

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AZURITY PHARMACEUTICALS, INC.,
Petitioner,

v.

HELSINN HEALTHCARE S.A.,
Patent Owner.

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

PETITION FOR INTER PARTES REVIEW

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I. INTRODUCTION

Petitioner Azurity Pharmaceuticals, Inc. (“Azurity”) requests *inter partes* review (“IPR”) to cancel claims 1-25 of U.S. Patent 8,623,826 (“Trento’826”, EX1001), assigned to Patent Owner (Helsinn). The prior art shows the claimed method is a routine variation on the existing standard, yet the examiner allowed the claims expressly relying on interested, undeposed, and materially-flawed testimony. These claims were never patentable.

II. STANDING CERTIFICATIONS

Trento’826 is available for IPR. Azurity is not barred or estopped from requesting IPR.

III. CHALLENGES AND PRECISE RELIEF REQUESTED

Claims 1-25 should be cancelled under 35 U.S.C. §103¹ over:

¹ All pre-AIA 35 U.S.C. §§102 and 103.

Ground	Claims	Combined Teachings of
1	19, 22-23 & 25	MASCC ² (EX1013) & Hoffmann ³ (EX1011)
2	19-20, 22-23 & 25	MASCC & Bös ⁴ (EX1014)
3	19-23 & 25	MASCC, Bös & ALOXI ⁵ (EX1015)

² 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 (2006).

³ T. Hoffmann et al., *Design and synthesis of a novel, achiral class of highly potent and selective, orally active neurokinin-1 receptor antagonists*, 16 BIOORGANIC & MEDICINAL CHEMISTRY LETTERS 1362 (2006).

⁴ M. Bös et al., *4-phenyl-pyridine derivatives*, US 6,297,375 B1 (issued 2 Oct. 2001).

⁵ ALOXI (palonosetron HCl) Capsules, label (Revised 09/2008).

4	1-3, 8-10, 15-18 & 24	Herrstedt ⁶ (EX1010), Hoffmann & Hargreaves ⁷ (EX1012)
5	1-3, 6-10, 15-18 & 24	Herrstedt, Bös & Hargreaves
6	4-5	Herrstedt, Bös, Hargreaves & Herrington ⁸ (EX1016)
7	10-14	Herrstedt, Bös, Hargreaves & ALOXI

Exhibits, including a declaration from Stephen Peroutka, M.D., Ph.D. (EX1009), support these grounds.

IV. TRENTO’826 PATENT

Trento’826 purports to provide “methods for treating nausea and vomiting in

⁶ J. Herrstedt & P. Dombernowsky, *Anti-Emetic Therapy in Cancer Chemotherapy: Current Status*, 101 BASIC & CLINICAL PHARMACOLOGY & TOXICOLOGY 143 (2007).

⁷ R. Hargreaves, *Imaging Substance P Receptors (NK₁) in the Living Human Brain Using Positron Emission Tomography*, 63(11) J. Clinical Psychiatry 18 (2002).

⁸ 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).

patients undergoing chemotherapy, radiotherapy, or surgery, comprising the co-administration of netupitant, palonosetron and dexamethasone.” EX1001, cover.

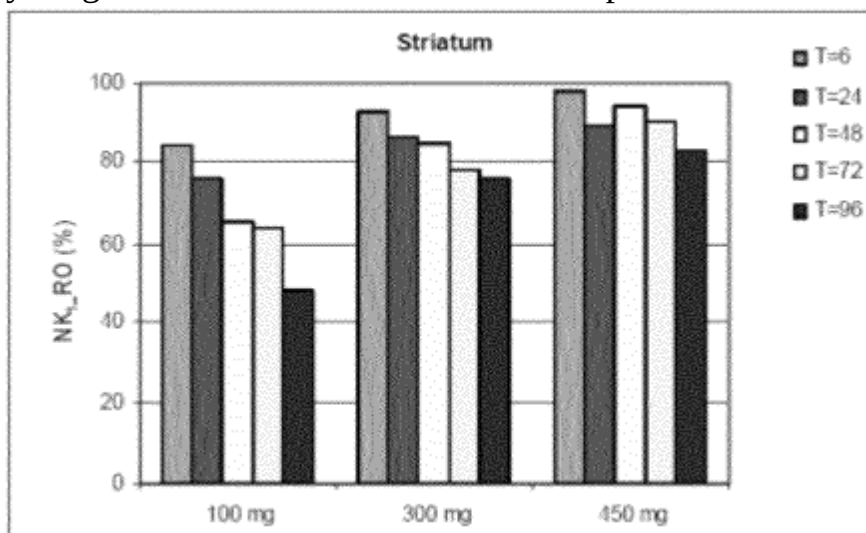
A. Specification

The specification “relates to the use of centrally acting NK₁ antagonists to treat nausea and vomiting, particular[ly] nausea and vomiting induced by highly emetogenic chemotherapy, and to the treatment of such nausea and vomiting over multiple consecutive days[, and] also relates to combined oral dosage forms of palonosetron and netupitant.” EX1001, 1:19-25. Using a 5-HT₃ antagonist (like palonosetron) with a steroid (like dexamethasone) “significantly improve[d] the standard of life for patients undergoing emetogenic medical procedures.” EX1001, 1:29-39. Indeed, “[p]alonosetron hydrochloride ha[d] recently emerged as a highly efficacious anti-nauseant and anti-emetic agent.” EX1001, 1:40-41.

NK₁ antagonists aprepitant and casopitant had been tested—FDA had approved aprepitant for preventing “nausea and vomiting”—but Trento’826 reported neither was effective. EX1001, 2:6-50. Nevertheless, Trento’826 reported NK₁ antagonists, specifically including netupitant, continued to be “suggest[ed]... for a variety of conditions in which substance P (the natural ligand for the NK₁ receptor) is active.” Listed conditions included “vomiting [but not] nausea specifically.” EX1001, 3:21-60. Trento’826 reported discovering netupitant is active against nausea, binds to striatum NK₁ receptors for 96 hours post-

administration, and makes both palonosetron and dexamethasone more effective, permitting subtherapeutic dexamethasone doses, and providing an effective 5-day combination therapy. EX1001, 4:37-5:20.

Trento'826 Example 4 discloses administering netupitant alone to healthy human volunteers and determining brain NK₁-receptor occupancy. As “anticipated” 90% or higher occupancy (“close to the expected C_{max} ”) of striatum receptors was reached for half the subjects with a single oral dose. Moreover, “[a]ll doses showed a relatively long duration of blockade of NK₁ receptors and the decline over time was dose dependent.” The results were provided in Figure 5 (detail, right). EX1001, 16:37-60.



B. Challenged Claims

Trento'826 has two independent claims. Claim 19 relates to treating acute- or delayed-phase chemotherapy-induced nausea and vomiting (CINV) with netupitant and palonosetron. Claim 1 relates to treating both nausea and vomiting for 5 days by administering (a) day-one netupitant, which occupies at least 70% of striatum NK₁ receptors 72 hours later, (b) day-one palonosetron, and (c) day-one

dexamethasone at 50-70% of its effective dose when used without netupitant, where the treatment is effective for 5 days, and where the treatment is more effective than steps (b) and (c) alone. EX1001, 21:39-63, 23:8-15.

C. Prosecution History

Trento'826 issued from application 13/077,462 (EX1005), filed 31 March 2011, which is a continuation of PCT/IB2010/003106,⁹ which claims priority to provisionals 61/382,709¹⁰ and 61/262,470.¹¹ Its earliest possible effective filing date is 18 November 2009; however, the earlier provisional never discloses co-administration with dexamethasone, so claims encompassing co-administering dexamethasone are not entitled to priority before 14 September 2010.

The examiner rejected claims over Reddy,¹² which teaches treating CINV by administering an NK₁ antagonist (aprepitant) with a 5-HT₃ antagonist, and dexamethasone. Reddy teaches a 5-HT₃ antagonist combined with dexamethasone was the “standard of care for highly emetic chemotherapy” and adding an NK₁

⁹ EX1055, filed 18 November 2010.

¹⁰ EX1056, at 154-190, filed 14 September 2010.

¹¹ EX1057, at 192-219, filed 18 November 2009.

¹² EX1021, G.K. Reddy et al., *Novel Neurokinin-1 Antagonists as Antiemetics for the Treatment of Chemotherapy-Induced Emesis*, 3 Support Cancer Ther. 140-42 (2006).

antagonist defined a new standard. EX1021, 141. Reddy also teaches netupitant was another NK₁ antagonist under development for the same use. *Id.* The examiner found “Reddy teaches enhanced treatment of CINV with the addition of aprepitant or casopitant. Accordingly, the artisan would have reasonably expected enhanced treatment of CINV with netupitant”; however, Reddy was not “anticipatory insofar as netupitant is not a preferred species” but nonetheless “it would have been obvious to select netupitant given its plain enumeration in the prior art reference.” EX1005, 285; EX1009, ¶¶29-30.

Helsinn responded with a declaration alleging unexpected results from combining netupitant with palonosetron. The declarants—a Trento’826 inventor and another Helsinn employee—argued using netupitant with palonosetron was synergistic because palonosetron inhibits the natural ligand for the NK₁ receptor, even though it is a 5-HT₃ antagonist, while other 5-HT₃ antagonists do not. EX1009, ¶31.

The examiner provided as reason for allowance: “132 Declaration, filed 5/17/2013, affiant showing evidence of synergy (unexpected result) from the combination of netupitant and palonosetron in regard to the claimed method.” EX1009, ¶32. The examiner did not identify the precise unexpected result, but Helsinn had argued (EX1005, 331)—

the combination of netupitant and palonosetron consistently reduced

significant nausea in response to HEC [highly-emetic chemotherapy], reduced nausea during the delayed phase in response to HEC, and reduced significant nausea during the overall phase in response to MEC [moderately-emetic chemotherapy]. These results were unexpected, and they plainly support the patentability of the claimed invention.

Significantly, Helsinn’s response materially altered the data tables to remove unsupportive data. EX1009, ¶¶1360-79.

V. LEVEL OF ORDINARY SKILL

A POSA was skilled in one of “clinical medicine, medical oncology, radiation oncology, oncology nursing, statistics, pharmacy, medical policy and decision making, and pharmacology.” EX1013, 20. In 2009, such professionals had advanced degrees in pharmacology, medicine, or allied fields, and would have worked in consultation with other specialists in these fields, and had practical knowledge and experience about metabolism studies, in-vitro and in-vivo testing, formulation, and combination therapy. Dr. Peroutka is a pharmacologist familiar with the level of skill at the critical date. EX1009, ¶¶1-7, 57-60.

Trento’826 itself notes the high level of skill in the art: “[t]he skilled artisan will be able to determine appropriate dosages[.]” EX1001, 7:57-61; 10:9-12 (POSA can determine “suitable dosing regimen”). *Cf. Immunogen, Inc. v. Stewart*, No. 23-1762, slip 10 (Fed. Cir. 2025) (affirming obviousness where art showed physicians could determine the claimed dose).

VI. CLAIM CONSTRUCTION

Trento’826 provides definitions of claim terms. EX1001, 7:3-9:5.

The phrase ***therapeutically effective amount***¹³ means “an amount sufficient to elicit the desired biological response.” EX1001, 7:55-57; EX1009, ¶140.

The phrase ***minimum effective dose of dexamethasone*** means 20 mg on day-one and on subsequent days 16 mg for HEC and 0 mg for MEC. EX1001, 7:62-8:4; EX1009, ¶¶147, 267. Correspondingly, ***sub-therapeutic dose of dexamethasone*** means less than these defined minimum amounts.

Trento’826 does not disclose or define what ***synergistically effective to antagonize NK1 activity*** means. EX1001, EX1009, ¶153. Indeed, Trento’826 does not disclose any synergism; hence, ***synergy*** means only an effect greater than what the prior art would have suggested for the combination. *Novo Nordisk v. Caraco Pharmaceutical*, 719 F.3d 1346, 1352 (Fed. Cir. 2013) (“more effective than what would have been expected in view of the prior art”).

For claim element 1(a)[2], “a therapeutically effective amount ***which***” means the functions following “which” describe inherent properties rather than therapeutic effects that might further restrict a therapeutically-effective amount. *In re Hyatt*, 708 F.2d 712, 714 (Fed. Cir. 1983) (ordinary grammar applies); EX1009,

¹³ Bold-italicized text indicates added emphasis.

¶¶257-60 (prior art identifies these functions as inherent in a therapeutic amount).

VII. PRIOR ART

All the applied and background references were publicly available over one year before the critical date and are thus section 102(b) prior art. No ground reference was applied in a rejection during examination.

A. MASCC

MASCC promulgates formal antiemetic recommendations of a multinational professional association on supportive care for cancer, updating the standard of care to the 2006 state-of-the-art. EX1013, 20.

1. Recognized benefit from NK₁-antagonist/5-HT₃-antagonist/dexamethasone combination

Two decades ago, antiemetic treatments received renewed attention, resulting in updated recommendations from the Multinational Association of Supportive Care (MASCC) “on antiemetic regimens to prevent emesis induced by high, moderate, low and minimal risk chemotherapy”. EX1013, 20. The state of the art had been—

a 5-HT₃-receptor antagonist plus dexamethasone as the regimen of choice for the prevention of acute emesis in cisplatin-treated patients[. However, a]prepitant is the first of a new class of drugs that selectively block the neurokinin-1 (NK₁) neurotransmitter receptor, the binding site of the regulatory peptide Substance P. Aprepitant has been studied extensively for the prevention of cisplatin-induced

emesis. Several phase II double-blind studies showed added antiemetic activity when combined with a 5-HT₃-receptor antagonist plus dexamethasone[].

EX1013, 22. Moreover, a “reduced dose of dexamethasone was given in combination with aprepitant because a prior pharmacokinetic study found that aprepitant increased dexamethasone levels approximately two-fold.” Using a “primary endpoint [of] complete response (no emesis, no use of rescue antiemetics) over the 5-day study period”, this triple therapy was superior to the standard 5-HT₃-antagonist/dexamethasone treatment. *Id.*

[T]o prevent acute vomiting and nausea following [HEC], a three-drug regimen including single doses of a 5-HT₃-receptor antagonist, dexamethasone and aprepitant given before chemotherapy is recommended (MASCC level of consensus: high; MASCC level of confidence: high).

Id. Similarly, for HEC-induced delayed emesis, and despite studies with the then-current standard,

the panel recommended that given the dependence of delayed emesis and nausea on acute antiemetic outcome, optimal acute antiemetic prophylaxis should be employed. For cisplatin, this includes a three-drug combination of aprepitant, a 5-HT₃-receptor antagonist and dexamethasone.

EX1013, 23. MASCC disclosed both oral and intravenous administration of the 5-HT₃ antagonist¹⁴ and dexamethasone, and oral administration of the NK₁ antagonist. EX1013, 23-24; EX1009, ¶¶87-90.

2. Palonosetron was a known, better 5-HT₃ antagonist

MASCC reported (EX1013, 24):

Palonosetron is a 5-HT₃-receptor antagonist that has a longer half-life and more avid receptor binding than the other 5-HT₃ receptor antagonists. Two studies in patients treated with [MEC] demonstrated efficacy with a single intravenous dose of palonosetron 0.25 mg that was equal or better to a single intravenous dose of dolasetron or ondansetron in both the acute and delayed phases[.]

MASCC also reported using palonosetron for HEC. EX1013, 22 (Table 3); EX1009, ¶91.

B. Hoffmann

Hoffmann, a 2006 journal article, teaches potent, orally-active NK₁ antagonists to control CINV, as well as treat mood disorders like anxiety and depression.

EX1011, Abstract. Hoffmann explains:

[R]ecent clinical trials have demonstrated an important therapeutic application for NK₁ receptor antagonists in the control of cancer

¹⁴ Reportedly palonosetron was only then-available intravenously.

chemotherapy-induced nausea and vomiting and in the treatment of mood disorders such as anxiety and depression.[Aprepitant] was the first NK₁ receptor antagonist to receive marketing approval. In March 2003, it was approved by the FDA for [CINV].

EX1011, 1362; EX1009, ¶¶92-93. This class includes netupitant, which Hoffmann teaches has favorable characteristics including high affinity, excellent penetration into the central nervous system (CNS), and excellent oral NK₁-antagonist activity. EX1011, 1364; EX1009, ¶94. Hoffmann tested its NK₁-antagonists (including netupitant) in vivo and showed they potently inhibit NK₁ agonist-induced foot-tapping behavior in gerbils. EX1011, 1365.

C. Bös

Bös, a 2001 patent, describes using NK₁ antagonists to inhibit conditions including chemotherapy-induced emesis. Bös teaches using NK₁ antagonists for “mediation of the emetic reflex and the modulation of central nervous system (CNS) disorders[.]” EX1014, 1:15-56. Specifically, “neurokinin-1 receptor antagonists are further useful for the treatment of motion sickness and for treatment induced vomiting” such as in “the reduction of cisplatin-induced emesis by a selective neurokinin-1-receptor antagonist.” EX1014, 1:59-67; EX1009, ¶¶95-96. Bös expressly identifies netupitant (“formula Ib”) as “characterized by valuable therapeutic properties as a highly selective antagonist of the Neurokinin 1”. EX1014, 14:32-38; EX1009, ¶¶97-98. Bös tested netupitant in model animals,

including a test of antiemetic effects in ferrets that showed pre-exposure netupitant administration “completely blocked the emesis induced by the emetogens.”

EX1014, 19:10-20; EX1009, ¶99. Bös disclosed that a POSA would be able to determine appropriate dosage “within wide limits”, particularly within a daily range of 10-1000 mg. EX1014, 42:5-11; EX1009, ¶¶100-01.

D. ALOXI

ALOXI, a 2008 FDA label revision, discloses “palonosetron HCl” as a potent, selective 5-HT₃ antagonist for MEC and HEC. EX1015, 1, 3; EX1009, ¶¶102-03, 107-10. ALOXI teaches a 0.56 mg palonosetron HCl capsule, corresponding to 0.5 mg palonosetron free base. EX1015, 1-4; EX1009, ¶104. ALOXI teaches administering these capsules one hour before chemotherapy. EX1015, 5; EX1009, ¶105. ALOXI also teaches administering palonosetron with chemotherapeutic agents, systemic corticosteroids (e.g., dexamethasone), and other antiemetic and antinausea agents. EX1015, 2; EX1009, ¶106. EX1015, 4, Table 3.

E. Herrstedt

Herrstedt, a 2007 journal article, summarizes 2007 CINV treatments, including antiemetic therapy with serotonin-receptor 5-HT₃ antagonists (e.g., palonosetron) and NK₁ antagonists (e.g., aprepitant). EX1010, Abstract. Herrstedt teaches adding a NK₁ antagonist to an antiemetic combination of 5-HT₃ antagonist plus corticosteroid (e.g., dexamethasone). *Id.* (“Aprepitant increases the effect...

against acute emesis induced by” HEC or MEC). *Id.* Herrstedt teaches antiemetic drugs should be administered in a combination therapy including a corticosteroid, 5-HT₃ antagonist, and NK₁ antagonist. EX1010, 145; EX1009, ¶111-12.

Herrstedt also teaches palonosetron as an improved 5-HT₃ antagonist. EX1010, 145-146 (palonosetron “has a very potent and specific binding at 5-HT₃ receptors and a half-life around 40 hr as compared to less than 10 hr for the other agents (table 3).”). While earlier 5-HT₃ antagonists had “limited or no efficacy in delayed emesis”, “[p]alonosetron might be an exception” because it had FDA approval “in the treatment of delayed emesis from MEC.” EX1010, 146; EX1009, ¶113.

Herrstedt summarizes phase-III clinical trials evaluating a 5-HT₃ antagonist, dexamethasone, and NK₁ antagonist (aprepitant). EX1010, 146. These trials showed a statistical benefit for CINV prophylaxis. EX1010; EX1009, ¶114. Moreover, using aprepitant “results in a two-time increase in the [area under curve] of dexamethasone indicating an inhibition of aprepitant on dexamethasone metabolism.” EX1010, 147. When using dexamethasone with an NK₁ antagonist (aprepitant), the dexamethasone concentration doubles due to decreased dexamethasone metabolism. EX1009, ¶115.

F. Hargreaves

Hargreaves, a 2002 journal article, teaches using positron emission

tomography (PET) to study the NK₁-receptor pathway and Substance P, which is implicated in pathophysiology of emesis and depression. EX1012, Abstract. Using aprepitant, the study evaluated NK₁-receptor occupancy within the brain, associating such occupancy with therapeutic effects. *Id.* Hargreaves associates a 75% or greater NK₁-receptor occupancy with blocked emesis. EX1012, 23; EX1009, ¶¶116-17.

G. Herrington

Herrington, a 2008 journal article, discloses a clinical trial evaluating three treatment arms for antiemetic effect for HEC, where all treatment arms received day-one 0.25 mg palonosetron intravenously and dexamethasone on each of days 1-4. EX1016, Abstract. Arm A also orally received day-one 125 mg aprepitant plus 80 mg aprepitant on days 2-3. Arm B received day-one 125 mg oral aprepitant but placebo on days 2-3. Arm C only received placebo. *Id.*; EX1009, ¶¶118-19.

Herrington reports that day-one administration is as effective as multi-day administration. EX1016, Abstract; EX1009, ¶120. Herrington reports no significant difference between a single, day-one versus multiple-day NK₁ antagonist doses for both acute and delayed phases. EX1016, Table 3; EX1009, ¶121.

VIII. LEGAL STANDARDS

Obviousness involves (1) the scope and content of the prior art, (2) differences between the prior art and the claims, (3) the level of ordinary skill in

the art, and (4) evidence of secondary considerations. *KSR Int'l v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). “[T]he fact that a combination was obvious to try might show that it was obvious under §103.” *Id.* at 421. If a property composition is inherent, reasonable expectation of success is assured. *Cytiva Bioprocess v. JSR Corp.*, 122 F.4th 876, 886-87 (Fed. Cir. 2024).

IX. GROUND 1: CLAIMS 19, 22-23 AND 25—OBVIOUS OVER MASCC AND HOFFMANN

These claims were obvious variants of a then-state-of-the-art 3-drug regimen with a newer NK₁ antagonist (netupitant) replacing an older one (aprepitant), with routine choices about dosage form, amount, and timing. MASCC teaches treating both nausea and vomiting for acute and delayed CINV following MEC or HEC by administering NK₁ antagonist with dexamethasone and 5-HT₃ antagonist for enhanced efficacy. EX1013, 22-23. MASCC teaches administering before chemotherapy, an effective amount of aprepitant, which MASCC explains is the first in a new class of selective NK₁ antagonists. *Id.* MASCC also teaches using palonosetron as the 5-HT₃ antagonist. *Id.*, 24. Hoffmann teaches netupitant as an improved NK₁ antagonist. EX1011, Abstract, 1364. Substituting netupitant for aprepitant in MASCC’s 3-drug regimen with palonosetron would have been obvious. EX1009, ¶¶127-30.

A. Claim 19

1. **[preamble]: “A method of treating both nausea and vomiting in a human subject in need thereof during the acute or delayed phases of chemotherapy induced nausea and vomiting (CINV) in response to moderately or highly emetogenic chemotherapy, comprising”**

If the preamble is limiting, MASCC teaches its “method of treating both nausea and vomiting in a human subject in need thereof during the acute or delayed phases of” CINV after MEC or HEC. EX1013, 22 (“Therefore, to prevent acute vomiting and nausea following chemotherapy of high emetic risk, a three-drug regimen including single doses of a 5-HT₃-receptor antagonist, dexamethasone and aprepitant given before chemotherapy is recommended (MASCC level of consensus: high; MASCC level of confidence: high).”); EX1009, ¶131.

2. **[a]: “administering to said subject before said chemotherapy a therapeutically effective amount of netupitant or a pharmaceutically acceptable salt thereof and”**

MASCC teaches administering therapeutically-effective amounts of a three-antiemetic combination to a human patient for both nausea and vomiting during the acute or delayed phases of CINV after MEC or HEC. EX1013, 22-24. MASCC recommends treating acute-phase nausea after HEC with 5-HT₃ antagonist (ondansetron or palonosetron), NK₁ antagonist (aprepitant), and dexamethasone

administered before chemotherapy. EX1013, 22-23 (“patients receiving cisplatin treated with a combination of aprepitant, a 5-HT₃-receptor antagonist and dexamethasone to prevent acute vomiting and nausea”). MASCC teaches 125 mg of oral aprepitant is a therapeutically-effective amount of day-one NK₁ antagonist. *Id.*; EX1009, ¶¶132-33.

MASCC teaches aprepitant, not netupitant, but also teaches aprepitant was the first in a new class of selective NK₁ antagonists. EX1013, 22 (“Aprepitant is the first of a new class of drugs that selectively block the neurokinin-1 (NK₁) neurotransmitter receptor, the binding site of the regulatory peptide Substance P.”); EX1009, ¶134. Hoffmann teaches netupitant is an “excellent” alternative to aprepitant. EX1011, Abstract (“The evaluation of this [NK₁ antagonist] class is briefly outlined, leading to the identification of netupitant 21[, one of] two new proprietary chemical entities with high affinity and excellent CNS penetration.”); EX1009, ¶135. Hoffmann provides ample reason to substitute netupitant in MASCC’s 3-drug regimen with palonosetron and dexamethasone and reasonably expect success based on netupitant’s excellent efficacy. EX1009, ¶136. A POSA knew how to determine therapeutically-effective oral dosages routinely: Hoffmann achieved therapeutic results in animal studies. EX1009, ¶¶137-41.

3. [b]: “a therapeutically effective amount of palonosetron or a pharmaceutically acceptable salt thereof.”

MASCC teaches administering a therapeutically-effective amount of palonosetron as the 5-HT₃ antagonist. EX1013, 24 (“Palonosetron is a 5-HT₃-receptor antagonist that has a longer half-life and more avid receptor binding than the other 5-HT₃ receptor antagonists. [MEC patients] demonstrated efficacy with a single intravenous dose of palonosetron 0.25 mg that was equal or better to a single intravenous dose of dolasetron or ondansetron in both the acute and delayed phases”); EX1009, ¶¶142-44.

B. Claim 22: “further comprising, if said patient is undergoing highly emetogenic chemotherapy, administering a sub-therapeutic dose of dexamethasone on days one, two, three and four, wherein day one is the day on which netupitant and palonosetron, or pharmaceutically acceptable salts thereof, are administered.”

For HEC, MASCC teaches administering dexamethasone on days 1-4 and NK₁ and 5-HT₃ antagonists on day 1. EX1013, 22 (“Two phase III trials with identical design compared a standard two-drug regimen with ondansetron 32 mg plus dexamethasone 20 mg on day 1, followed by dexamethasone 8 mg twice a day on days 2-4 with **a three-drug regimen** of ondansetron 32 mg, **dexamethasone 12 mg** and aprepitant 125 mg **on day 1**, followed by **dexamethasone 8 mg daily on days 2-4** and aprepitant 80 mg days 2 and 3. A reduced dose of dexamethasone was given in combination with aprepitant because a prior pharmacokinetic study

found that aprepitant increased dexamethasone levels approximately two-fold.”) EX1013, 22; EX1009, ¶¶145-46 (explaining these “studies were conducted in patients undergoing highly emetogenic chemotherapy (i.e., cisplatin).”). The sub-20 mg dexamethasone doses for MASCC’s 3-drug regimen are *sub-therapeutic* as Trento’826 defines this term. EX1009, ¶147, see §VI above. Claim 22’s regimen would have been obvious and expected to work for the reasons given for claim 19. EX1009, ¶¶148-49.

C. Claim 23: “further comprising, if said patient is undergoing highly emetogenic chemotherapy, orally administering 12 mg of dexamethasone on day one and 8 mg of dexamethasone on days two, three and four, wherein day one is the day on which netupitant and palonosetron, or pharmaceutically acceptable salts thereof, are administered.”

MASCC teaches orally administering dexamethasone in the claimed amounts as discussed for claim 22. MASCC, 22, Table 3; EX1009, ¶¶150-52.

D. Claim 25: “wherein said netupitant or pharmaceutically acceptable salt thereof and said palonosetron or pharmaceutically acceptable salt thereof are synergistically effective to antagonize NK1 activity.”

Trento’826 does not define *synergistically effective*. EX1009, ¶153, see §VI above. Helsinn conceded this undisclosed synergistic effect would always occur. EX1008, 186 (“At *all* concentrations where the netupitant and palonosetron have an effect on the EC50 of substance P, they have a synergistic effect when combined.”); EX1009, ¶153. Post-filing publications confirm palonosetron has this “synergistic”

effect with NK₁ antagonists generally because it palonosetron uniquely (for 5-HT₃ antagonists) indirectly affects *NK₁ receptors* as well and thus would “synergistically” work with *any* NK₁ antagonists. EX1009, ¶¶154-56. Hence, this “synergy” is an inherent property of an obvious combination, not an unexpected result. *Cytiva*, 122 F.4th at 888-89 (explaining discovery of a property inherent does not distinguish prior art).

E. Obvious to Combine and Reasonably Expect Success

By the critical date, a POSA had good reason to use the 3-drug regimen MASCC recommended (including “sub-therapeutic” dexamethasone doses) to treat acute- and delayed-phase CINV in response to MEC or HEC, using palonosetron as the 5-HT₃ antagonist as MASCC recommended. Hoffmann suggesting substituting netupitant for the older aprepitant due to netupitant’s improved profile. EX1009, ¶¶157-61; *cf.* EX1051 (reporting Helsinn’s in-licensing of netupitant for use with palonosetron). The palonosetron’s “synergistic” efficacy was inherent when used with NK₁ antagonists, and thus both inherent in the combination and not unexpectedly better than palonosetron’s use in MASCC’s 3-drug regimen (with aprepitant). A POSA would have reasonably expected success using netupitant and palonosetron in MASCC’s 3-drug combination because MASCC itself recommended using palonosetron for its known advantages. EX1013, 22, 25; EX1009, ¶162. Similarly, netupitant and aprepitant in the same class and known to

be therapeutically effective via the same mechanism—antagonizing the NK₁ receptor. EX1011, 1362; EX1009, ¶¶163-64. *KSR*, 550 U.S. at 416 (“mere substitution of one element for another known in the field” requires the inventor to show “more than...a predictable result”).

X. GROUND 2: CLAIMS 19-20, 22-23, AND 25—OBVIOUS OVER MASCC AND BÖS

A. Claim 19

As with Ground 1, MASCC provides the 3-drug combination, with sub-therapeutic dexamethasone and with a suggestion to use palonosetron as the 5-HT₃ antagonist. For Ground 2, the Bös patent provides the suggestion to substitute netupitant as the NK₁ antagonist. EX1009, ¶¶165-68

- 1. [preamble]: “A method of treating both nausea and vomiting in a human subject in need thereof during the acute or delayed phases of chemotherapy induced nausea and vomiting (CINV) in response to moderately or highly emetogenic chemotherapy, comprising”**

As explained in §IX.A.1 above, if the preamble is limiting, MASCC teaches it. EX1013, 22; EX1009, ¶169.

- 2. [a]: “administering to said subject before said chemotherapy a therapeutically effective amount of netupitant or a pharmaceutically acceptable salt thereof and”**

MASCC explicitly recommends treating acute-phase nausea and vomiting after HEC with 5-HT₃ antagonist (e.g., palonosetron), NK₁ antagonist (day-one

125 mg aprepitant), and dexamethasone. EX1013, 22-24; EX1009, ¶¶170-71.

MASCC uses aprepitant, not netupitant, but anticipates new drugs in the same class of selective NK₁ antagonists. MASCC, 22 (“Aprepitant is the first of a new class of drugs that selectively block the neurokinin-1 (NK₁) neurotransmitter receptor, the binding site of the regulatory peptide Substance P.”); EX1009, ¶172.

Bös discloses netupitant is a potent, selective NK₁ antagonist useful for treating emesis. EX1014, 14:31-38 (“valuable therapeutic properties as a highly selective antagonist of the Neurokinin 1”); 17:61-18:48 (“a potent and selective antagonist”), 18:60-63 (“a competitive antagonist at human recombinant NK₁ receptors”), 19:26-30 (“a potent antagonist of NK₁ induced behaviours in gerbil and blocks emesis in ferrets ... with similar potency.”); 4:15-24 (“the most preferred indications ... are those which include disorders of the central nervous system, for example indications for the treatment or prevention of ... emesis by the administration of NK-1 receptor antagonists”); 39:42-48 (“pharmacological activity of the compounds of this invention as NK-1 receptor antagonists” have activity “correlated with treatment of” CNS disorders); 9:22-29 (“particularly useful for treating CNS disorders, such as ... emesis.”); 19:10-30; EX1009, ¶173.

Bös teaches a range for therapeutically-effective amounts of NK₁ antagonists (including netupitant). EX1014, 42:5-11 (“The effective amount for the dosage can vary within wide limits and will, of course, be fitted to the individual requirements

in each particular case. In general, in the case of ***oral administration a daily dosage of about 10 to 1000 mg per person of a compound of this invention*** should be appropriate, although the above upper limit can also be exceeded when necessary.”); EX1009, ¶174.

Bös provides ample reason to replace MASCC’s aprepitant with Bös’ new, improved netupitant. Indeed, MASCC suggested new species in the same class, while Bös suggests netupitant is an attractive oral replacement for aprepitant, particularly because its good CNS penetration would allow netupitant to reach CNS NK₁ receptors to treat emesis with a reasonable expectation of success. EX1009, ¶175. Moreover, Bös teaches netupitant works well when administered orally before HEC (e.g., cisplatin). EX1014, 19:11-20 (“***Emesis was induced*** in ferrets by various emetogens (apomorphine, morphine, ipecacuanha, ***cisplatin*** and CuSO₄. Pretreatment of this compound [netupitant] (0.3 mg/kg, p.o.) 2 hours before the emet[o]gen, ***completely blocked the emesis*** induced by all emetogens.”); EX1009, ¶¶176-77.

MASCC and Bös provide a POSA with guidance for routinely determining therapeutically-effective netupitant doses, including a clear starting range—10 to 1000 mg—for a dose-ranging study. EX1014, 42:5-11. MASCC suggests using a dose-ranging study to determine “the most favorable benefit:risk profile.” EX1013, 22. A POSA had good reason to study doses ranging from 10 mg to 1000 mg to

determine the most favorable benefit:risk profile and reasonably expect to identify therapeutically-effective netupitant amounts for treating CINV. EX1009, ¶¶178-80.

3. [b]: “a therapeutically effective amount of palonosetron or a pharmaceutically acceptable salt thereof.”

As explained in §IX.A.3 above, MASCC suggests using palonosetron as the 5-HT₃ antagonist. EX1013, 22; EX1009, ¶¶181-83.

B. Claim 20: “comprising orally administering from about 200 to about 400 mg of netupitant or a pharmaceutically acceptable salt thereof, and from about 0.25 to about 0.75 mg of palonosetron or a pharmaceutically acceptable salt thereof.”

MASCC teaches administering palonosetron in the range of from about 0.25 to about 0.75 mg. EX1013, 24 & Table 4 (“a single intravenous dose of *palonosetron 0.25 mg* ... was equal or better to a single intravenous dose of dolasetron or ondansetron in both the acute and delayed phases”). MASCC also teaches oral 5-HT₃-antagonists administration was as efficacious as intravenous. MASCC, 24 (“Furthermore, there is no difference in the efficacy of oral or iv administration of a 5-HT₃-receptor antagonist (palonosetron is only [commercially] available as an iv formulation and is further discussed below).”). A POSA would have appreciated oral administration is simpler, less costly, and more convenient than intravenous administration. EX1009, ¶¶184-85.

Bös suggests orally administering NK₁ antagonists, including from about 200 to about 400 mg of netupitant. EX1014, 42:5-11 (“oral administration [of] a

daily ***dosage of about 10 to 1000 mg*** per person of a compound of this invention should be appropriate”) EX1014, 42:5-11. Bös reports successful dosing in animal models. EX1014, 18:64-19:10 (gerbils), 19:11-20 (ferrets), 19:21-24 (*Suncus murinus*). A POSA would have known to optimize Bös’ range (including from about 200 to about 400 mg) to determine a therapeutically-effective amount of netupitant and reasonably expect success. EX1009, ¶¶186-88; *In re Urbanski*, 809 F.3d 1237, 1242 (Fed. Cir. 2016) (routine to optimize result-effective variable).

C. Claims 22-23: MASCC teaches these limitations

As explained in §§IX.B-IX.C above, MASCC teaches the dexamethasone limitations in a 3-drug antiemetic combination. EX1013, 22; EX1009, ¶¶189-96.

D. Claim 25: “wherein said netupitant or pharmaceutically acceptable salt thereof and said palonosetron or pharmaceutically acceptable salt thereof are synergistically effective to antagonize NK1 activity.”

As explained in §IX.D above, “synergy” is inherent in MASCC’s combination of palonosetron with an NK₁ antagonist. EX1009, ¶¶197-200.

E. Obvious to Combine and Reasonably Expect Success

By the critical date, a POSA had good reason to treat acute- and delayed-phase CINV after MEC or HEC with MASCC’s 3-drug regimen, including “sub-therapeutic” dexamethasone, with palonosetron as the 5-HT₃ antagonist. Bös suggests substituting netupitant for the older aprepitant due to netupitant’s

improved profile. EX1009, ¶¶201-04; cf. EX1051 (reporting Helsinn’s in-licensing of netupitant for use with palonosetron). The palonosetron’s “synergistic” efficacy is inherent when palonosetron is used with NK₁ antagonists, and thus both inherent in the combination and not unexpectedly better than using palonosetron with MASCC’s aprepitant. A POSA would have reasonably expected success using netupitant and palonosetron in MASCC’s 3-drug combination for the reasons discussed in §IX.E above. EX1009, ¶¶205-07.

XI. GROUND 3: CLAIMS 19-23, AND 25—OBVIOUS OVER MASCC, BÖS AND ALOXI

A. Claims 19-20, 22-23, and 25: ALOXI provides additional disclosure about palonosetron

The claims in Ground 2 were obvious as explained in §X above. EX1009, ¶¶165-209. Additionally, for claim 19’s step [b], the ALOXI label provides further disclosure about palonosetron dosing.

ALOXI teaches administering before chemotherapy a therapeutically-effective amount of palonosetron salt. ALOXI capsules contain 0.56 mg palonosetron HCl (equivalent to 0.50 mg palonosetron free base), which demonstrated efficacy for treating emetogenic chemotherapy. EX1015, 3-4 (clinical studies). ALOXI teaches capsules are pre-administered “one hour prior to” administration of “emetogenic chemotherapy.” EX1015, 4; EX1009, ¶¶211-12.

MASCC teaches intravenous palonosetron was available, but oral

administration is also advantageous. ALOXI's palonosetron HCl has the same active ingredient as MASCC's free-base palonosetron, giving a POSA good reason to employ ALOXI capsules and reasonably expect success combining the teachings of MASCC, Bös, and ALOXI. EX1009, ¶210-11.

For claim 20 (“...from about 0.25 to about 0.75 mg of palonosetron or a pharmaceutically acceptable salt thereof”), ALOXI teaches orally administering 0.56 mg of palonosetron HCl, which is within the claimed range of about 0.25 to about 0.75 mg of palonosetron or a pharmaceutically acceptable salt. ALOXI, 3-4; ES1002, ¶¶219-23. *UCB, Inc. v. Actavis Labs.*, 65 F.4th 679, 687 (Fed. Cir. 2023) (a point within the claimed range anticipates).

For claims 22-23 and 25, ALOXI teaches pre-administering day-1 palonosetron to treat CINV after MEC or HEC. EX1015, 2-3, 4 (“one hour before the start of chemotherapy”); EX1009, ¶¶232-39. MASCC teaches intravenous palonosetron, but a POSA also would have appreciated the benefits of oral administration. Because ALOXI's palonosetron HCl has the same active ingredient as MASCC's free-base palonosetron, the POSA would have reasonably expected success combining the teachings of MASCC, Bös, and ALOXI. EX1009, ¶¶240-44.

B. Claim 21: “comprising orally administering about 300 mg of netupitant as the free base and about 0.56 mg of palonosetron hydrochloride.”

Bös suggests orally administering about 300 mg of NK₁ antagonists including netupitant. EX1014, 42:5-11 (“oral ... daily ***dosage of about 10 to 1000 mg*** per person”). A POSA would have known a range this magnitude (10 to 1,000 mg) is a common starting range when determining therapeutic doses and would identified “about 300 mg” through routine optimization. EX1009, ¶¶224-28; *Urbanski*, 809 F.3d at 1242 (routine to optimize result-effective variable).

Trento’826 does not identify any criticality or unexpected result for 300 mg netupitant. While Trento’826’s netupitant-dexamethasone drug interaction study (EX1001, 16:1-36, Fig. 4) shows increasing dexamethasone bioavailability with each of the 100 mg, 300 mg, and 450 mg doses, the 300 mg dose was not correlated to any particular benefits. Indeed, the PET receptor-occupancy study for netupitant (EX1001, 16:36-65, Fig. 5), unsurprisingly achieved the greatest duration of NK₁-receptor blockade with the ***450 mg dose*** because “the decline over time was dose dependent.” While a 300 mg dose was the highest dose evaluated in a clinical efficacy study (EX1001, Example 5), even that study simply showed the expected iterative efficacy increase with increasing doses, indicating no critical or unexpected benefit specifically associated with 300 mg. EX1009, ¶229.

ALOXI teaches orally administering capsules containing “***0.56 mg of***

palonosetron HCl equivalent to palonosetron 0.5 mg” to prevent CINV after emetogenic chemotherapy. ALOXI, 3-4. A POSA had good reason to administer its palonosetron in the ALOXI formulation and reasonably expect success. EX1009, ¶¶230-31.

C. Obvious to Combine and Reasonably Expect Success

The combination of MASCC’s 3-drug combination substituting netupitant and palonosetron would have been obvious to try and reasonably expect success as explained in §X.E above. Adding the FDA-approved ALOXI label bolsters the reasons for using palonosetron as the label instructs. EX1009, ¶¶240-44. Similarly, using 300 mg of netupitant—a noncritical value within the range Bös teaches—was facially obvious. *Beckson Marine v. FNM, Inc.*, 292 F.3d 718, 727 (Fed. Cir. 2002) (“[O]bviousness does not require the prior art to reach expressly each limitation exactly.”).

XII. GROUND 4: CLAIMS 1-3, 8-10, 15-18 AND 24—OBVIOUS OVER HERRSTEDT, HOFFMANN, AND HARGREAVES

Herrstedt teaches treating both nausea and vomiting for five days, by administering therapeutically-effective amounts of NK₁ antagonist (aprepitant), 5-HT₃ antagonist (e.g., palonosetron), and a first (sub-therapeutic) dose of dexamethasone on day 1. EX1010, 143, 146-147. Herrstedt reports dexamethasone concentration doubles in combination, so dexamethasone is reduced by about 50% versus the standard minimum-effective dose. EX1010, 147. Herrstedt teaches this

effectively treats both nausea and vomiting for five days, and treats both nausea and vomiting better than 5-HT₃ antagonist and dexamethasone. EX1010, 146-147; EX1009, ¶¶245-47.

Hoffmann teaches netupitant is an improved NK₁ antagonist. EX1011, Abstract, 1364. A POSA would have known to try an improved NK₁ antagonist (netupitant) instead of aprepitant in Herrstedt's combination. EX1009, ¶247.

Hargreaves associates NK₁-receptor occupancy greater than 75% with therapeutic effectiveness. EX1012, Abstract, 23, Fig. 6B. Hargreaves teaches measuring NK₁-receptor occupancy in the striatum. A POSA would have expected a therapeutically-effective dose of netupitant to occupy at least 70% of striatum NK₁ receptors 72 hours after administration. EX1009, ¶¶248-49.

A. Claim 1

- 1. [preamble]: “A method of treating both nausea and vomiting for five consecutive days in a patient in need thereof, comprising:”**

If it is limiting, Herrstedt teaches the preamble terms; e.g., prophylactically treating “[c]hemotherapy-induced *nausea and vomiting*”. EX1010, 143.

Herrstedt's primary endpoint was no emesis for five days after chemotherapy with cisplatin. EX1010, 146 (“Complete response, defined as ‘no emesis and no rescue therapy on days 1-5 postcisplatin’, was the primary end-point in all studies.”). EX1009, ¶250.

2. (a)[1] administering to said patient on day one netupitant or a pharmaceutically acceptable salt thereof,

Herrstedt teaches treating HEC with a triple-drug combination administered on day 1, including NK₁ antagonist (aprepitant). EX1010, 146 (“Two of the HEC studies used an identical design...ondansetron [NK₁ antagonist], dexamethasone and *aprepitant day 1* followed by dexamethasone days 2-4 plus aprepitant days 2-3.”). Herrstedt describes benefits from day-1 triple-antiemetic (including NK₁ antagonist) administration. *Id.* (“a complete response of 72.7% in the aprepitant arm versus 52.3% in the control arm” and “complete response rates were 62.7% versus 43.3%” in another study); *id.* (“Again a statistical[] benefit favouring aprepitant was seen, resulting in a complete response in the aprepitant arm of 72.0% versus 60.6% in the control arm.”); EX1009, ¶¶251-52.

Herrstedt teaches aprepitant was merely the first in a class of selective NK₁ antagonists. EX1010, Abstract. Hoffmann teaches netupitant is a selective NK₁ antagonist and an “excellent” alternative to aprepitant. EX1011, Abstract (“The evaluation of this class is briefly outlined, leading to the identification of netupitant 21[, one of] two new proprietary chemical entities with high affinity and excellent CNS penetration.”). From Hoffmann, a POSA had ample reason to replace Herrstedt’s aprepitant with Hoffmann’s new, improved NK₁ antagonist—netupitant—not least because its excellent CNS penetration was highly desirable, allowing it to reach CNS NK₁ receptors involved in emesis. EX1009, ¶¶253-54.

Hargreaves teaches entering the CNS for inhibiting emesis. EX1012, 18 (“The SP-NK₁ receptor pathway is the most abundant and the most extensively studied NK pathway in both the central nervous system (CNS) ..., where it plays an important role in the regulation of response to a broad range of ... noxious ... stimuli. * * * High concentrations of SP are also present in the brain ... regions that have been implicated in the control of the vomiting reflex. A role for SP in the regulation of emesis is further supported by observations that local application of SP ... causes retching in ferrets and that the chemotherapeutic agent cisplatin increases plasma levels of SP in cancer patients. Most importantly, [NK₁ antagonists] were recently shown to block emesis in animal models and to prevent acute and delayed” CINV). A POSA had ample reason to substitute Hoffmann’s netupitant) for Herrstedt’s older aprepitant in Herrstedt’s antiemetic combination and reasonably expect success because both compounds are NK₁ antagonists and achieve their purpose (decreased nausea and vomiting) the same way (NK₁ antagonism). EX1009, ¶¶254-55.

3. (a)[2] in a therapeutically effective amount which enters the systemic circulation, crosses the blood brain barrier and occupies at least 70% of neurokinin-1 (NK) receptors in the striatum seventy-two hours after said administration;

Netupitant circulates systemically and crosses the blood-brain barrier to occupy striatum NK₁ receptors. Hoffmann teaches administering netupitant orally.

EX1011, 1364 (“Animals were orally pretreated (2 h) with the test compound followed by central injection (icv) of the NK₁-selective receptor agonist GR73632. Excellent oral activity was observed...for netupitant.”). Orally-administered netupitant cannot act locally; instead, Hargreaves teaches, for therapeutic efficacy, NK₁ antagonists must interfere with Substance P in the CNS, which includes the striatum—a region of the brain with abundant NK₁ receptors. EX1012, 21-23 (“The highest [¹⁸F]SPA-RQ activity was found in brain regions with high NK₁ receptor density, such as striatum....”), Fig. 4. Hoffmann lauded netupitant precisely because it penetrates the CNS. EX1011, Abstract (“excellent CNS penetration”). Because oral netupitant acts on CNS NK₁ receptors, it must enter systemic circulation and cross the blood-brain barrier to reach the striatum. EX1009, ¶¶256-57.

Hargreaves teaches a therapeutically-effective amount occupies at least about 75% of striatum NK₁ receptors. EX1012, Fig. 4(A); EX1009, ¶258. Hargreaves also teaches targeted inhibition of striatum NK₁ receptors. EX1012, 21-23 (“After treatment, a dose-proportional reduction in tracer binding to NK₁ receptors in the striatum was observed with aprepitant, but not with placebo (Figure 5). ...[¹⁸F]SPA-RQ binding in other regions of the brain known to express NK₁ ... was also reduced, in line with observations made in the striatum. On the basis of these findings, a plasma concentration vs. receptor occupancy relationship

was established (Figure 6A).”), Fig. 5. Hargreaves directly associates striatum NK₁-receptor occupancy and antiemetic effectiveness for CINV. EX1012, 23 (“...occupancy of $\geq 90\%$ of NK₁ receptors requires aprepitant doses ≥ 100 mg. Curve fitting to the plasma concentration—receptor occupancy curves showed that **high levels of NK₁ receptor occupancy were associated with** significant antidepressant effects and **optimal activity against CINV**. ...the initial 125-mg [aprepitant] dose studied for treatment of emesis blocked $\geq 90\%$ of NK₁ receptors in the CNS (Figure 6B), whereas the initial 40-mg dose used in the study of emesis resulted in lower **(75%) receptor occupancy (Figure 6B)**.”). Hargreaves Fig. 6B shows “CINV Efficacy” for antiemetic therapy beginning at approximately 75% NK₁-receptor occupancy, corresponding with 40 mg of aprepitant. Hargreaves further teaches CINV efficacy with 125 mg aprepitant having at least 90% occupancy; hence, a therapeutically-effective netupitant dose would occupy at least 75% of striatum NK₁ receptors seventy-two hours after administration. EX1009, ¶259. In sum, the effects following **which** in element 1(a)[2] are what therapeutically-effective NK₁ antagonist dose must do.

Helsinn conceded as much in a related examination, where Helsinn did not rebut the examiner’s finding that a therapeutically-effective netupitant dose inherently satisfies the “at least 70%” occupancy limitation. *E.g.*, EX1008, 120; EX1009, ¶260. Seventy-two hours falls squarely within the 5-day therapeutic

period and simply reflects netupitant's known prolonged half-life. EX1009, ¶¶260-61; EX1014, 19:7-38; EX1001, 4:37-51 (“netupitant binds to NK₁ receptors in the striatum in a long-lasting manner, and [] less than 20 or 30% of netupitant is release from striatum NK₁ receptors even ninety-six hours after administration.”).

4. (b) administering to said patient on day one a therapeutically effective amount of palonosetron or a pharmaceutically acceptable salt thereof; and

Herrstedt identifies palonosetron as a favorable 5-HT₃ antagonist for treating emesis on day 1. EX1010, 146. Herrstedt also teaches palonosetron efficacy in treating “*delayed* emesis from MEC” with an order-of-magnitude increase in half-life versus ondansetron. EX1010, 146, Table 3 (palonosetron half-life 38-40 hours; ondansetron half-life 4-6 hours), 146 (“in the MEC studies some of the evaluable parameters *significantly favoured palonosetron.*”); 146 (“three randomized, double-blind trials ... demonstrated that palonosetron was not inferior to dolasetron and ondansetron.”). A POSA had ample reason to substitute the “significantly favoured” palonosetron as the 5-HT₃ antagonist and reasonably expect of success because both palonosetron and ondansetron worked through an identical mechanism (5-HT₃ antagonism) to achieve an identical therapeutic result (antiemesis). EX1009, ¶¶262-63.

Herrstedt teaches the 5-HT₃ antagonist should be administered on day 1, both with and without an NK₁ antagonist. EX1010, 146 (“Two of the HEC studies

used an identical design comparing **ondansetron**, dexamethasone and placebo **day 1** followed by dexamethasone plus placebo days 2-4 with **ondansetron**, dexamethasone and aprepitant **day 1** followed by dexamethasone days 2-4 plus aprepitant days 2-3.”), 146 (“The most recently published HEC study used the same design, except that ondansetron was [also] included in the control arm for delayed protection days 2-4.”); EX1009, ¶¶264-65.

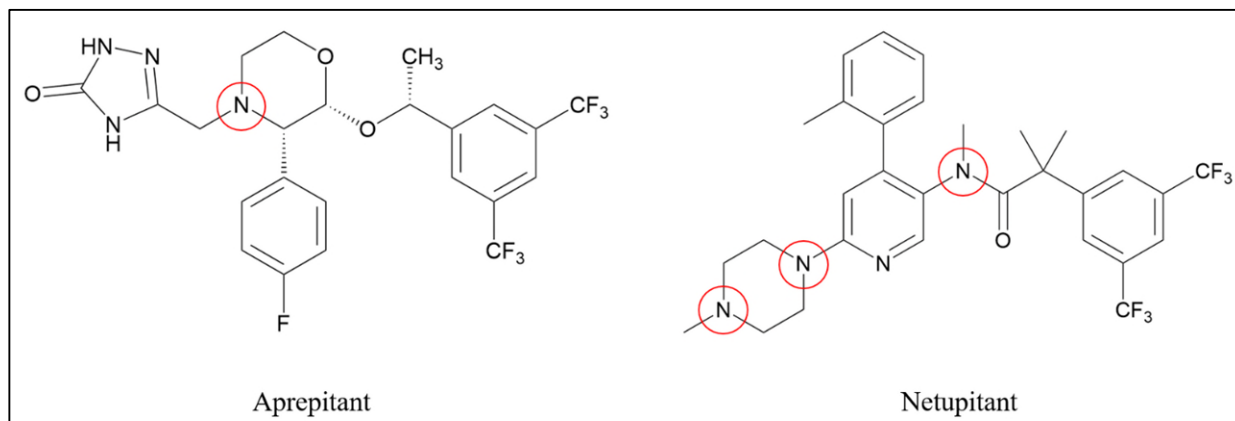
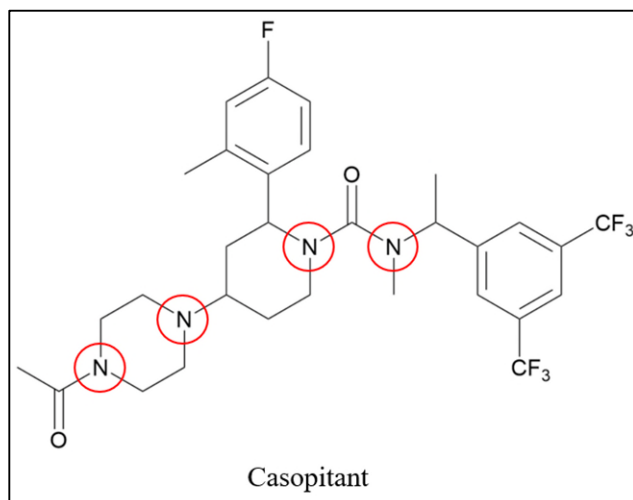
5. (c) administering to said patient on day one a first dose of dexamethasone which is ineffective against chemotherapy induced nausea and vomiting (CINV) when administered alone, but effective against CINV when administered in combination with said netupitant,

Trento’826 defines dexamethasone’s standard minimum effective dose as 20 mg on day 1, and 16 mg (for HEC) or 0 mg (for MEC) on each of days 2-4. EX1001, 7:62-8:4; EX1009, ¶¶266-67; §VI above. Herrstedt teaches administering a day-1 first dose of dexamethasone less than 20 mg with a NK₁ antagonist. EX1010, 145-147. Indeed, Herrstedt teaches day-1 corticosteroids should be administered in a reduced amount—about 25% to 50% less than the 20 mg standard dose because metabolic interactions between dexamethasone and NK₁ antagonists require reducing the dexamethasone. EX1010, 147 (“Dexamethasone and methylprednisolone are sensitive to substrates of CYP3A4. The combination of aprepitant and oral dexamethasone results in a **two-time increase in the AUC of dexamethasone indicating an inhibition of aprepitant on dexamethasone**

metabolism. When methylprednisolone is given in combination with aprepitant the intravenous dose can be **reduced by 25%** and **the oral dose by 50%** to obtain the same exposure of methylprednisolone, when given without concomitant administration of aprepitant.”), 146 (“During the development of aprepitant, **it became clear that the dose of oral** (and to a minor degree intravenous) **corticosteroids had to be reduced** due to interaction at the cytochrome P450 (CYP) 3A4 enzyme system between corticosteroids and aprepitant.”); EX1009, ¶¶268-69.

Given aprepitant’s effect, a POSA would have monitored dexamethasone used with netupitant because evaluating such drug-drug interactions was well-known and routine in the field.

EX1009, ¶270. Indeed, Herrstedt warned of drug-drug interactions for antiemetic therapy. EX1010, 147 (“Risk of drug-drug interactions with the use of anti-emetics” due to



“concomitant treatment with supportive care drugs” should be evaluated).

Understanding drug metabolism provides necessary insight for evaluating drug-drug interactions; particularly cytochrome P450 (CYP) 3A4 (“CYP3A4”) enzyme-mediated metabolism because cytochrome P450 was known to metabolize more than half of clinically-used drugs and a variety of substrates sharing common structural features with aprepitant and netupitant, such as tertiary amines (shown in red circles), were known to inhibit CYP3A4. EX1009, ¶270.

Aprepitant was a known CYP3A4 substrate and inhibitor. EX1010, 147. Similarly, the NK₁ antagonist casopitant (above)—structurally similar to netupitant—was also a known CYP3A4 substrate and inhibitor, requiring a 40-50% reduction in dexamethasone when co-administered with oral casopitant. EX1009, ¶270. A POSA would have reasonably expected netupitant to act similarly on CYP3A4 and would have reduced dexamethasone accordingly. EX1009, ¶¶270-72. Any reduction from the standard day-1 20 mg dose satisfies claim 1.

6. (d) wherein said first dose of dexamethasone comprises from 50 to 70% of a minimum effective dose when administered alone against CINV;

As shown for element 1(c), Herrstedt teaches day-1 dexamethasone should be reduced—including by about 50%—compared to the standard 20 mg dose. EX1010, 146-47; EX1009, ¶¶273-75. Herrstedt thus teaches reducing day-1 oral

dexamethasone, when administered with an NK₁ antagonist, by about 50% to achieve the same effective AUC concentration.

7. (e) steps a b [sic] and (c) are effective to treat both nausea and vomiting during the period defined by days one through five; and

Herrstedt teaches or suggests each of claim 1's steps (a), (b), and (c) with Hoffmann suggesting netupitant. Herrstedt teaches these steps are effective to treat both nausea and vomiting over days 1-5. EX1010, 146 ("Four phase III trials have investigated the use of aprepitant in patients receiving cisplatin-based, highly emetogenic chemotherapy.... ***Complete response, defined as 'no emesis and no rescue therapy on days 1-5 postcisplatin,' was the primary end-point in all studies.*** Two of the HEC studies used...ondansetron, dexamethasone and aprepitant day 1 followed by dexamethasone days 2-4 plus aprepitant days 2-3. In the Hesketh study, a complete response of 72.7% in the aprepitant arm versus 53.3% in the control arm was seen[.]"). Herrstedt recommends the triple-therapy combination (5-HT₃ antagonist, dexamethasone, and NK₁ antagonist) "for ***prevention of acute and delayed nausea and vomiting.***" EX1010, 148 & Table 4 (MASCC guidelines). The acute phase (0-24 hours) and delayed phase (24-120 hours) constitutes all five days. EX1010, 143; EX1009, ¶¶276-78.

8. (f) steps (a), (b) and (c) are effective to treat both nausea and vomiting to a greater extent during the period defined by days one through five than steps (b) and (c) alone.

Herrstedt teaches the triple therapy (with a NK₁ antagonist) is a more effective than without. EX1010, 146 (“Complete response, defined as ‘no emesis and no rescue therapy on days 1-5 postcisplatin,’ was the primary end-point in all studies. Two of the HEC studies used an identical design comparing *ondansetron [5-HT₃ antagonist]*, *dexamethasone [corticosteroid]*, and *placebo* day 1 followed by dexamethasone plus placebo days 2-4 with *ondansetron, dexamethasone and aprepitant [NK₁ antagonist]* day 1 followed by dexamethasone days 2-4 plus aprepitant days 2-3. In the Hesketh study, *a complete response of 72.7% in the aprepitant arm versus 52.3% in the control arm was seen*, and in the Poli-Bigelli study complete response rates were 62.7% versus 43.3%. The most recently published HEC study used the same design, except that ondansetron was included in the control arm for delayed protection days 2-4. Again a *statistical[] benefit favouring aprepitant was seen*, resulting in a complete response in the aprepitant arm of 72.0% versus 60.6% in the control arm.”) (parentheticals omitted). A POSA would have known adding a NK₁ antagonist increased overall efficacy. EX1009, ¶¶279-80; EX1010, 148 (recommending the triple therapy for treating HEC to “prevent[] of *acute and delayed nausea and vomiting*.”), Table 4 (MASCC recommendations). Because each drug in the combination targets an additional

mechanism, a POSA had ample reason to combine the medications and reasonably expect success preventing both acute- and delayed-phase CINV. EX1009, ¶¶280-83.

B. Claim 2: “further comprising: d) administering to said patient, on days two, three and four, a second dose of dexamethasone which is ineffective against vomiting when administered alone against vomiting, but effective against vomiting when administered in combination with steps (a) and (b), wherein said second dose comprises from 40 to 60% of a minimum effective dose when administered alone against vomiting.”

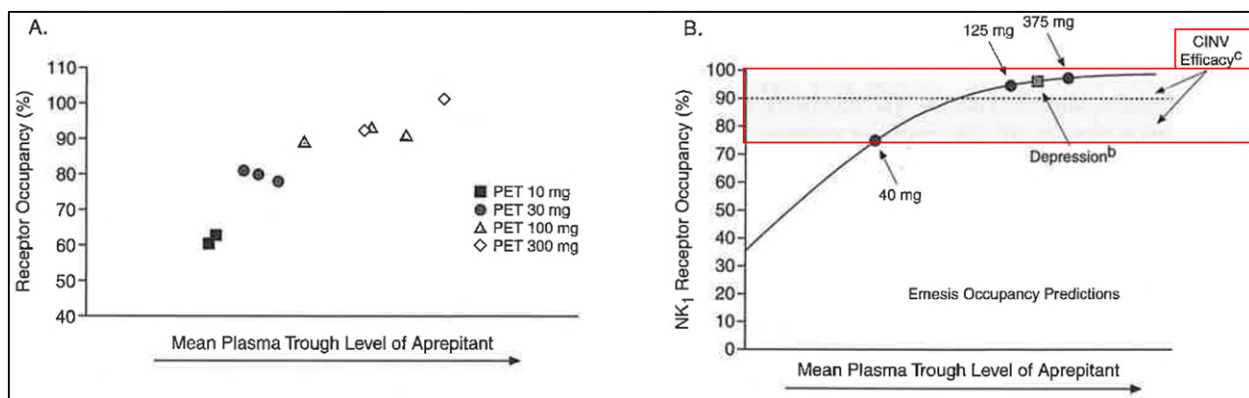
Herrstedt teaches administering dexamethasone on days 2-4. EX1010, 146 (“Two of the HEC studies used an identical design comparing ondansetron, dexamethasone and placebo day 1 followed by *dexamethasone* plus placebo *days 2-4* with ondansetron, dexamethasone and aprepitant day 1 followed by *dexamethasone days 2-4* plus aprepitant days 2-3.... The most recently published HEC study used *the same design*, except that ondansetron was included in the control arm for delayed protection days 2-4.”). Herrstedt suggests additional dexamethasone doses alone are ineffective against vomiting, but effective when combined with NK₁ antagonist and 5-HT₃ antagonist. EX1010, 147-48; EX1009, ¶¶284-87; §A.5 above. Herrstedt also teaches an effective amount of NK₁ antagonist during subsequent days; for example, when aprepitant is used as the NK₁ antagonist, it is dosed on days 2-3. EX1010, 146. Netupitant was known to have increased receptor affinity and associated increased half-life, so a POSA had

good reason to administer doses of dexamethasone on days two, three, and four in a reduced amount of about 50% to account for netupitant's continuing presence.

EX1009, ¶¶288-90.

C. Claim 3: “wherein said netupitant occupies at least 80% of NK receptors in the striatum seventy-two hours after said administration.”

Hargreaves teaches NK₁ antagonists occupy at least 80% of striatum NK₁ receptors, due to the direct relationship between CNS NK₁-receptor occupancy and antiemetic effects. EX1012, 23 (“On the basis of these findings, a plasma concentration vs. receptor occupancy relationship was established (Figure 6A). The data suggest that a trough concentration following treatment with the 10-mg dose of aprepitant corresponds to approximately 60% receptor occupancy, whereas *the occupancy of ≥ 90% of NK₁ receptors* requires aprepitant doses ≥ 100 mg. Curve fitting to the plasma concentration—receptor occupancy curves showed that *high levels of NK₁ receptor occupancy were associated with ... optimal activity against CINV*. ...the initial 125-mg dose studied for treatment of *emesis blocked ≥ 90% of NK₁ receptors* in the CNS (Figure 6B), whereas *the* initial 40-mg dose used in the study of emesis resulted in lower (75%) receptor occupancy (Figure 6B) [below, CINV efficacy in red box].”).



Hargreaves Fig. 6B teaches “CINV Efficacy” occurs in a grayed-out region beginning at approximately 75% of NK₁-receptor occupancy; thus, an optimally-effective amount of NK₁ antagonist is one that occupies high levels (greater than 75% and preferably greater than 90%) of striatum NK₁ receptors. EX1009, ¶¶290-93.

Trento’826 identifies no criticality for 80% occupancy, but Hargreaves suggests it by defining an optimally-effective dose in terms of NK₁-receptor occupancy of at least 75% and preferably 90%. During examination of a related application, the examiner found (and Helsinn did not rebut) that high occupancy was inherent for a therapeutically-effective amount of netupitant and satisfies the “at least 80%” occupancy limitation. EX1008, 120; EX1009, ¶¶294-96; §XII.A.3 above. Seventy-two hours falls squarely within the five days and reflects netupitant’s known prolonged half-life. EX1009, ¶294. Trento’826 also indicates high occupancy is a characteristic of netupitant itself. EX1001, 4:37-51 (“netupitant binds to NK₁ receptors in the striatum in a long-lasting manner, and []

less than 20 or 30% of netupitant is release from striatum NK₁ receptors even ninety-six hours after administration.”).

D. Claim 8: “wherein said therapeutically minimum effective dose of dexamethasone when administered alone comprises from about 16 mg to about 20 mg of dexamethasone.”

Herrstedt confirms the standard dose for dexamethasone used without an NK₁ antagonist is about 20 mg. EX1010, 145 (“In patients receiving cisplatin-based, highly emetogenic chemotherapy (HEC), a single intravenous dose [of dexamethasone] of 20 mg is superior to lower doses....”). Trento’826 defines the minimum effective dose of dexamethasone as 20 mg on day 1, and 16 mg (for HEC) on subsequent days, citing the prior art. EX1009, ¶¶297-300; §VI above.

E. Claim 9: “wherein only one dose of said palonosetron or a pharmaceutically acceptable salt thereof is administered during said five days.”

Herrstedt teaches administering only one dose of 5-HT₃ antagonist during days 1-5. EX1010, 146 (“Complete response, defined as ‘no emesis and no rescue therapy on **days 1–5 postcisplatin**’, was the primary end-point in all studies. Two of the HEC studies used an identical design comparing **ondansetron**, dexamethasone and placebo **day 1** followed by dexamethasone plus placebo days 2-4 with **ondansetron**, dexamethasone and aprepitant **day 1** followed by dexamethasone days 2-4 plus aprepitant days 2-3.”). Herrstedt teaches single-dose administration of 5-HT₃ antagonist is the norm. EX1010, 145-46 (“Ondansetron

and granisetron were initially developed as 8 mg t.i.d. and 3 mg plus up to two additional doses within the first 24 hr after chemotherapy, respectively. ***Today, all these agents are primarily used as a single oral or intravenous dose....*** Originally ondansetron and granisetron were prescribed for up to 5 days after chemotherapy, but it is now recognized that the 5-HT₃-receptor antagonists are primarily effective in the prophylaxis of acute emesis with limited or no efficacy in delayed emesis. ***Palonosetron might be an exception and it has been approved by the Food and Drug Administration*** (but not by the European Medicines Agency) ***in the treatment of delayed emesis*** from MEC.”), Table 3 (showing palonosetron’s half-life is greater than other 5-HT₃ antagonists by an order of magnitude). Hence, a POSA had good reason to administer only one palonosetron dose during days 1-5. EX1009, ¶¶301-05.

F. Claim 10: “wherein said therapeutically effective amount of palonosetron or pharmaceutically acceptable salt thereof is from about 0.25 to about 0.75 mg based on the weight of the free base.”

Herrstedt teaches administering a 0.25 mg intravenous dose of palonosetron free base. EX1010, Table 3 (palonosetron 0.25 mg intravenously); EX1009, ¶¶306-09.

G. Claim 15: “wherein said nausea and vomiting is chemotherapy induced nausea and vomiting (‘CINV’), radiation therapy induced nausea and vomiting (‘RINV’), or post-operative nausea and vomiting (‘PONV’).”

Herrstedt teaches using a triple-drug combination for treating CINV.

EX1010, 146 (“Four phase III trials have investigated the use of aprepitant in patients receiving *cisplatin-based, highly emetogenic chemotherapy* or a combination of cyclophosphamide plus an anthracycline. Complete response, defined as ‘*no emesis and no rescue therapy* on days 1-5 postcisplatin’, was the primary end-point in all studies.”). Herrstedt generally reports on “treatment of nausea and vomiting from chemotherapy.” EX1010, Abstract; EX1009, ¶¶310-13.

H. Claim 16: “wherein said nausea and vomiting is induced by moderately or highly emetogenic chemotherapy.”

Herrstedt teaches treating “cisplatin-based, highly emetogenic chemotherapy” and MEC. EX1010, 146; EX1009, ¶¶314-17. The claim is drafted in the alternative so either HEC or MEC is sufficient.

I. Claim 17: “comprising administering moderately or highly emetogenic chemotherapy within from about one hour to about two hours of said administration of said netupitant or pharmaceutically acceptable salt thereof.”

Herrstedt discloses administering MEC or HEC after administering NK₁ antagonist, with Hoffmann suggesting using netupitant. §XII.A above. Herrstedt discusses two triple-drug studies, Poli-Bigelli and Hesketh. EX1010, 146. A POSA would have known that in both studies chemotherapy was administered 1-2 hours

after the NK₁ antagonist, which is the usual practice. EX1009, ¶¶318-22; *In re Baxter Travenol Labs.*, 952 F.2d 388, 390 (Fed. Cir. 1991) (“[E]xtrinsic evidence may be considered when it is used to explain, but not expand, the meaning of a reference.”).

J. Claim 18: “comprising treating nausea and vomiting in response to highly emetogenic chemotherapy during the acute phase, or in response to highly emetogenic chemotherapy during the delayed phase, or in response to moderately emetogenic chemotherapy during the acute phase, or in response to moderately emetogenic chemotherapy during the delayed phase.”

Because claim 18 is drafted in the alternative, treating either acute- or delayed-phase CINV for either HEC or MEC is sufficient. Herrstedt discloses treating nausea and vomiting following HEC. EX1010, 146 (“cisplatin-based, highly emetogenic chemotherapy”). Herrstedt also teaches attaining a “complete response”, which covers both acute- and delayed-phase CINV. EX1010, 146 (“Complete response, defined as ‘no emesis and no rescue therapy on days 1-5 postcisplatin’, was the primary end-point in all studies.”), 143; EX1009, ¶¶323-28.

K. Claim 24: “wherein said netupitant or pharmaceutically acceptable salt thereof and said palonosetron or pharmaceutically acceptable salt thereof are synergistically effective to antagonize NK1 activity.”

Trento’826 does not define *synergistically effective*. EX1009, ¶329, see §VI above. Helsinn conceded this undisclosed synergistic effect would always occur. EX1008, 186 (“At *all* concentrations where the netupitant and palonosetron have an

effect on the EC50 of substance P, they have a synergistic effect when combined.”); EX1009, ¶329. Post-filing publications confirm palonosetron has “synergistic” effect with NK₁ antagonists generally because palonosetron uniquely (for 5-HT₃ antagonists) indirectly affects NK₁ receptors as well and thus would “synergistically” work with other NK₁ antagonists too. EX1009, ¶¶330-32. Hence, this “synergy” is an inherent, not unexpected, result.

L. Obvious to Combine and Reasonably Expect Success

By the critical date, a POSA had good reason to treat acute and delayed CINV following MEC or HEC with Herrstedt’s triple-antiemetic combination therapy, substituting new, improved NK₁ and 5-HT₃ antagonists. Herrstedt describes the three-drug combination administered on day 1 yielded superior response rates (complete response) compared to the combination lacking NK₁ antagonist. EX1010, 146 (“Again a statistical[] benefit favouring aprepitant was seen, resulting in a complete response in the aprepitant arm of 72.0% versus 60.6% in the control arm (P = 0.003).”); EX1009, ¶¶333-39. The POSA would have enhanced the efficacy of Herrstedt’s antiemetic combination with new, improved drugs targeting the same mechanistic pathways. Palonosetron was known to have an order of magnitude half-life greater than ondansetron. EX1010, 146 & Table 3 (palonosetron half-life 38-40 hours; ondansetron half-life 4-6 hours). Plus, palonosetron was available in an oral formulation (0.56 mg palonosetron HCl).

EX1015. The POSA had reason to administer oral palonosetron HCl as the 5-HT₃ antagonist for ease to both patient and practitioner, as well as for improved patient perception and comfort. EX1009, ¶335.

A POSA also had reason to modify Herrstedt’s triple therapy to include the improved NK₁ antagonist, netupitant. The POSA would have sought the enhanced efficacy of Herrstedt’s antiemetic combination with new, improved drugs targeting the same mechanistic pathway—NK₁-receptor antagonism. As Hoffmann explains, netupitant “potently inhibit[s] NK₁ agonist-induced foot tapping...after oral administration”, which indicates successful NK₁ antagonism, and netupitant has “[e]xcellent oral antagonist activity.” EX1011, 1364-1365; EX1009, ¶336.

To determine a minimum-effective dose, a POSA had good reason to consider NK₁-receptor occupancy. Hargreaves teaches administering NK₁ antagonist in an amount that occupies at least about 75% of striatum NK₁ receptors. EX1012, 23 & Fig. 6(B); EX1009, ¶¶337-39; *see also id.*, ¶¶340-43 (combination reasonably expected to succeed).

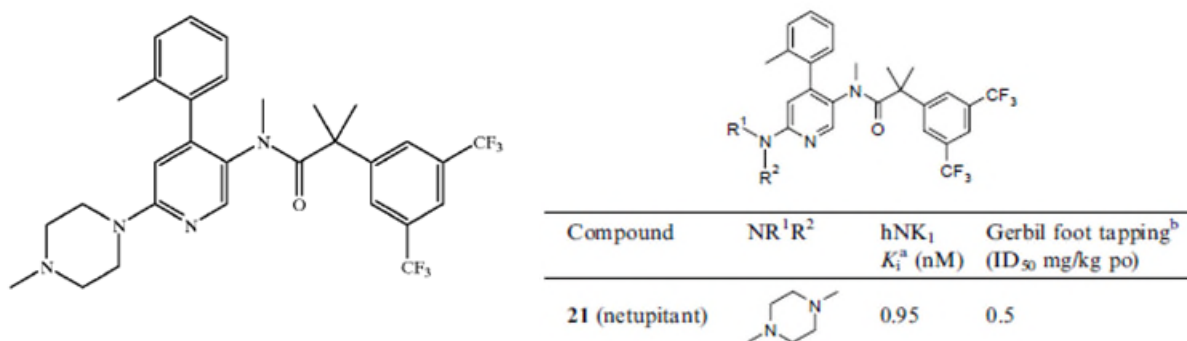
XIII. GROUND 5: CLAIMS 1-3, 6-10, 15-18, AND 24—OBVIOUS OVER HERRSTEDT, BÖS, AND HARGREAVES

A. Claims 1-3, 8-10, 15-18, and 24

Claims 1-3, 8-10, 15-18, and 24 were obvious over the combined teachings of Herrstedt, Bös, and Hargreaves for the reasons provided in Ground 4 except with Bös teaching netupitant as the NK₁ antagonist, as in Ground 2, instead of

Hoffmann. EX1009, ¶¶344-97, 412-53.

Bös teaches its “Formula Ib” (netupitant) is an improved NK₁ antagonist. EX1014, 14:31-38 (“The compound of formula Ib and its salts is also characterized by *valuable therapeutic properties* as a *highly selective* antagonist of the Neurokinin 1 (NK-1, substance P)”). Bös evaluated formula Ib’s affinity for human NK₁ receptors and determined it is “a potent and selective antagonist.” EX1014, 17:61-18:48; *see also id.*, 18:60-63 (“a competitive antagonist at human recombinant NK₁ receptors”); *id.*, 19:26-30 (“a potent antagonist of NK₁ induced behaviours in gerbil and blocks emesis in ferrets ... with similar potency.”). A POSA would have known Bös formula Ib was netupitant. EX1009, ¶¶346-48, comparing Bös’ formula Ib (below, left) and Hoffmann’s netupitant (below, right):



B. Claims 6 (200-400 mg netupitant) and 7 (300 mg free base)

Claim 6 further requires “wherein said therapeutically effective amount of netupitant comprises from about 200 to about 400 mg of netupitant or a pharmaceutically acceptable salt thereof.” Claim 7 further requires the same but with “about 300 mg of netupitant as a free base.” The claims are similar except

claim 6 permits a netupitant salt and provides a dose range of about 200 to about 400 mg, while claim 7 is limited to 300 mg of netupitant free base.

Bös teaches a therapeutically-effective amount of NK₁ antagonist—including netupitant—selected from a range encompassing the claimed amounts. EX1014, 42:5-11 (“The effective amount for the dosage can vary within wide limits and will, of course, be fitted to the individual requirements in each particular case. In general, in the case of oral administration a daily *dosage of about 10 to 1000 mg* per person of a compound of this invention should be appropriate, although the above upper limit can also be exceeded when necessary.”).

Trento’826 does not identify any criticality for doses at 200, 300, or 400 mg, and optimization within a range is routine. *Urbanski*, 809 F.3d at 1242 (routine to optimize result-effective variable). Optimizing to a range of 200-400 mg or to 300 mg would have been obvious for the reasons given for claims 20-21 in Grounds 2 and 3. §§X.B, XI.B above; EX1009, ¶¶389-411. Bös teaches both compounds and pharmaceutically acceptable salts. EX1014, 14:9-30; *see also* EX1009, ¶¶446-52 (POSA had reason to combine with reasonable expectation of success).

XIV. GROUND 6: CLAIMS 4-5—OBVIOUS OVER HERRSTEDT, BÖS, HARGREAVES, AND HERRINGTON

Claims 4 and 5 both require only a single dose of netupitant (or its salt) during the 5-day treatment. Claim 5 further requires the dose to be administered

orally. EX1001, 22:8-10 (“4. The method of claim 1, wherein only one dose of netupitant or a pharmaceutically acceptable salt thereof is administered during said five days.”), 22:11-14 (“5. The method of claim 1, wherein only one dose of netupitant or a pharmaceutically acceptable salt thereof is administered during said five days, and said one dose is administered orally.”); EX1009, ¶¶454-56, 462-63.

Herrington compares single-dose aprepitant to multi-dose aprepitant and teaches single-dose aprepitant provides similar effectiveness to Herrstedt’s repeated dosing of aprepitant. EX1016, Background (“The purpose of this pilot study was to ***ascertain the effectiveness of 1-day versus 3-day aprepitant*** in the prevention of acute and delayed nausea and vomiting in patients who were receiving highly emetogenic chemotherapy.... From this pilot study of patients who were receiving palonosetron, aprepitant, and dexamethasone for highly emetogenic chemotherapy, a ***single dose of aprepitant displayed similar effectiveness compared with 3-day aprepitant.***”). A POSA would have understood that day-1, single-administration of NK₁ antagonist was similarly effective to Herrstedt’s dosing protocol administering NK₁ antagonist over multiple days, and had reason to use a single dose for increased simplicity and ease of patient compliance. EX1009, ¶¶458-59. Moreover, Bös teaches oral netupitant had a long half-life. EX1014, 19:3-10 (functional half-life of 30 hours). Because netupitant has a long half-life, substituting Bös’ netupitant for Herrstedt’s aprepitant provides

further reason for omitting subsequent administrations of NK₁ antagonist. EX1009, ¶460-61, 464-66.

XV. GROUND 7: CLAIMS 10-14—OBVIOUS OVER HERRSTEDT, BÖS, HARGREAVES, AND ALOXI

Claims 10-14 were obvious, particularly with ALOXI's additional teachings. EX1009, ¶¶471-72.

A. Claim 10: “wherein said therapeutically effective amount of palonosetron or pharmaceutically acceptable salt thereof is from about 0.25 to about 0.75 mg based on the weight of the free base.”

B. Claim 11: “wherein said palonosetron is administered as palonosetron hydrochloride, and said therapeutically effective amount of said palonosetron hydrochloride is about 0.56 mg of palonosetron hydrochloride, corresponding to about 0.5 mg of palonosetron as a free base.”

Herrstedt discloses a therapeutically-effective amount of palonosetron is within the range of about 0.25 to about 0.75 mg based on the weight of the free base. EX1010, Table 3; EX1009, ¶¶473-75. ALOXI teaches doses from 0.25 mg to 0.75 mg of palonosetron free base. EX1015 (testing 0.25 mg, 0.5 mg, and 0.75 mg palonosetron). ALOXI also teaches palonosetron HCl capsules for antiemetic treatment containing 0.56 mg palonosetron HCl, corresponding with 0.50 mg of palonosetron free base. EX1015, 3; EX1009, ¶476.

ALOXI discloses capsules contained 0.56 mg palonosetron HCl (corresponding to 0.5 mg of palonosetron free base) formulated for oral administration for preventing acute nausea and vomiting following initial and

repeat courses of MEC. EX1015, 1-4, 3 (“Each light beige opaque soft gelatin ALOXI Capsule ***contains 0.56 mg of palonosetron HCl*** equivalent to palonosetron 0.5 mg.”). A POSA had good reason to use FDA-approved 0.56 mg palonosetron HCl as the therapeutically-effective amount of palonosetron and reasonably expect success. EX1009, ¶¶476-77. Note Trento’826 does not ascribe any critical or unexpected results to the 0.56 mg dose of palonosetron hydrochloride. EX1009, ¶481.

C. Claim 12: “wherein said palonosetron is administered orally.”

ALOXI teaches administering palonosetron orally as a capsule of palonosetron HCl for treatment of emetogenic chemotherapy. EX1015, 1, 4. Orally administered palonosetron HCl had near equivalency to intravenously administered palonosetron. *Id.* (“Efficacy was based on demonstrating non-inferiority of oral palonosetron doses compared to the approved I.V. formulation.... [F]or the 20 to 120 hour time period, non-inferiority was not shown.”). The POSA would have reasonably expected success in achieving the therapeutic effect using ALOXI’s FDA-approved orally-administered palonosetron HCl in Herrstedt’s triple therapy combination. EX1009, ¶¶483-87.

D. Claim 13: “comprising orally administering: a) about 300 mg of netupitant as a free base on day one; b) about 0.56 mg of palonosetron hydrochloride, corresponding to about 0.5 mg of palonosetron as a free base, on day one; and c) about 12 mg of dexamethasone on day one”

Bös suggests orally administering about 300 mg of netupitant as a free base, by teaching oral administration of NK₁ antagonists including netupitant in a dose range including 300 mg of netupitant as a free base. EX1009, ¶475; §XIII.B above. Herrstedt teaches a triple-combination therapy in which the NK₁ antagonist is administered on day 1. EX1010, 146. A POSA had good reason to administer Bös’ netupitant on day one in Herrstedt’s therapy so the therapeutic agent could begin to take effect prior to administration of the emetogenic chemotherapy. EX1009, ¶¶488-90. This dosing protocol was consistent with other NK₁ antagonists. EX1010, 146.

ALOXI teaches orally administering palonosetron in a dose of about 0.56 mg of palonosetron hydrochloride, corresponding to about 0.5 mg of palonosetron as a free base, on day 1. EX1009, ¶491; EX1015, 1.

Herrstedt teaches orally administering dexamethasone with the NK₁ antagonist and 5-HT₃ antagonist; for example, Herrstedt provides a summary of two studies employing the triple antiemetic drug combination. EX1010, 146; EX1009, ¶492. A POSA would have understood that in Herrstedt, 12 mg dexamethasone was orally administered on day 1. EX1009, ¶¶492-93.

E. Claim 14: “comprising orally administering: a) about 300 mg of netupitant as a free base on day one; b) about 0.56 mg of palonosetron hydrochloride, corresponding to about 0.5 mg of palonosetron as a free base, on day one; c) about 12 mg of dexamethasone on day one; and d) about 8 mg of dexamethasone on days two, three and four.”

Building from the obviousness of claims 1 and 13, claim 14 adds an 8 mg dose of dexamethasone on days 2-4. Herrstedt discloses orally administering dexamethasone with the NK₁ antagonist and 5-HT₃ antagonist. Herrstedt summarizes two studies testing this triple antiemetic drug combination. A POSA reviewing Herrstedt would have understood to disclose orally administering 8 mg dexamethasone on days two, three and four. EX1009, ¶¶494-98.

A POSA had ample reason to use ALOXI’s FDA-approved orally-administered capsule of palonosetron HCl to provide antiemetic effect after emetogenic chemotherapy. EX1015, 2-4; EX1009, ¶¶499-503.

XVI. NO SECONDARY CONSIDERATIONS

Although Helsinn asserts unexpected properties for netupitant, aprepitant had these properties. An expected result is the opposite of an unexpected result. *In re Skoll*, 523 F.2d 1392, 1397 (CCPA 1975) (“Expected beneficial results are evidence of obviousness of a claimed invention, just as unexpected beneficial results are evidence of unobviousness.”). In any case, “the expected properties of a claimed compound may be sufficient to lead to a reasonable expectation of success in modifying a prior art compound to make that claimed compound.” *Bristol-*

Myers Squibb v. Teva Pharms., 752 F.3d 967, 976 (Fed. Cir. 2014).

A. Aprepitant Shows Efficacy for Nausea

During examination for Trento’826, Helsinn sought to distinguish netupitant from aprepitant. Helsinn contended “aprepitant’s effect was limited principally to vomiting, not nausea, and that aprepitant did not provide as much benefit during the acute phase of CINV.” EX1001, 2:12-26. Trento’826 alleges “it has unexpectedly been discovered that netupitant is active against nausea” EX1001, 4:37-39. Helsinn also argued the prior art “did not distinguish between vomiting and nausea as separate therapeutic targets, and instead lumped them together as one indication commonly referred to as CINV.” EX1005, 328-39. Helsinn sought to distinguish methods using netupitant (in substitution for aprepitant) because “the claimed regimen treats both nausea and vomiting.” EX1005, 330.

Similarly, during examination for Trento’297 patent, Helsinn alleged unexpected results for a netupitant-palonosetron combination versus aprepitant because, in its selected aprepitant trials, “in none of these trials was aprepitant able to demonstrate a statistically significant effect against nausea or significant nausea. This was true throughout the acute and delayed phases of emesis, and it was true regardless of whether moderately emetogenic chemotherapy (MEC) or highly emetogenic chemotherapy (HEC) was administered.” EX1008, 181. Helsinn asserted a POSA “would not have had a reasonable expectation of successfully

treating nausea from the combination of netupitant and palonosetron” because aprepitant allegedly did not provide such effect. EX1008, 181-182. Despite Helsinn’s representations to the examiner, however, experimental data shows a POSA knew aprepitant treats nausea effectively. EX1009, ¶¶1329-32.

1. Emend label

The common specification reports the Emend label shows “[w]hen tested against nausea in humans, aprepitant was unable to induce a significant reduction in the incidence or severity of nausea following moderately or highly emetogenic chemotherapy when compared to 5-HT₃ antagonist alone.” EX1001, 2:4-26. During examination, Helsinn reproduced Emend label snippets to argue aprepitant “did not achieve statistically significant reduction in either nausea or significant nausea[.]” EX1005, 330. Yet the Emend label shows reduction of nausea, particularly significant nausea. EX1009, ¶¶1333-34. Statistical significance was not calculated for nausea parameters, but “***complete protection***” *includes* a lack of significant nausea. EX1030 (Emend label), 7 (“***complete protection*** (defined as no emetic episodes, no use of rescue therapy, ***and a maximum nausea visual analogue scale [VAS] score <25 mm*** on a 0 to 100 mm scale)”). Hence, for “***complete protection***,” the Emend label requires (1) ***no*** emetic episodes; (2) ***no*** rescue therapy; ***and*** (3) ***no significant nausea***. EX1009, ¶1334. Emend’s Table 1, which shows results of the first of two studies the label describes, indicates

substantial improvement in ***complete protection*** for overall, acute phase, and delayed phase parameters, and identifies the delayed phase and overall parameters were also statistically significant. EX1009, ¶1334. Although not calculated for statistical significance, a POSA would have recognized improved treatment of nausea, particularly significant nausea. EX1030, Table 1 (e.g., 66% → 73% overall in significant nausea). This was true during the delayed phase as well as overall (which includes acute and delayed phases). EX1009, ¶1335.

Emend shows similar benefits in a second study, which reports “***complete protection***” with statistical significance for ***each of*** the overall, acute phase, and delayed phases. EX1009, ¶1336. Emend also reports “[i]n each of the 2 studies, a higher proportion of patients receiving the aprepitant regimen reported minimal or no impact of nausea and vomiting on daily life (Study 1: 74% versus 64%; Study 2: 75% versus 64%).” EX1030, 6. Patients reported significant improvement in their daily lives due to less nausea and vomiting versus a treatment group without aprepitant. EX1009, ¶¶1337-40.

2. Trento’826 Example 5

Despite Helsinn’s representations, Example 5 (EX1001, 16:62-19:43) shows aprepitant’s effect on nausea is comparable to netupitant. Data in Table 6 corresponds to columns 1, 2, and 6 of Table 2 from Helsinn’s Rule 132 Declaration and shows Helsinn misleadingly excised information from Table 6’s larger data

set. EX1009, ¶1341 (acute and delayed values missing from Declaration Table 2).

The patents' Example 5 was never designed to compare netupitant against aprepitant—and never alleges any benefits of netupitant versus aprepitant.

EX1009, ¶1342. The Helsinn declaration data compared ***the highest dose of netupitant*** with palonosetron (EX1001, Table 6, “Palo + Netu 300 mg” column) with an aprepitant and ondansetron combination (*id.*, “Aprepitant Regimen” column), but even if a POSA assumed these data sets were comparable, they show—at best—only marginal improvement for the ***highest netupitant dose*** versus a ***standard*** aprepitant combination in treating nausea. EX1009, ¶1343. Indeed, the patent data shows aprepitant actually had ***improved*** anti-nausea effect versus lower netupitant doses (a comparably-sized day 1 dose as given for aprepitant). EX1009, ¶1344. Significantly, most claims do not specify a netupitant dose amount, much less the highest dose, and aprepitant often performed better than netupitant. EX1009, ¶¶1344-45.

Table 6's “Palo + Aprep” data is not comparable with any of the other columns, and thus cannot show any surprising results or particular benefit for netupitant versus aprepitant because the data comes from a study with a significantly different design such that comparison would overstate netupitant's antiemetic effect versus aprepitant in the combination. EX1009, ¶¶1345-51.

3. Campos

Helsinn alleged “aprepitant’s effect was limited principally to vomiting, *not nausea*, and that aprepitant *did not provide as much benefit during the acute phase* [i.e., 0-24 hours] of CINV.” EX1001, 2:12-15. Yet Campos discloses aprepitant’s beneficial effect for *nausea* and shows it provided significant additive benefit during the acute phase of CINV. EX1009, ¶1352; EX1023, Abstract, 1763 & Table 4. Campos teaches a triple therapy (5-HT₃ antagonist, dexamethasone, plus aprepitant) provides “nausea ratings [that] were significantly lower” in “the first 24 hours rank analysis” compared to 5-HT₃ antagonist plus dexamethasone. EX1023, 1763. Campos also explains median nausea scores were lower with the triple therapy in the delayed phase (days 2-5). EX1023, 1763-1764; EX1009, ¶1353. What Helsinn told the examiner was wrong: a POSA knew aprepitant provides a beneficial effect for nausea, including specifically therapeutic effect preventing acute-phase nausea CINV. EX1009, ¶1354. Post-critical date data add further confirmation. EX1009, ¶¶1355-59.

B. Data misrepresented during examination

Helsinn responded to an obviousness rejection with a declaration that exaggerates the difference between its triple therapy of netupitant, palonosetron, and dexamethasone versus the prior-art combination. EX1009, ¶1360.

1. Differences Between the Declaration and Helsinn's Arguments

Helsinn told the examiner a POSA “would not have expected netupitant to successfully treat nausea because aprepitant – the only other NK₁ antagonist approved for CINV, and the NK₁ antagonist that allegedly supports the examiner’s prima facie case of obviousness – was ***unable to demonstrate a statistically significant effect on nausea*** in its clinical trials.” But the Emend label, the specifications’ own data, prior art, and post-critical date references ***all*** indicate aprepitant has a substantial effect on nausea. EX1009, ¶1361. Helsinn’s response also asserted it reproduced a “table [that] is taken from the 132 Declaration...filed concurrently” but materially altered the table without noting alterations that skewed the data in Helsinn’s favor. EX1009, ¶¶1362-63. Helsinn’s alterations falsely suggested combining netupitant with palonosetron was more effective than other combinations. EX1009, ¶¶1363-64.

2. Helsinn’s Data During Examination Was Lacking

a. Internal Helsinn Studies (Columns 1-3)

Helsinn never provided the examiner with underlying data for any palonosetron-netupitant combination, yet relied on its own internal studies. EX1005, 346; EX1009, ¶1365. A POSA would not rely on Helsinn’s studies without seeing the underlying data. EX1009, ¶1366.

b. Ondansetron-Aprepitant MEC Studies (Columns 4 and 7)

Helsinn’s Rule 132 Declaration excluded data from the studies it summarized when the data showed a similar effect for ondansetron and aprepitant versus netupitant and palonosetron, and instead indicated the data was “not reported.” EX1009, ¶¶1367-68. For example, excluded data showed substantially similar results, particularly for significant nausea, in MEC patients receiving either aprepitant-ondansetron or netupitant-palonosetron; indeed, during the acute phase, aprepitant showed a slight **improvement** compared to Helsinn’s netupitant study. EX1009, ¶1369. This withheld data confirms Helsinn’s unexpected results for the combination of netupitant and palonosetron are illusory—not unexpectedly beneficial or surprising. EX1009, ¶1370.

c. FDA-Approved Prescribing Information for Emend (Column 4a)

The Emend label shows aprepitant prevents nausea for HEC patients, yet Helsinn’s Rule 132 Declaration does not include Emend’s “**complete protection**” data, despite this parameter requiring evaluation of significant nausea. EX1009, ¶¶1371-72. A POSA knew **complete protection** incorporates an evaluation of no significant nausea, which was reported with statistical significance. EX1009, ¶1373.

d. Grunberg (Column 6)

The common specification contends aprepitant-palonosetron “were far from promising” due to “the results reported in Grunberg.” EX1001, 2:25-28 (citing EX1035 (Grunberg)). Yet both Helsinn’s common specification and Declaration masked substantial, material differences in dosing across cohorts, which render Grunberg incomparable to the Helsinn internal studies. EX1009, ¶1374. For example, in Grunberg, participants could receive additional chemotherapy, which would cause additional emesis. EX1035 (Grunberg), 591; EX1009, ¶1375. Moreover, Grunberg administered dexamethasone only on the first day. EX1035, 590-591 (“Patients received aprepitant 285 mg p.o. and ***dexamethasone 20 mg*** p.o. 1 h prior and palonosetron 0.25 mg i.v. 30 min prior to scheduled Day 1 chemotherapy.”); *id.*, Abstract (“patients received *a single dose of* aprepitant...*dexamethasone*...and palonosetron”). In contrast, each of the specification’s other study groups received antiemetic dexamethasone on each of day one, day two, day three, *and* day four. EX1001, 17:19-64; EX1009, ¶¶1376-77. Each difference precludes direct comparison between Grunberg’s results and the specification’s results because such a flawed comparison would overstate the antiemetic effect of netupitant versus aprepitant. EX1009, ¶1378.

C. No Unexpected Synergy Between Netupitant and Palonosetron

The common specification contends “palonosetron is much more effective in

combinations with netupitant than it is in combination with aprepitant” and “palonosetron shows an improved pharmacokinetic profile...in combination with netupitant as opposed to palonosetron in single dose administration.” EX1001, 5:2-12. No such unexpected difference exists. EX1009, ¶¶1379-80.

The specification neither defines nor discusses “synergy” within the claims’ context or purported unexpected results. Synergy often indicates a combination has a greater benefit than the sum of its distinct parts. EX1009, ¶1381. Yet Helsinn’s own data show combining palonosetron with **any** NK₁ antagonist had a beneficial effect on nausea. Thus, if a synergistic effect existed, the data shows that such effect also occurs with the prior-art palonosetron-aprepitant combination. EX1009, ¶¶1382-85. Helsinn’s declarants contend they “observed an unanticipated statistically significant effect against nausea from the combination of netupitant and palonosetron that has not previously been observed in clinical studies involving the combination of...aprepitant with palonosetron.” EX1005, 345. However, even assuming Helsinn’s Table 2 data is accurate (it is hearsay), the data at most indicates a benefit from combining palonosetron with aprepitant *or* netupitant because the underlying values for nausea are substantially similar. A POSA would not have understood these data to show “an unanticipated statistically significant effect” only the netupitant-palonosetron combination. EX1009, ¶1386.

D. No Nexus Between Alleged Synergy and Claimed Effect

The examiner allowed Trento'826 solely because the "132 Declaration, filed 5/17/2013, affiant showing evidence of synergy (unexpected result) from the combination of netupitant and palonosetron *in regard to the claimed method.*" EX1005, 369. Yet Helsinn made no such showing. Any benefit observed with the netupitant-palonosetron combination is substantially the same as the aprepitant-palonosetron benefit; indeed, the data indicate a benefit from combining palonosetron with *any* NK₁ antagonist. EX1009, ¶¶1387-88. Moreover, most claims do not specify a dose, yet some palonosetron-aprepitant combinations outperform netupitant combinations. EX1009, ¶1389. In-vitro effects presented during examination (EX1005, 343-44 & Table 1) lack nexus with nausea. EX1009, ¶1390.

E. Single Dose of Netupitant Was Expected

During examination of a related patent, Helsinn argued unexpectedly "only a single dose of netupitant is required during the acute and delayed phases of emesis." EX1007, 203. The common specification makes a similar claim. EX1001, 4:38-42 ("unexpectedly been discovered...a single dose of netupitant is able to treat nausea and vomiting in response to highly and moderately emetogenic chemotherapy for five consecutive days"). Yet Herrington describes a single aprepitant dose is sufficient to treat acute- and delayed-phase emesis. EX1009,

¶¶1391-92; EX1016, Abstract, Table 3. From Herrington, a POSA would have also expected a single netupitant dose to provide therapeutic effect during acute- and delayed-phase emesis. EX1009, ¶1393.

F. Acute-Phase Treatment with Netupitant Was Expected

During examination of a related patent, Helsinn argued unexpectedly “netupitant also treats emesis during the acute phase”. EX1007, 203. Yet Herrstedt teaches NK₁ antagonists treat acute-phase emesis. EX1010, Abstract (“Aprepitant increases the effect of a serotonin₃-receptor antagonist plus a corticosteroid against *acute emesis* induced by highly or moderately emetogenic chemotherapy.”). Similarly, Hargreaves reports NK₁ antagonists “were recently shown to block emesis in animal models and to *prevent acute* and delayed chemotherapy-induced *nausea and vomiting* (CINV) in the clinic.” EX1012, 18. Other prior art shows the same. EX1009, ¶1395-96. From Bös, a POSA would have expected similar results for netupitant, a new NK₁ antagonist in the same class as aprepitant. EX1009, ¶1397.

G. Characteristics of Netupitant Were Expected

Helsinn’s patents present properties of netupitant—a prior-art compound—as allegedly unexpected. EX1001, 4:37-51, 5:13-20; EX1009, ¶¶1398-1400. Because netupitant was in the prior art, any asserted unexpected property cannot support patentability. *In re Baxter Travenol*, 952 F.2d 388, 392 (Fed. Cir. 1991)

(“Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention.”).

XVII. CONCLUSION

Claims 1-25 are unpatentable. Azurity respectfully requests these claims be canceled.

Respectfully submitted,

Dated: 1 May 2025

/Richard Torczon/

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

XVIII. PAYMENT OF FEES - §§42.15(a) AND 42.103

The required fees have been paid. If any additional fees are due at any time during this proceeding, the Office is authorized to charge such fees to Deposit Account No. 23-2415.

XIX. MANDATORY NOTICES - §42.8

A. Real Parties-In-Interest

Petitioner Azurity Pharmaceuticals, Inc. is the real party-in-interest. Helsinn Healthcare S.A. is the assignee of record for Trento'826.

B. Related Matters

Azurity is not aware of any pending related matter, except it has also petitioned for *inter partes* review of three more Helsinn patents:

9,186,357, IPR2025-00946 and IPR2025-00947, filed 1 May 2025;

9,943,515, IPR2025-00948, filed 1 May 2025; and

10,828,297, IPR2025-00949, filed 1 May 2025.

C. Lead and Back-up Counsel

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XX. EXHIBIT LIST - §42.63(e)

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

Exhibit	Description
1011	T. Hoffmann et al., <i>Design and synthesis of a novel, achiral class of highly potent and selective, orally active neurokinin-1 receptor antagonists</i> , 16 Bioorganic & Medicinal Chemistry Letters 1362-1365 (2006)
1012	R. Hargreaves, <i>Imaging Substance P Receptors (NK₁) in the Living Human Brain Using Positron Emission Tomography</i> , 63(11) J. Clinical Psychiatry 18-24 (2002)
1013	The Antiemetic Subcommittee of the Multinational Association of Supportive Care in Cancer (MASCC), <i>Prevention of chemotherapy- and radiotherapy-induced emesis: results of the 2004 Perugia International Antiemetic Consensus Conference</i> , 17 Annals of Oncology 20-28 (2006)
1014	M. Bös et al., <i>4-phenyl-pyridine derivatives</i> , U.S. Patent 6,297,375 B1 (issued 2 Oct. 2001)
1015	Eisai, Inc., ALOXI (palonosetron HCl) Capsules, package insert (Aug. 2008)
1016	J.D. Herrington et al., <i>Randomized, Placebo-controlled, Pilot Study Evaluating Aprepitant Single Dose Plus Palonosetron and Dexamethasone for the Prevention of Acute and Delayed Chemotherapy-induced Nausea and Vomiting</i> , 112 Cancer 2080 (2008).
1017	D. Bonadeo et al., <i>Soft Capsules Comprising Palonosetron Hydrochloride Having Improved Stability and Bioavailability</i> , PCT Publication WO 2008/049552 (published 2 May 2008)
1018	R.J. Gralla et al., <i>Recommendations for the use of antiemetics: evidence-based, clinical practice guidelines</i> , 17 Journal of Clinical Oncology 2971 (1999).

Exhibit	Description
1019	K. Jordan et al., <i>Guidelines for Antiemetic Treatment of Chemotherapy-Induced Nausea and Vomiting: Past, Present, and Future Recommendations</i> , 12 <i>The Oncologist</i> 1143-1150 (September 2007)
1020	Curriculum Vitae of Dr. Stephen J. Peroutka
1021	G.K. Reddy et al., <i>Novel Neurokinin-1 Antagonists as Antiemetics for the Treatment of Chemotherapy-Induced Emesis</i> , 3 <i>Support Cancer Therapy</i> 140-42 (2006).
1022	M.S. Aapro et al., <i>A phase III, double-blind, randomized trial of palonosetron compared with ondansetron in preventing chemotherapy-induced nausea and vomiting following highly emetogenic chemotherapy</i> , 17 <i>Annals of Oncology</i> 1441-49 (2006)
1023	D. Campos et al., <i>Prevention of cisplatin-induced emesis by the oral neurokinin-1 antagonist, MK-869, in combination with granisetron and dexamethasone or with dexamethasone alone</i> , 19(6) <i>Journal of Clinical Oncology</i> , 1759 (2001)
1024	A.E. Chang et al., eds., <i>Oncology: An Evidence-Based Approach</i> (2006)
1025	S.P. Chawla et al., <i>Establishing the Dose of the Oral NK₁ Antagonist Aprepitant for the Prevention of Chemotherapy-Induced Nausea and Vomiting</i> , 97 <i>Cancer</i> 2290 (2003).
1026	S.P. Chawla et al., <i>Establishing the Dose of the Oral NK₁ Antagonist Aprepitant for the Prevention of Chemotherapy-Induced Nausea and Vomiting</i> , 37th Annual Meeting of the American Society of Clinical Oncology, in 20 <i>Proceedings of ASCO</i> 383a (2001)

Exhibit	Description
1027	A. De Leon, <i>Palonosetron (Aloxi): a second-generation 5-HT₃ receptor antagonist for chemotherapy-induced nausea and vomiting</i> , in 19(4) Baylor University Medical Center Proceedings 413 (2006)
1028	R.A. Duffy, <i>Potential therapeutic targets for neurokinin-1 receptor antagonists</i> , 9(1) Expert opinion on emerging drugs, 9 (2004)
1029	Press Release, Eisai Co., FDA Approves ALOXI [®] (Palonosetron HCl) Capsules for Prevention of Acute Chemotherapy-induced Nausea and Vomiting (Aug. 24, 2008)
1030	Merck & Co., EMEND, package insert (2008)
1031	DailyMed, EMEND (aprepitant) Capsule, https://web.archive.org/web/20090202144735/http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=7355 (archived Feb. 2, 2009)
1032	U.S. Food and Drug Administration, General Considerations for the Clinical Evaluation of Drugs (1978)
1033	U.S. Food and Drug Administration, Q3A Impurities in New Drug Substances (2008)
1034	D.G. Warr et al., <i>Efficacy and tolerability of aprepitant for the prevention of chemotherapy-induced nausea and vomiting in patients with breast cancer after moderately emetogenic chemotherapy</i> , 23(12) Journal of Clinical Oncology 2822 (2005)
1035	S.M. Grunberg et al., <i>Effectiveness of a single-day three-drug regimen of dexamethasone, palonosetron, and aprepitant for the prevention of acute and delayed nausea and vomiting caused by moderately emetogenic chemotherapy</i> , 17 Supportive Care in Cancer 589 (2009)

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

Exhibit	Description
1043	R. Saito et al., <i>Roles of substance P and NK1 receptor in the brainstem in the development of emesis</i> , 91(2) Journal of Pharmacological Sciences 87 (2003)
1044	Ronald D. Schoenwald, <i>Pharmacokinetics in Drug Discovery and Development</i> (2002)
1045	A.G. Thomas, <i>Netupitant and palonosetron trigger NK1 receptor internalization in NG108-15 cells</i> , 232 Experimental Brain Research 2637 (2014)
1046	K.E. Thummel, <i>Gut instincts: CYP3A4 and intestinal drug metabolism</i> , 117(11) Journal of Clinical Investigation 3173 (2007)
1047	D.S. Wang, <i>Effect of aprepitant for the prevention of chemotherapy-induced nausea and vomiting in women: a randomized clinical trial</i> , 4(4) JAMA Network Open e215250 (2021)
1048	W. Yeo et al., <i>A randomized study of aprepitant, ondansetron and dexamethasone for chemotherapy-induced nausea and vomiting in Chinese breast cancer patients receiving moderately emetogenic chemotherapy</i> , 113 Breast Cancer Research and Treatment 529 (2009)
1049	S.F. Zhou, <i>Drugs Behave as Substrates, Inhibitors and Inducers of Human Cytochrome P450 3A4</i> , 9(4) Current Drug Metabolism 310 (2008)
1050	<i>Parenteral</i> , Merriam-Webster, https://www.merriam-webster.com/dictionary/parenterally
1051	NK1 receptor antagonist by Roche, <i>Advances in Drug Discovery</i> (Feb. 23, 2006), https://web.archive.org/web/20080215091703/http://leaddiscovery.blogs

Exhibit	Description
	pot.com/2006/02/nk1-receptor-antagonist-by-roche.html (archived Feb. 15, 2008)
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?archivedid=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

Exhibit	Description
1058	Drugs@FDA: FDA-Approved Drugs, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=022233
1059	P. Li & L. Zhao, <i>Developing Early Formulations: Practice and Perspective</i> , 341 International Journal of Pharmaceutics 1 (2007)
1060	G. Sanso, <i>Double capsule for the administration of active principles in multiple therapies</i> , U.S. Patent 6,350,468 B1 (issued 26 Feb. 2002)
1061	B. Cromie, <i>Drug Combinations</i> , 1(2) Current Medical Research and Opinion 78 (1972)

XXI. CERTIFICATIONS

A. Rule 42.24(d) Certification

Pursuant to 37 C.F.R. §42.24(d), the undersigned certifies that this Petition complies with the type-volume limitation of 37 C.F.R. §42.24(a). The word count application of the word processing program used to prepare this Petition indicates that the Petition contains 13,495 words, excluding the parts of the brief exempted by 37 C.F.R. §42.24(a).

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

I certify that today this petition and exhibits EX1001-EX1061 were served by **Priority Mail Express Delivery** on the Patent Owner's correspondence address of record for this patent as follows:

Sullivan IP Solutions
PO Box 4452
New York, NY 10163

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: 1 May 2025

/ Yawen Wang /
Yawen Wang