table Helsinn presented during examination omitted data showing comparable—and even ***improved***—nausea treatment with aprepitant versus netupitant. Pet., 55; EX1009, ¶¶1367-1370; *see*

also EX1009, ¶1369 (describing Yeo's data showing treatment of nausea and the above annotations); Pet., 55. 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.2.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., 56. Grunberg's study differed in important ways that made direct comparison inappropriate. Pet., 56; 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., 56-57).

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.2.c), no unexpected synergy exists between netupitant-palonosetron versus prior-art aprepitant-palonosetron. Pet., 57-58. 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., 57). See, for example, the combination of palonosetron and either netupitant or aprepitant for use with highly emetogenic chemotherapy (HEC):

TABLE 2

Efficacy Endpoint	1 Palo + Netu (HEC)[a]	2 Ondan + Aprep (HEC)[a]	3 Palo + Netu (MEC)[b]	4 Ondan + Aprep (MEC)[c]	4a Ondan + Aprep (HEC)[c1]	5 Palo + Aprep (HEC)[d]	6 Palo + Aprep (MEC)[e]	7 Ondan + Aprep (MEC)[f]	8 Palo + Aprep (HEC)[g]
Percentage of Patients with No Nausea									
Overall (0-120h)	61.5	58.2	50.3	33	48,49	nr	32[ncs]	30.6	59.9[ncs]
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[ncs]	66.1	91[ncs]
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

EX1009, ¶¶1383 (cited at Pet., 57), 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_1 receptor antagonists***—aprepitant and netupitant." EX1009, ¶¶1383 (cited at Pet., 57). 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., 48.

At most, palonosetron combined with ***any*** NK_1-receptor antagonist confers

intrinsic benefit as compared to other ***5-HT₃***-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)[a]	2 Ondan + Aprep (HEC)[a]	3 Palo + Netu (MEC)[b]	4 Ondan + Aprep (MEC)[c]	4a Ondan + Aprep (HEC)[c1]	5 Palo + Aprep (HEC)[d]	6 Palo + Aprep (MEC)[e]	7 Ondan + Aprep (MEC)[f]	8 Palo + Aprep (HEC)[g]
Percentage of Patients with No Nausea									
Overall (0-120h)	61.5	58.2	50.3	33	48,49	nr	32[nrs]	30.6	59.9[nrs]
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[nrs]	66.1	91[nrs]
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
[nrs] Non-Comparative Study; statistical significance not evaluated

EX1009, ¶1385 (cited at Pet., 57). 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_1 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., 57-58).

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

As shown above (§II.A.2.d), Helsinn falsely stated "Azurity completely fails to address the underlying evidence of synergistic effects". PODD, 26. The petition directly rebutted Helsinn's purported synergistic effects. Pet., 57-58; EX1009, ¶¶1387-1390. Further, Dr. Peroutka discussed the lack of "any evidence of synergy in a way that corresponds to the challenged claims." EX1009, ¶1387 (cited at Pet., 58).

Instead, Helsinn has failed to grapple with any of the petition arguments illustrating Helsinn's inability to show unexpected synergy between netupitant and palonosetron. Pet., 58. As the petition explained, (1) any synergy between netupitant and palonosetron was ***expected*** because such synergy was also observed with other NK_1-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_1-receptor antagonist, which is beyond the scope of Helsinn's claims (and includes prior-art combinations). Pet., 58; EX1009, ¶1388; §II.A.3.c. A POSA would have understood any synergistic effect between palonosetron and an NK_1-receptor antagonist was not limited to netupitant—it included *inter alia* prior-art aprepitant. Pet., 57; 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., 58; 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., 58. SP was a known target of multiple therapeutic effects, including mood disorders and pain. EX1009, ¶1390 (cited at Pet., 58). 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, 17-19. Although the secondary reference Bös was available during examination, Helsinn admitted the Office never applied it and, in any case, the examiner failed to note that it singles netupitant out as a particularly good species. *Id.*, 19-20 & n.10. 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 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_1-receptor antagonist, but it was an ***improved*** NK_1 antagonist. Pet., 14, 14-15 (Bös); EX1009, ¶¶843-846. 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. Section II.B.1, above. 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 '357 patent has been in force since 2015, which creates strong settled expectations…."), 10 ("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. *Embody, 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. Instead, Helsinn brazenly blames the examiner for failing to require Helsinn to provide its materially-contrary omitted material information. PODD, 25-26 ("If the Office had believed that an evaluation of the underlying data was merited, the Office simply could have asked Helsinn for the data, and Helsinn would have obliged without issue."). 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.[5] For example, Helsinn relies on a single instance of litigation, but admits that it settled, and pointedly omits the terms of the settlement. PODD, 13 n.7. 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

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[5] Helsinn should not be permitted to bolster its arguments later, when Azurity can no longer respond.

showed. Similarly, Helsinn relies (*id.*, 12) 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 over half of the challenged claims (it is not at least because it does not include dexamethasone). *Compare* EX1002, 21:39-47 *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 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 2-4, 11-16, 40-42, and 52-62 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., *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)

VII. 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 discretionary-denial opposition complies with the type-volume limitation of Rule 42.24 and Webpage, *Interim Director Discretionary Process*, §III.C.iii[6] (" For discretionary denial requests due before September 1, 2025, a petitioner's opposition to the patent owner's discretionary denial brief is limited to 14,000 words…."). The word count for this paper is 9,306 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: September 4, 2025 / Yawen Wang /
Yawen Wang

[6] https://www.uspto.gov/patents/ptab/interim-director-discretionary-process (viewed September 2, 2025).