

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 IPR2025-00947
Patent US 9,186,357 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, 5-10, 17-39, and 43-51 of U.S. Patent 9,186,357 (“Trento’357”, EX1002), assigned to Patent Owner (Helsinn). This petition covers 49 of 133 closely related claims spread over four patents. The prior art amply shows the claimed method is just a routine variation on the existing standard, yet the examiner allowed the claims, relying on interested, undeposed, irrelevant, and materially-flawed testimony. As this petition and accompanying exhibits with expert testimony show, these claims were never patentable.

II. STANDING CERTIFICATIONS

Trento’357 is available for IPR. Azurity is not barred or estopped from requesting IPR on these grounds.

III. CHALLENGES AND PRECISE RELIEF REQUESTED

Claims 1, 5-10, 17-39, and 43-51 should be cancelled as unpatentable under 35 U.S.C. §103¹ on these grounds:

¹ All references to §§102 and 103 are to the pre-AIA versions.

Ground	Claims	Obvious from the Combined Teachings of
1	1, 5-10 & 17	Herrstedt ² (EX1010) & Bös ³ (EX1014)
2	18-19, 25-27 & 30-32	Herrstedt, Bös & Herrington ⁴ (EX1016)
3	20	Herrstedt, Bös, Herrington & ALOXI ⁵ (EX1015)
5	24 & 29	Herrstedt, Bös, Hargreaves ⁶ (EX1012) & Herrington
6	28	Herrstedt, Bös, Bonadeo (EX1017) ⁷ & Herrington
7	21-23, 33-35, 37-39, 43-44 & 46-51	Herrstedt, Bös, Bonadeo, Herrington & ALOXI
8	36 & 45	Herrstedt, Bös, Bonadeo, Hargreaves, Herrington & ALOXI

² J. Herrstedt & P. Dombernowsky, *Anti-Emetic Therapy in Cancer Chemotherapy: Current Status*, 101 BASIC & CLINICAL PHARMACOLOGY & TOXICOLOGY 143-150 (2007).

Azurity has also filed a second IPR petition challenging the remaining claims of Trento’357; the grounds are assigned numbers in parallel across these two IPRs, and ground 4 is omitted from this IPR. Exhibits, including a declaration from Stephen Peroutka, M.D., Ph.D. (EX1009), support these grounds. None of these references was applied in a rejection against these claims.

IV. TRENTO’357 PATENT

Trento’357 is entitled “Compositions and methods for treating centrally mediated nausea and vomiting”, claims priority to a provisional filed on November 18, 2009, and purports to provide “methods for treating nausea and vomiting in patients undergoing chemotherapy, radiotherapy, or surgery, comprising the co-

³ M. Bös et al., *4-phenyl-pyridine derivatives*, US 6,297,375 B1 (issued 2 Oct. 2001).

⁴ 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).

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

⁶ R. Hargreaves, *Imaging Substance P Receptors (NK₁) in the Living Human Brain Using Positron Emission Tomography*, 63(11) J. Clinical Psychiatry 18-24 (2002).

⁷ D. Bonadeo et al., *Soft Capsules Comprising Palonosetron Hydrochloride Having Improved Stability and Bioavailability*, WO 2008/049552 (published 2 May 2008).

administration of netupitant, palonosetron and dexamethasone.” EX1002, 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. The present invention also relates to combined oral dosage forms of palonosetron and netupitant.” EX1002, 1:19-25. Treatment with a 5-HT₃ antagonist (like palonosetron) and a steroid (like dexamethasone) “ha[d] been demonstrated to significantly improve the standard of life for patients undergoing emetogenic medical procedures.” EX1002, 1:29-39. Indeed, “[p]alonosetron hydrochloride ha[d] recently emerged as a highly efficacious anti-nauseant and anti-emetic agent.” EX1002, 1:40-41.

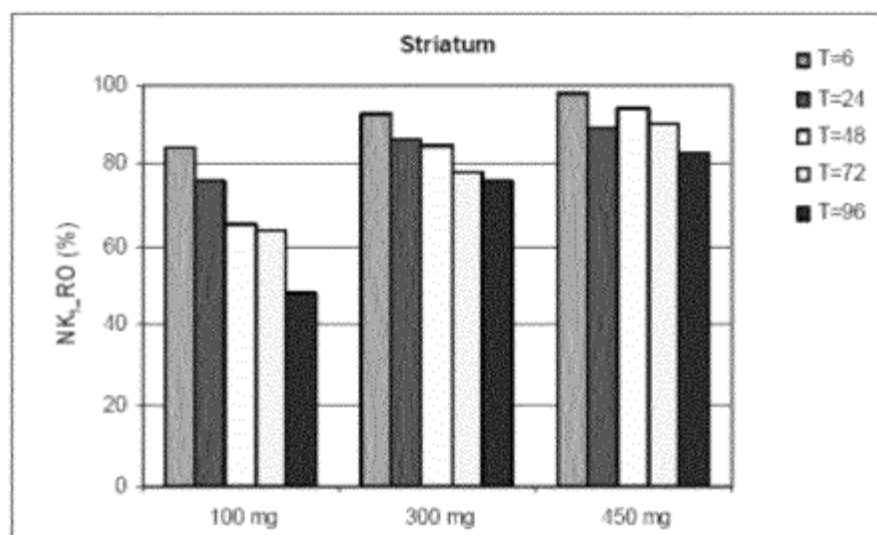
NK₁ antagonists aprepitant and casopitant had been tested—FDA had even approved aprepitant “for the prevention of nausea and vomiting”—but Trento’357 reported neither was effective. EX1002, 2:6-50. (Actually, Helsinn reported similar or better results for the standard “Aprepitant Regimen” versus netupitant regimens. EX1002, 19:Table 6; EX1009, ¶24.) Nevertheless, Trento’357 reported that 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.”

EX1002, 3:21-60. Trento'357 reported discovering, however, that netupitant is active against nausea and binds to striatum NK₁ receptors in the brain for 96 hours after administration, and that it makes both palonosetron and dexamethasone more effective, permitting the use of subtherapeutic dexamethasone doses, and providing a combination therapy that could be effective for 5 days. EX1002, 4:37-5:20.

Example 4 in Trento'357 discloses the results administering netupitant alone to healthy human volunteers to determine occupancy of brain NK₁ receptors. As “anticipated” 90% or higher occupancy (“close to the expected C_{max} ”) of the striatum receptors was reached with half of 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). EX1002, 16:37-60.



B. Challenged Claims

Trento'357 has 62 claims; three (1, 2, 4) are independent. This petition addresses claim 1 and its dependent claims (5-10, 17-39, and 43-51). Claim 1

relates to treating chemotherapy-induced nausea and vomiting (“CINV”) by administering a regimen of netupitant, palonosetron, and dexamethasone. EX1002, claim 1.

C. Prosecution History

Trento’357 issued from application 14/069,927 (EX1006), filed 1 November 2013, which claims priority to PCT/IB2010/003106,⁸ and to provisionals 61/382,709⁹ and 61/262,470.¹⁰ 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 only office action during prosecution was a double patenting rejection over U.S. Patent No. 8,623,826 (Trento’826), of which Trento’357 is a continuation. EX1006, 233-36. During prosecution of Trento’826, the examiner rejected claims over Reddy,¹¹ which taught treating CINV by administering an

⁸ EX1055, filed 18 November 2010.

⁹ EX1056, at 154-190, filed 14 September 2010.

¹⁰ EX1057, at 192-219, filed 18 November 2009.

¹¹ 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).

NK₁ antagonist (aprepitant) with a 5-HT₃ antagonist, and dexamethasone. Reddy taught a 5-HT₃ antagonist combined with dexamethasone was the “standard of care for highly emetic chemotherapy” and adding an NK₁ antagonist defined a new standard. EX1021, 141. Reddy also taught netupitant was an 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.

In response, Helsinn submitted a declaration alleging unexpected results from combining netupitant with palonosetron. The declarants were a Trento’826 inventor (Giorgia Rossi) and another Helsinn employee (Pietra) who argued the combination of netupitant and palonosetron provided a synergistic effect because palonosetron inhibits the natural ligand for the NK₁ receptor, even though it is an 5-HT₃ antagonist, while other 5-HT₃ antagonists do not. EX1009, ¶31.

In allowing the claims, the examiner provided as reasons 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. While the examiner did not identify the precise unexpected result, Helsinn had argued (EX1005, 331) that—

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 would be 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 would have 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’357 itself notes the high level of skill in the art. For example, “[t]he skilled artisan will be able to determine appropriate dosages[.]” EX1002, 7:57-61.

Similarly, the art can determine the “suitable dosing regimen”. EX1002, 10:9-12; *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

No terms need be construed to find the claims unpatentable in view of the prior art. *Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017). In mapping the prior art to the claims, Petitioner has applied “the meaning that [a] term would have to a person of ordinary skill in the art in question at the time of the invention.” *Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005) (en banc).

In several instances, claims either lack or have inconsistent antecedent basis. For example, Claim 35 recites “moderately emetogenic” chemotherapy, but its dependent claim 37 is limited to cisplatin, a highly emetogenic chemo. Without conceding any question under 35 U.S.C. §112, Azurity has been able to apply the prior art to each claim by focusing on the limitation in the claim being analyzed. Under long-established precedent, if prior art may be applied, §112 defects will not prevent a determination of obviousness. *Ex parte Tanksley*, 26 USPQ2d 1384, 1387 (BPAI 1991) (reaching merits where claim meaning was sufficiently clear to apply the prior art); *accord Samsung Elecs. Am. v. Prisia Eng’g*, 948 F.3d 1342, 1355 (Fed. Cir. 2020) (“[T]hat the claim is subject to invalidation on the ground of

indefiniteness ... does not speak to whether the claim is also invalid for obviousness”).

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. Herrstedt Teaches NK₁ Antagonist/5-HT₃ Antagonist/Dexamethasone Antiemetic Prophylaxis

Herrstedt, a 2007 journal article, provides a summary of treatments in 2007 for CINV. EX1010, Abstract. It describes the development of antiemetic therapy including serotonin receptor 5-HT₃ antagonists (e.g., palonosetron) and the NK₁ antagonists (e.g., aprepitant). *Id.* Herrstedt taught adding an NK₁ antagonist to the antiemetic combination of 5-HT₃ antagonist plus corticosteroid (e.g., dexamethasone). *Id.* (“Aprepitant increases the effect of a serotonin₃-receptor antagonist plus a corticosteroid against acute emesis induced by highly or moderately emetogenic chemotherapy.”). *Id.*, abstract. Herrstedt describes generally that antiemetic drugs should be administered in a combination therapy that includes a corticosteroid, a 5-HT₃ antagonist, and an NK₁ antagonist. EX1010, 145; EX1009, ¶¶111-12.

Herrstedt also taught 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).” EX1010, 145, Table 3. Moreover, while 5-HT₃ antagonists had shown “limited or no efficacy in delayed emesis” (i.e., emesis occurring 24-120 hours after chemotherapy), “[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 drug-dosing regimen including administering a 5-HT₃ antagonist (e.g., palonosetron), dexamethasone, and an NK₁ antagonist (e.g., aprepitant). EX1010, 146. These trials showed a statistical benefit for these combined therapeutics as prophylaxis for CINV. *Id.*; 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. Thus, when dexamethasone is administered with an NK₁ antagonist (aprepitant), the concentration of dexamethasone doubles due to decreased dexamethasone metabolism. EX1009, ¶115.

B. Bös: Netupitant is a New Antiemetic NK₁ Antagonist

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.

C. ALOXI Label Teaches FDA-Approved Palonosetron Dosing

ALOXI, a 2008 FDA label revision (available through the FDA website before the critical date), discloses palonosetron hydrochloride (“palonosetron HCl”) as a potent and selective 5-HT₃ antagonist for “[m]oderately emetogenic cancer chemotherapy – prevention of acute nausea and vomiting associated with initial and repeat courses” and also for highly emetogenic chemotherapy (HEC), like cisplatin. EX1015, 1, 3; EX1009, ¶¶102-03, 107-10. ALOXI teaches an orally-administered capsule with 0.56 mg palonosetron HCl, corresponding to 0.5 mg of

palonosetron free base, which ALOXI also describes as a 0.5 mg capsule. EX1015, 1-4; EX1009, ¶104. ALOXI teaches administering palonosetron HCl capsules one hour before chemotherapy. EX1015, 5; EX1009, ¶105. ALOXI also teaches administering palonosetron with chemotherapeutic agents, systemic corticosteroids (e.g., dexamethasone), and with other antiemetic and antinausea agents. EX1015, 2; EX1009, ¶106. EX1015, 4, Table 3 (comparing 0.5 mg capsules to 0.25 intravenous palonosetron).

D. Hargreaves Links Receptor Occupancy to Effective Dose

Hargreaves, a 2002 journal article, taught using positron emission tomography (PET) to study the NK₁-receptor pathway and its association with Substance P, which is implicated in pathophysiology of emesis and depression. EX1012, Abstract. Using aprepitant, the study evaluated NK₁-receptor occupancy within the brain and associated such occupancy with therapeutically-effective doses. *Id.* Hargreaves teaches a 75% or greater NK₁-receptor occupancy was associated with therapeutic doses that blocked emesis. EX1012, 23; EX1009, ¶¶116-17.

E. Herrington Establishes Day-One Dosing

Herrington, a 2008 journal article, discloses a clinical trial evaluating three different treatment arms for antiemetic therapeutic effect for patients receiving highly emetogenic chemotherapy, in which all treatment arms received day-one

0.25 mg palonosetron intravenously and dexamethasone on each of Days 1-4.

EX1016, Abstract. Arm A also received day-one 125 mg oral aprepitant plus 80 mg oral aprepitant on days 2-3. Arm B received day-one 125 mg oral aprepitant but received placebo rather than aprepitant on days 2-3. Arm C received placebos on days 1-3. *Id.*; EX1009, ¶¶118-19. Herrington reports that day-one oral administration of a therapeutically effective amount of NK₁ antagonist is as effective as multi-day administration. EX1016, Abstract; EX1009, ¶120.

Herrington concluded no significant difference exists between a single (Day 1, 125 mg) NK₁ antagonist dose and multiple-day NK₁ antagonist doses for both the acute phase (i.e., 0-24 hours following chemotherapy) and the delayed phase (i.e., 24-120 hours following chemotherapy). EX1016, Table 3; EX1009, ¶121.

F. Bonadeo Teaches Single-Dose Form and Avoiding Palonosetron-Degradation Products

Bonadeo, a 2 May 2008 PCT publication, describes formulations of palonosetron hydrochloride for oral administration, “preferably in the form of liquid filled capsules.” EX1017, Abstract. Bonadeo identifies degradation products of palonosetron including a product called Cpd1 ((3S)-3-[(3aS)-1-oxo-2,3,3a,4,5,6-hexahydro-1*H*-benzo[*de*]isoquinoline-2-yl)-1-azoniabicyclo[2.2.2]octan-1-olate). EX1017, 3, 11 (limiting maximum content). Bonadeo teaches capsules “for the treatment of emesis,” describes including multiple active ingredients in its capsules, and describes embodiments “wherein said palonosetron comprises Cpd1

in an amount of less than 1.0 wt%.” EX1013, 3, 5, 16; EX1009, ¶¶123-24.

VIII. LEGAL STANDARDS

An obviousness analysis involves (1) determining the scope and content of the prior art, (2) ascertaining the differences between the prior art and the claims at issue, (3) resolving the level of ordinary skill in the art, and (4) evaluating any evidence of secondary considerations. *KSR Int’l Co. 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 of a composition is inherent, reasonable expectation of success is assured. *Cytiva Bioprocess v. JSR Corp.*, 122 F.4th 876, 886-87 (Fed. Cir. 2024).

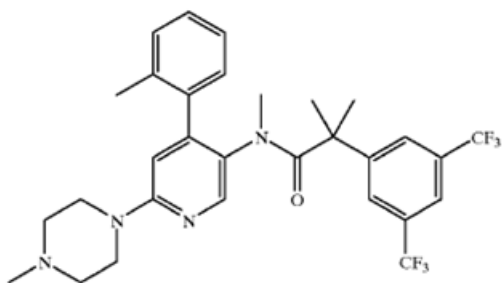
IX. GROUND 1: CLAIMS 1, 5-10, AND 17 WERE OBVIOUS OVER HERRSTEDT AND BÖS

Herrstedt teaches treating both nausea and vomiting. Herrstedt describes administering therapeutically-effective amounts of an NK₁ antagonist (aprepitant), a 5-HT₃ antagonist (e.g., palonosetron), and a first (sub-therapeutic) dose of dexamethasone on day 1. EX1010, 143, 146-147. Herrstedt reports dexamethasone has twice the AUC concentration in this combination therapy, and teaches decreasing the first dose of dexamethasone by about 50% compared to the standard minimum-effective dose. EX1010, 147. Herrstedt teaches these steps effectively treat both nausea and vomiting during a 5-day period, and treat both nausea and vomiting to a greater extent during the 5-day period than a combination of just the

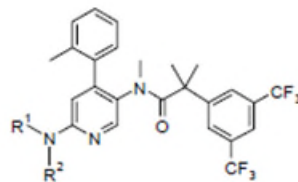
5-HT₃ antagonist and dexamethasone. *Id.*, 146-147; EX1009, ¶¶247, 843-45.

Bös teaches its “Formula Ib” (netupitant) is an improved NK₁ antagonist. Bös, 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)”).¹² Bös evaluated formula Ib’s affinity for human NK₁ receptors and determined it is “a potent and selective antagonist.” *Id.*, 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 and [S]cancus murinus with similar potency.”). A POSA would have known Bös formula Ib was netupitant. *See* EX1009, ¶¶845-46 (comparing Bös’ formula Ib to the formula identified as netupitant by Hoffmann, as shown below).

¹² Bold-italicized text indicates added emphasis.



Formula Ib
EX1014, 14:9-30.



Compound	NR ¹ R ²	hNK ₁ K _i ^a (nM)	Gerbil foot tapping ^b (ID ₅₀ mg/kg po)
21 (netupitant)		0.95	0.5

Netupitant
EX1011, Table 4.

A. Claim 1

1. [preamble]: “A method of treating chemotherapy induced nausea and vomiting (CINV) comprising”

To the extent it is limiting, Herrstedt teaches the preamble terms, for example, methods for prophylactically treating “[c]hemotherapy-induced **nausea and vomiting**” in a patient. EX1010, 143. Herrstedt’s primary therapeutic endpoint was no emesis for five consecutive days after chemotherapy with cisplatin (i.e., five days “postcisplatin”). *Id.*, 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, ¶¶847-48.

2. [a]: “administering to a subject receiving chemotherapy a regimen of palonosetron, netupitant and dexamethasone.”

Herrstedt teaches treating highly-emetogenic chemotherapy with a triple-drug combination administered to patients on day 1 including a 5-HT₃ antagonist, an NK₁ antagonist (aprepitant), and dexamethasone. 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 patients benefiting from the triple-drug antiemetic combination (including NK₁ antagonist) administered on day one. *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.”). Herrstedt identifies palonosetron as a “significantly favoured” 5-HT₃ antagonist for treating emesis. *Id.* Based on Herrstedt’s teachings, as POSA would have had good reason to employ a therapeutically effective amount of the 5-HT₃ antagonist palonosetron in combination with dexamethasone and an NK₁ antagonist. EX1009, ¶¶849-51.

Herrstedt uses aprepitant, not netupitant, but teaches aprepitant was merely “the first drug” in a class of selective NK₁ antagonists. EX1010, Abstract. Bös discloses netupitant is a potent and selective NK₁ antagonist that is 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 and [*S*]ancus murinus 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
(netupitant effective for treating emesis); EX1009, ¶852.

Bös teaches a therapeutically-effective amount of its NK₁ antagonists (including netupitant) for a patient to be in the range of about 10 mg to 1000 mg. 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, ¶852.

Bös provides ample reason to replace Herrstedt’s NK₁ antagonist aprepitant with a therapeutically-effective amount of Bös’ new and improved NK₁ antagonist netupitant. Indeed, Herrstedt taught aprepitant was just the first species of this new class, while Bös suggests netupitant is an attractive replacement for aprepitant, particularly because its good CNS penetration described would allow netupitant to

reach NK₁ receptors in the CNS to treat emesis with a reasonable expectation of success. EX1009, ¶¶852-54; *see also* EX1012, 18 (explaining importance of entering the CNS for antagonism of Substance P receptors in the brain).

Moreover, Bös taught netupitant works well when administered before highly emetogenic chemotherapy (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, 997.

In light of Herrstedt and Bös’ teachings, a POSA had good reasons to use a therapeutically effective amount of palonosetron, netupitant, and dexamethasone for treatment of CINV, such as in the method disclosed in Herrstedt, because Herrstedt discloses administering to a subject receiving chemotherapy a regimen of a 5-HT₃ antagonist such as palonosetron, an NK₁ antagonist, and dexamethasone, and Bös discloses netupitant as a favorable alternative NK₁ antagonist to aprepitant. EX1009, ¶¶996-1002.

B. Claim 5: “The method of claim 1, wherein the chemotherapy comprises moderately or highly emetogenic chemotherapy.”

Herrstedt also describes efficacy of the drug combination on “emesis induced by ***highly or moderately emetogenic chemotherapy***.” EX1010, Abstract; *see id.*, 146, Table 1 (use with “highly emetogenic” cisplatin), Table 4 (other

highly to moderately emetogenic chemotherapy). Bös also teaches netupitant works well when administered before highly emetogenic chemotherapy (e.g., cisplatin). EX1014, 19:11-20. Accordingly, claim 5 was obvious over Herrstedt and Bös. EX1009, ¶¶176, 894-97.

C. Claim 6: “The method of claim 1, wherein said chemotherapy comprises carboplatin.”

Herrstedt teaches its combination therapy is broadly applicable to treating CINV, including moderate CINV. EX1010, Abstract, Table 1. For example, Herrstedt expressly discloses that such moderately emetogenic chemotherapy includes carboplatin. *Id.* Applying Herrstedt’s teachings to use the combination therapy discussed above for claim 1 when administering a moderately emetogenic chemotherapy like carboplatin would have been well within the skill of the POSA. EX1009, ¶¶898-903.

D. Claim 7: “The method of claim 1, wherein the netupitant and palonosetron are administered no more than one hour prior to administration of the chemotherapy.”

As discussed for claim 1, Herrstedt and Bös render obvious administering a combination including netupitant and palonosetron to address CINV. Herrstedt discloses that administration details are provided “in the Poli-Bigelli study” (EX1039) and “the Hesketh study” (EX1037). EX1010, 146. A POSA would have understood from Herrstedt’s disclosure that, as these studies confirm, the NK₁ and 5-HT₃ antagonists (e.g., netupitant and palonosetron) are administered no more

than one hour prior to administration of the chemotherapy. See EX1039 (NK₁ antagonist administered one hour prior to cisplatin; 5-HT₃ antagonist administered thirty minutes prior to cisplatin); EX1037 (same); EX1009, ¶¶906-07. Thus, a POSA had good reason to administer the NK₁ antagonist and 5-HT₃ antagonist no more than one hour prior to administration of the chemotherapy with a reasonable expectation of success. EX1009, ¶¶904-08.

E. Claims 8-10: highly or moderately emetic chemotherapy

Claims 8-10 recite that the chemotherapy is selected from a group of chemotherapies. Claim 8 recites a group of “highly emetic” chemotherapies (“carmustine, cisplatin, cyclophosphamide ≥ 1500 mg/m², dacarbazine, dactinomycin, mechlorethamine, streptozotocin and combinations thereof”), claim 9 recites a group of “moderately emetic” chemotherapies (“carboplatin, cyclophosphamide < 1500 mg/m², cytarabine > 1 mg/m², daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, oxaliplatin and combinations thereof”), and claim 10 recites a group encompassing all chemotherapies recited in claims 8 and 9 (including cyclophosphamide with no concentration restriction).

Herrstedt discloses its antiemetic drug combination is administered to treat CINV for “cisplatin-based, highly emetogenic chemotherapy,” as well as other highly emetic chemotherapies recited in claims 8 and 10. EX1010, 146, Table 1. Herrstedt also teaches its combination is usable with “moderately emetogenic

chemotherapy” such as carboplatin and other moderately emetic chemotherapies recited in claims 9 and 10. *Id.*, Table 1. Table 1 of Herrstedt lists numerous highly and moderately emetic chemotherapies as recited in claims 8-10. Table 1 is reproduced in relevant parts below with first the highly emetic chemotherapies of claim 8 highlighted and then the moderately emetic chemotherapies of claim 9 highlighted, with each highlighted chemotherapy also listed in claim 10:

Table 1.	
Emetic potential of cytotoxins.	
Risk of emesis 0–24 hr after initiation of chemotherapy, if no antiemetics are given	
High (>90%)	Intravenous
	Cisplatin
	Mechlorethamine, streptozocin, dacarbazine
	Cyclophosphamide >1500 mg/m ²
	Oral
	Procarbazine

EX1010, Table 1;

Table 1.	
Emetic potential of cytotoxins.	
Risk of emesis 0–24 hr after initiation of chemotherapy, if no antiemetics are given	
High (>90%)	Intravenous
	Cisplatin
	Mechlorethamine, streptozocin, dacarbazine
	Cyclophosphamide >1500 mg/m ²
	Oral
Moderate (30–90%)	Procarbazine
	Intravenous
	Oxaliplatin
	Cytarabine >1000 mg/m ²
	Carboplatin
	Ifosfamide
	Cyclophosphamide <1500 mg/m ²
	Doxorubicin, epirubicin, daunorubicin, idarubicin
	Irinotecan
	Oral
	Cyclophosphamide, etoposide, temozolomide
	Vinorelbine, imatinib

Id.; EX1009, ¶¶909-24. Accordingly, a POSA knew Herrstedt taught its antiemetic drug combination is administered to treat CINV where the chemotherapy is a member of any of the groups recited in claims 8, 9, or 10. EX1009, ¶¶909-24.

F. Claim 17: “The method of claim 1, wherein said treatment of CINV is defined as no emetic episodes and no use of rescue medication following said chemotherapy.”

Herrstedt teaches treatment of CINV, defined as no emetic episodes and no use of rescue medication following chemotherapy. Herrstedt defines “complete response” as “no emesis and no rescue therapy on days 1-5” following chemotherapy, which was the “primary end-point in all studies.” EX1010, 146. This includes “no emesis” and “without the need of rescue anti-emetics.” *Id.* The studies cited in Herrstedt confirm these definitions. EX1039, 3092; EX1037, 4113; EX1009, ¶¶925-29; *see* EX1010, 146.

G. Obvious to Combine and Reasonably Expect Success

By the critical date, a POSA had good reason to treat nausea and vomiting during the acute and delayed phases of CINV in response to moderately or highly emetogenic chemotherapy with Herrstedt’s triple-antiemetic combination therapy, using therapeutically-effective amounts of new and improved NK₁ and 5-HT₃ antagonists. Herrstedt teaches the three-drug combination of 5-HT₃ antagonist (ondansetron), NK₁ antagonist (aprepitant), and dexamethasone administered on day 1 yielded superior response rates (complete response) compared to the two-drug combination lacking an 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,

¶¶334, 996. The POSA would have sought to enhance the efficacy of Herrstedt's antiemetic combination with new and improved drugs targeting the same mechanistic pathways. Palonosetron was known to have an order of magnitude half-life greater than the ondansetron Herrstedt evaluated. EX1010, 146 & Table 3 (palonosetron half-life 38-40 hours; ondansetron half-life 4-6 hours). And 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, 996.

The POSA also would have modified the Herrstedt triple therapy to include the improved NK₁ antagonist, netupitant. The POSA would have sought to continue to enhance the efficacy of the antiemetic drug combination of Herrstedt with new and improved drugs targeting the same mechanistic pathway—e.g., antagonism of the NK₁ receptor. The POSA thus would have had good reason to modify the Herrstedt drug combination to replace NK₁ antagonist aprepitant with Bös' NK₁ antagonist netupitant ("formula Ib") because, as Bös explains, netupitant was shown to potently and selectively inhibit the NK₁ receptor, and likewise antagonized NK₁ receptor-induced foot tapping after oral administration, which was indicative of successful NK₁ receptor antagonism. EX1014 (Bös), 14:32-19:37. Bös reported in vivo studies evaluating emesis blocking, showing netupitant

had a long half-life (e.g., 30 hours) and high bioavailability, and Bös also provided a dosing range of about 10 to about 1,000 mg. EX1014, 19:10-37, 42:5-11.

Netupitant was thus a known second generation NK₁ antagonist, and the POSA had reason to modify Herrstedt by replacing aprepitant with a therapeutically-effective amount of netupitant with a reasonable expectation of success. EX1009, ¶¶997.

Accordingly, a POSA had good reason to modify the Herrstedt triple active combination therapy with the new 5-HT₃ antagonist (palonosetron) and Bös' NK₁ antagonist (netupitant) as claimed to have an antinausea and antivomiting effect for patients receiving emetogenic chemotherapy. EX1009, ¶¶998.

A POSA reasonably expected success modifying Herrstedt's antiemetic combination with netupitant because the substituted newer NK₁ antagonist (netupitant for the older aprepitant) would have been expected to act in the same manner to achieve a similar (or better) outcome. EX1010, 145-146, Table 3; EX1009, ¶¶999. Both netupitant and aprepitant were known to be therapeutically effective via the same mechanism—by antagonizing the NK₁ receptor. *Id.*; EX1014 (Bös), 14:31-38 (“a highly selective antagonist”), 18:42-48 (“a potent and selective antagonist”). Thus, a POSA would have expected therapeutically-effective amounts of aprepitant and netupitant to achieve at least comparable effect of antiemesis. EX1009, ¶¶1000-02. As netupitant was known to have favorable qualities as compared to aprepitant, POSAs would have reasonably expected

netupitant to be clinically comparable to or better than Herrstedt's antiemetic drug combination using aprepitant. Additionally, because each of the drugs in Herrstedt's triple combination targets a different mechanism providing relief for a patient suffering from nausea and vomiting, a POSA would have had a reasonable expectation of success in further improving both nausea and vomiting following CINV during both the acute and delayed period when the triple therapy was administered. *Id.*

Accordingly, POSAs had good reason to combine Herrstedt and Bös to arrive at the claimed invention with a reasonable expectation of success. EX1009, ¶1002.

X. GROUND 2: CLAIMS 18-19, 25-27, AND 30-32 WERE OBVIOUS OVER HERRSTEDT, BÖS AND HERRINGTON

A. Claims 18 and 19

Claim 18 depends from claim 1 and additionally recites a) said regimen comprises a single administration of netupitant or pharmaceutically acceptable salt thereof and a single administration of palonosetron or pharmaceutically acceptable salt thereof; b) said netupitant or pharmaceutically acceptable salt thereof and said palonosetron or pharmaceutically acceptable salt thereof are administered concomitantly and prior to said chemotherapy, without administering a second dose of either for at least five days after said chemotherapy; and c) said regimen is effective to treat said CINV for a five day period after said chemotherapy.

EX1009, ¶¶1005-06. Claim 19 is identical to claim 18 except that it adds the limitations of claim 17 as element 19(a). EX1009, ¶¶1015-18.

Herrstedt's triple therapeutic regimen includes a single prophylactic administration of NK₁ antagonist (aprepitant) on day 1. EX1010, 146; EX1009, ¶1007. While Herrstedt teaches administering aprepitant on days 2 and 3, the combination of Herrstedt and Bös suggests administering netupitant on day 1 without administering a second dose for at least five consecutive days, as Bös teaches netupitant had a long half-life. EX1014, 19:3-10 (functional half-life of 30 hours); EX1009, ¶1008.

Herrington confirms a single-dose NK₁ antagonist administered prophylactically on day one of said five consecutive days, where no further NK₁ antagonist is administered during a five-day treatment period, is effective to treat CINV for the five day period after chemotherapy. Herrington teaches single-dose aprepitant provided similar effectiveness to Herrstedt's repeated dosing of aprepitant. Herrington, 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 knew that day-one, single-administration of an NK₁ antagonist was similarly effective to Herrstedt’s dosing protocol administering the NK₁ antagonist over multiple days and had reason to use a single dose for increased simplicity and ease of patient compliance. EX1009, ¶¶1009-10. Moreover, Bös teaches 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 reason to omit subsequent administrations of NK₁ antagonist.

Regarding palonosetron, Herrstedt teaches that whereas ondansetron was originally “prescribed for up to 5 days after chemotherapy,” [p]alonosetron might be an exception,” as it was FDA-approved for “treatment of delayed emesis.” EX1010, 145-146. Supporting this suggestion, Herrstedt teaches palonosetron has an order of magnitude greater half-life as compared to ondansetron. EX1010, Table 3 (half-life 38-40 hours, compared to ondansetron’s 4-6 hours). Accordingly, POSAs had good reason to prophylactically administer a single administration of palonosetron or a pharmaceutically acceptable salt thereof, without further administration during the five-day treatment period. EX1009, ¶¶1011-12.

Herrstedt discloses the NK₁ and 5-HT₃ antagonists are administered concomitantly with chemotherapy. Herrstedt summarizes two studies administering the triple antiemetic drug combination described above, noting that

administration details are provided in those studies. EX1010, 146. These studies reported by Herrstedt teach administration one hour or less prior to administration of the chemotherapy, which a POSA would have understood to be concomitant administration. *Id.*; EX1039, 3092; EX1037, 4113; EX1009, ¶1013. Thus, a POSA had good reason to administer the NK₁ antagonist and 5-HT₃ antagonist concomitantly and prior to chemotherapy, and reasonably expected such dosing to be effective to treat CINV, including with netupitant as the NK₁ antagonist and palonosetron as the 5-HT₃ antagonist. EX1009, ¶1013. Accordingly claim 18 was obvious over Herrstedt, Bös and Herrington. EX1009, ¶¶1005-14.

Claim 19 is identical to claim 18, except that it adds the limitations of claim 17. These limitations were obvious over Herrstedt and Bös as explained for claim 17. *Supra* §IX.D. Thus, claim 19 was obvious over Herrstedt, Bös and Herrington for similar reasons. EX1009, ¶¶904-08, 1015-19.

B. Claims 25-27

Claim 25 depends from claim 19 and additionally recites a) said chemotherapy is highly emetogenic chemotherapy; and b) said netupitant is effective to treat said CINV during the acute and delayed phases of said CINV.

Claim 26 is the same, except that its element b) recites “said regimen is effective to prevent nausea or reduce the severity of nausea in said patient during the acute and delayed phases of said CINV.” Claim 27 is identical to claim 26, except that it

recites “said chemotherapy is moderately emetogenic chemotherapy.” EX1009, ¶¶1020-21, 1028-29, 1034-35.

As explained for claim 8-9, Herrstedt discloses a method for preventing CINV in a subject receiving **highly** emetogenic or **moderately** emetogenic cancer chemotherapy by administering an antiemetic drug combination. EX1010, 143-44, 146; *supra* §IX.E. For example, Herrstedt discloses administering its combination therapy to prevent or reduce the severity of nausea and vomiting “in patients receiving cisplatin-based, highly emetogenic chemotherapy.” EX1010, 146; EX1009, ¶¶1022-23, 1030-31. Herrstedt also identifies that the NK₁ antagonist is more broadly applicable to treating chemotherapy-induced nausea and vomiting, including in “moderately emetogenic chemotherapy.” EX1010, Abstract; EX1009, ¶¶1036-37. Herrstedt explains its triple combination antiemetic improves efficacy against both “acute emesis” and “delayed emesis” for “highly or moderately emetogenic chemotherapy.” EX1010, Abstract, Table 1. A POSA would have known the acute phase refers to the antiemetic protection provided during the first 24 hours following chemotherapy, while the delayed phase is the period 24 to 120 hours after chemotherapy. EX1009, ¶¶1023, 1031, 1038 (citing EX1010, 143). As Dr. Peroutka explains, the studies cited by Herrstedt confirm Herrstedt’s report that administering such a triple therapy combination is effective to treat CINV during the acute and delayed phases of CINV. EX1009, ¶¶1024-28, 1031-33 (citing

EX1037, 4115-17, Fig. 2; EX1039, 1096-97). A POSA would have expected similar anti-nausea effect for treatment of nausea where the chemotherapy is moderately emetogenic (as in claim 27) because the mechanism of treatment is the same. EX1009, ¶1036-41; *see* EX1010, Abstract (confirming regimen's applicability with both highly and moderately emetogenic chemotherapies).

C. Claims 30-32

Claims 30, 31, and 32 depend from claim 19 and additionally recite that said chemotherapy comprises cisplatin (claim 30); carboplatin, cisplatin, oxaliplatin, or doxorubicin (claim 31); or cyclophosphamide (claim 32).

Herrstedt discloses the chemotherapy comprises cisplatin, satisfying both claims 30 and 31. EX1010, 146; EX1009, ¶¶1042-44. Herrstedt also discloses the NK₁ antagonist is broadly applicable to treat CINV, and it specifically lists the alternatives of carboplatin, oxaliplatin, and doxorubicin recited in claim 31, as well as cyclophosphamide, recited in claim 32. EX1010, Abstract, Table 1; EX1009, ¶¶1045-52. Accordingly, a POSA knew Herrstedt taught its antiemetic drug combination is administered to treat CINV for each of the chemotherapies recited in claims 30-32. EX1009, ¶¶1042-53.

D. Obvious to Combine and Reasonably Expect Success

By November 2009, a POSA had good reason to treat both the acute and delayed phases of CINV after either HEC or MEC with Herrstedt's antiemetic

combination, using Bös' newer NK₁ antagonist netupitant with a reasonable expectation of determining therapeutically-effective doses that would provide antiemetic effect. A POSA also had good reason to use just a single, day-one dose of Bös' NK₁ antagonist (netupitant) for the 5-day treatment period because Herrington had shown no added benefit to dosing with an NK₁ antagonist on subsequent days of the 5-day period, particularly because reducing doses would be expected to be preferred by patients and easier in administration for both provider and patient. EX1009, ¶1087.

A POSA would have reasonably expected success modifying Herrstedt's antiemetic combination with netupitant because the substituted newer NK₁ antagonist (netupitant for the older aprepitant) would have been expected to act in the same manner to achieve a similar (or better) outcome. EX1009, ¶1088.

Similarly, a POSA would have reasonably expected a single therapeutically-effective dose of netupitant to work for 5-days, just as the older aprepitant that it replaced did. EX1009, ¶¶1088-89.

XI. GROUND 3: CLAIM 20 WAS OBVIOUS OVER HERRSTEDT, BÖS, HERRINGTON, AND ALOXI

Claim 20 depends from claim 19 and further recites that "a) said netupitant is administered orally as the free base in a dose of from about 200 mg to about 400 mg; and b) said palonosetron is administered orally as palonosetron hydrochloride in a dose of from about 0.25 mg to about 0.75 mg based on the weight of the free

base.”

Bös suggests orally administering NK₁ antagonists, including from about 200 to about 400 mg of netupitant as a free base. 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, although the above upper limit can also be exceeded when necessary.”), 14:9-30 (teaching “formula 1b” as free base, separate from “pharmaceutically acceptable acid addition salts thereof”). 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 as a free base) to determine a therapeutically-effective amount of netupitant with a reasonable expectation of success. EX1009, ¶¶1090-97; *In re Urbanski*, 809 F.3d 1237, 1242 (Fed. Cir. 2016) (routine to optimize result-effective variable).

Herrstedt teaches administration of palonosetron as a free base. *See* EX1010, Table 1 (intravenous dosing), 145-47 (referring repeatedly to palonosetron, rather than specifying a salt or other non-free-base form); EX1009, ¶1098. ALOXI teaches administering before chemotherapy a therapeutically-effective amount of palonosetron in a pharmaceutically acceptable salt form. 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 the capsules are administered orally “one hour prior to” administration of “emetogenic chemotherapy.” *Id.*, 4; EX1009, ¶1099.

Additionally, POSAs appreciated oral administration is simpler, less costly, and more convenient than intravenous administration, and that patients preferred oral formulations over intravenous administration. EX1009, ¶¶1100-01.

The combination of Herrstedt’s 3-drug combination substituting netupitant (as taught by Bös) and palonosetron (as taught by Herrstedt), administered on as a day-one treatment without need for further dosage of either on days 2-5 (as taught by Herrington) would have been obvious to try with a reasonable expectation of success for the reasons given in §§IX-X above. The addition of the FDA-approved ALOXI label only strengthens the case for using palonosetron as the label instructs, including in free-base form as taught by Herrstedt. EX1009, ¶¶1002-07. Optimizing to a range of 200-400 mg or to 300 mg netupitant as a free base, which are noncritical values within the range Bös teaches, would have been facially obvious, and a POSA would have reasonably expected success in doing so.

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 5: CLAIMS 24 AND 29 WERE OBVIOUS OVER HERRSTEDT, BÖS, HARGREAVES, AND HERRINGTON

Claims 24 and 29 are identical, each depending from claim 19 and reciting “wherein said netupitant occupies at least 70% of said patient’s striatum NK₁

receptors ninety-six hours after said administration.” These claims were obvious over Herrstedt, Bös, Hargreaves, and Herrington. EX1009, ¶¶1124-27.

Netupitant enters systemic circulation and crosses the blood brain barrier to occupy NK₁ receptors in the striatum. 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 where it is administered; instead, Hargreaves teaches that, to be therapeutically effective, NK₁ antagonists interfere with Substance P in the CNS, including the striatum—a region of the brain having a particularly abundant density of 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; *see also* EX1011, Abstract (lauding netupitant’s “excellent CNS penetration”). Because oral netupitant has the desired therapeutic effect on the NK₁ receptors, orally-administered netupitant must enter systemic circulation and cross the blood brain barrier to arrive at CNS NK₁ receptors, including in the striatum. EX1009, ¶1128.

Hargreaves teaches that, to be a therapeutically-effective amount, an NK₁ antagonist occupies at least about 75% of NK₁ receptors in the striatum, where the striatum is the densest location of NK₁ receptors. EX1012, Fig. 4(A); EX1009,

¶1129. Hargreaves also teaches therapeutic success by targeted inhibition of NK₁ receptors in the striatum. 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). It is noteworthy that [¹⁸F]SPA-RQ binding in other regions of the brain known to express NK₁ receptors (e.g., amygdala) 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 teaches a direct relationship between NK₁-receptor occupancy in the striatum and antiemetic therapeutic effectiveness for patients suffering from chemotherapy-induced nausea and vomiting. EX1012, 23 (“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 $\geq 90\%$ 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**. Both the 300-mg dose of aprepitant used in the treatment of depression and the initial 125-mg 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% of NK₁-receptor occupancy, corresponding with a 40 mg dose of aprepitant. Hargreaves further discloses a CINV efficacy using the 125 mg dose with at least 90% occupancy. Hence, administering a therapeutically-effective dose of netupitant would occupy at least 75% or at least 90% (i.e., at least 70%) of neurokinin-1 (NK₁) receptors in the striatum ninety-six hours after administration. EX1009, ¶¶1130-32. In sum, the effects recited in claims 24 and 29 simply reflexively define what is required of a therapeutically-effective netupitant (or any NK₁ antagonist) dose.

Helsinn conceded as much in a related examination, where Helsinn did not rebut the examiner’s finding this occupancy was an inherent property of administering a therapeutically-effective amount of netupitant that satisfies the “at least 70%” occupancy limitation. For example, the examiner stated that netupitant occupying at least 70% of a patient’s striatum NK₁ receptors seventy-two hours after administration is an inherent feature of administering a therapeutically effective dose of netupitant. EX1008, 120-21, 155 (not disputing inherency). Similarly, ninety-six hours falls squarely within the 5-day therapeutic period and simply reflects the known prolonged half-life of netupitant. EX1009, ¶1032; EX1014, 19:7-38; EX1002, 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.”).

Claim 19 was obvious over Herrstedt, Bös, and Hargreaves as discussed in Ground 2. EX1009, ¶¶1134, 1137. It would further have been obvious to evaluate the NK₁-receptor occupancy to determine a minimum effective dose. Hargreaves taught administering doses of NK₁ antagonist in an amount that will occupy at least about 75% of NK₁ receptors in the striatum. EX1012, 23 & Fig. 6(B). Thus, at the critical date, a POSA had good reason to use NK₁-receptor occupancy to determine therapeutically-effective dose amounts for NK₁ antagonists, such as netupitant. EX1009, ¶¶1135-36.

A POSA would also have had a reasonable expectation of success in evaluating therapeutic efficacy of netupitant by applying PET NK₁ receptor occupancy as described in Hargreaves. POSAs understood that such studies were routinely conducted, and because the receptor occupancy being evaluated would be the same (NK₁ receptors in the striatum), it would have been routine to evaluate the effect of netupitant in the same manner described in Hargreaves. EX1009, ¶¶1138-39.

XIII. GROUND 6: CLAIM 28 WAS OBVIOUS OVER HERRSTEDT, BÖS, BONADEO, AND HERRINGTON

Claim 28 depends from claim 19 and further recites “recites (3S)-3-[(3aS)-1-oxo-2,3,3a,4,5,6-hexahydro-1H-benzo[de]isoquinoline-2-yl]-1-azoniabicyclo[2.2.2]octan-1-olate is substantially absent from said palonosetron.”

Trento’357 describes this formula as “a degradation by-product of palonosetron.” EX1002, 5:62-6:1. Trento’357’s specification does not describe what “substantially absent” means, and the only disclosure related to quantities involves soft-gel capsules comprising palonosetron with a weight percentage of this by-product that “does not exceed 3 wt.%. ” EX1002, 6:11-23; EX1009, ¶¶1140-44.

Bonadeo refers to this by-product as “an oxygen mediated degradation product” that it calls “Cpd1.” EX1017, 3, 11 (providing structure); EX1009, ¶¶1145-46. Bonadeo describes and claims oral formulations, including soft-gelatin capsules, in which said palonosetron comprises Cpd1 in an amount of less than 1.0 wt%. ” EX1017, 3; *see id.*, 4, 28, 29, 30; *see also id.*, 6, 9-10, 11-12 (less than 0.5 wt%). A POSA would have understood Bonadeo to teach palonosetron with (3S)-3-[(3aS)-1-oxo-2,3,3a,4,5,6-hexahydro-1H-benzo[de]isoquinoline-2-yl]-1-azoniabicyclo[2.2.2]octan-1-olate substantially absent, as it describes even lower amounts of the degradant than taught by the Trento’357.

A POSA would have reasonably expected to achieve palonosetron substantially free from the recited byproduct based on Bonadeo’s teachings. Indeed, this expectation is confirmed by ALOXI. ALOXI includes a list of active and inactive ingredients matching lists in Bonadeo, none of which includes the byproduct. *See* EX1015, 3; EX1017, Table 1; EX1009, ¶1147. Bonadeo reports low formation of the degradant Cpd1 with the as-formed 0.50 mg tablets, and also

reports forming capsules at commercial scale. EX1017, Example 5, Table 1. These lists also match lists provided in Trento'357 for its palonosetron, further confirming that the formulations disclosed by Bonadeo satisfy claim 28's requirements. EX1009, ¶1147. *Compare* EX1002, 14:1-26, *with* EX1015, 3. Further, ALOXI indicates its capsules are FDA-approved, which a POSA would expect to indicate substantial absences of impurities such as the recited degradant. EX1009, ¶1148. Accordingly, a POSA would have viewed ALOXI as confirming the reasonable expectation that Bonadeo's palonosetron capsules are substantially free from (3S)-3-[(3aS)-1-oxo-2,3,3a,4,5,6-hexahydro-1H-benzo[de]isoquinoline-2-yl]-1-azoniabicyclo[2.2.2]octan-1-olate. EX1009, ¶¶1147-50.

A POSA would have looked to Herrstedt, Bös, and Herrington as discussed above in ground 2 (*supra* §X), and would have had good reason to turn to Bonadeo for its disclosure of known degradants. The POSA formulating administrations containing palonosetron would have sought prior art identifying known degradants and would have good reason to apply known formulations that minimize said degradants as a starting point for further formulation. Bonadeo discloses known degradants including (3S)-3-[(3aS)-1-oxo-2,3,3a,4,5,6-hexahydro-1H-benzo[de]isoquinoline-2-yl]-1-azoniabicyclo[2.2.2]octan-1-olate and provides formulations minimizing its formation, thus the POSA had good reason to apply the teachings of Bonadeo as part of routine formulation development. EX1009,

¶¶1151-55.

XIV. GROUND 7: CLAIMS 21-23, 33-35, 37-39, 43-44, AND 46-51 WERE OBVIOUS OVER HERRSTEDT, BÖS, BONADEO, HERRINGTON, AND ALOXI

Claims 21-23, 33-35, 37-39, 43-44, and 46-51 depend directly or indirectly from claim 19, which was obvious over Herrstedt, BöS, and Herrington as discussed above. *Supra* §X. Claims 21-23 each recite limitations related to dosing and administration of palonosetron, netupitant, and (for claims 22-23) dexamethasone. The remaining claims depend directly or indirectly from claim 21. As discussed below, these claims were obvious over Herrstedt, BöS, and Herrington, and further in view of Bonadeo and ALOXI. EX1009, ¶¶1156-57.

A. Claim 21: “The method of claim 19, wherein: a) said netupitant is administered orally as the free base in a dose of about 300 mg; b) said palonosetron is administered orally as palonosetron hydrochloride in a dose of about 0.50 mg based on the weight of the free base; c) said netupitant and palonosetron are administered as a single unit dosage form less than 2 hours prior to said chemotherapy.”

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, and arriving at the recited 300 mg dose was within the skill of the POSA. EX1009, ¶1158-65; *supra* §XI. Herrstedt teaches a triple-combination therapy in which the NK₁ antagonist is administered on day 1. Herrstedt, 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, ¶¶1171-73. This dosing protocol was consistent with other NK₁ antagonists. Herrstedt, 146; EX1009, ¶¶1173-74

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. EX1015, 3-4; EX1009, ¶1166-70; *see also supra* §XI (dose ranging obvious).

Herrstedt teaches an effective amount of the antiemetic regimen is administered prophylactically prior to administering the chemotherapy. EX1009, ¶¶1171-72. Herrstedt further discloses that the administration details are provided "in the Poli-Bigelli study" and in "the Hesketh study." EX1010 (Herrstedt), 146. These studies reported by Herrstedt both teach administering the NK₁ antagonist and 5-HT₃ antagonist concomitantly within one hour prior to chemotherapy. *Id.*; EX1039, 3092; EX1037, 4113; EX1009, ¶¶1173-74. As explained for claim 1, it was obvious to use netupitant and palonosetron as these respective antagonists. *Supra* §IX.

Regarding claim 21's "single unit dosage form," Bonadeo suggests its oral formulations of palonosetron include palonosetron and at least a second active ingredient. For example, Bonadeo describes that "[u]pon swallowing the capsule,

the gelatin shell rapidly dissolves or ruptures in the gastrointestinal tract thereby introducing the ***pharmaceutical actives*** from the liquid core into the body.” EX1017, 16; *see also id.*, 5 (“[R]eference to ‘an active pharmaceutical agent’ includes ***more than one active pharmaceutical agent.***”). Bonadeo also teaches that the pills it discloses increase stability and convenience and reduce risk of human error, providing further reason to use such a dosage form. EX1017, 2-3; EX1009, ¶¶1177-80.

B. Claim 22

Claim 22 depends from claim 19 and recites five elements. Elements 22(b)-(d) are identical to elements 21(a)-(c), except that claim 22 refers to the “single unit dosage” of claim 21 as a “combination unit dosage.” These elements were obvious as discussed for claim 21. EX1009, ¶¶1158-82, 1187-89; *supra* §XIV.B.

Regarding elements 22(a) and 22(e), element 22(a) recites that the “chemotherapy comprises moderately emetogenic chemotherapy,” and element 22(e) recites that “dexamethasone is administered in a dose of about 12 mg, in a dosage form independent of said combination unit dosage form, less than 2 hours prior to said chemotherapy.” Herrstedt suggests the chemotherapy is moderately emetogenic chemotherapy as discussed above for claim 27. *Supra* §X.B; EX1009, ¶¶1183-86; EX1010, Abstract, Table 1.

Herrstedt further reports dexamethasone has twice the AUC concentration in

an NK₁ antagonist/5-HT₃ antagonist/dexamethasone combination therapy, and it teaches decreasing the first dose of dexamethasone by about 50% compared to the standard minimum-effective dose. EX1010, 147. Herrstedt teaches that administration details are provided by the “MEC” study (Warr, EX1034). EX1010, 146. As Dr. Peroutka explains, a POSA knew the Warr study reported by Herrstedt indicates 12 mg dexamethasone are administered 30 minutes prior to chemotherapy (i.e., less than 2 hours before), which is administered in a dosage form independent of the other medications. EX1034, Abstract, Table 1; EX1010, 146; EX1009, ¶¶1190-93. A POSA would have had good reason to use an independent dosage form as recited, as dexamethasone is administered at variable, rather than constant dosage. EX1009, ¶¶1194-96.

C. Claim 23

Claim 23 depends from claim 19, and recites limitations identical to claim 22, except that element 23(a) recites highly rather than moderately emetogenic chemotherapy and element 23(f) adds that “dexamethasone is further administered in a dose of about 8 mg on days 2, 3 and 4 following said chemotherapy.” As discussed above for claims 25-26, the prior art renders obvious using the recited combination therapy for both highly and moderately emetogenic chemotherapies (*see supra* §§X.B, XIV.B; EX1009, ¶¶1197-1210; EX1010, Table 1), so the reasoning for claim 22 applies similarly for elements 23(a)-(e). EX1009, ¶¶1197-

1210.

Regarding element 23(f), this element 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 studies testing this triple antiemetic drug combination. A POSA reviewing Herrstedt would have understood it to teach orally administering 8 mg dexamethasone on days two, three and four as well as 12 mg on day 1 for highly emetogenic chemotherapy. EX1009, ¶¶1211-15; *see* EX1010, 146; EX1039, Abstract; EX1037, 4113.

D. Claims 33-35

Claims 33-35 depend from claim 21, but are otherwise identical to claims 25-27. Claims 33-35 were obvious over Herrstedt, Bös, Bonadeo, Herrington, and ALOXI for the reasons described above for claims 21 and 25-27. *Supra* §§X.B, XIV.A; EX1009, ¶¶1216-1237.

E. Claims 37-39 and 49-51

Claims 37-39 depend from claim 21 and claims 49-51 depend from claim 35. These sets of three claims each repeat the limitations of claims 30-32 verbatim. Claims 37-39 and 49-51 were obvious over Herrstedt, Bös, Bonadeo, Herrington, and ALOXI for the reasons described above for claims 21, 25, and 30-32. *Supra* §§X.B, X.C, XIV.A; EX1009, ¶¶1238-48, 1294-1304; *see also* EX1010, Abstract, 146, Table 1.

F. Claims 43-44

Claims 43 and 44 each depend from claim 35. Claim 43 recites the same limitations as claim 22, except claim 43 (1) omits limitations regarding palonosetron; (2) refers to “said single administration of dexamethasone”; and (3) describes the 12 mg dexamethasone doses with slightly different language. Claim 44 recites the same limitations as claim 23, except claim 44 (1) omits limitations regarding palonosetron; (2) refers to “said first” and “said second” doses of dexamethasone; and (3) phrases the 12 mg and 8 mg doses with slightly different language. None of these limitations materially affect the obviousness of claims 43 and 44; accordingly, claims 43-44 were obvious over Herrstedt, Bös, Bonadeo, Herrington, and ALOXI for the reasons described above for claims 22-23 and 35. *Supra* §§XIV.B-C; EX1009, ¶¶1249-80.

G. Claims 46-48

Claims 46-48 each depend from claim 35 and recite limitations relating to the netupitant or the regimen’s effectiveness to treat, prevent, or reduce severity of nausea or CINV during acute and delayed phases of CINV or following administration of chemotherapy. These limitations are not materially different from limitation (b) of claims 25-27, as well as limitation (b) of claims 33-35. Accordingly, claims 46-48 were obvious over Herrstedt, Bös, Bonadeo, Herrington, and ALOXI for the reasons described above for claims 25-27 and 33-

35. *Supra* §§X.B, XIV.D; EX1009, ¶¶1281-93.

H. Obvious to Combine and Reasonably Expect Success

A POSA would have had good reason to formulate netupitant and palonosetron together into a fixed combination (a single unit dosage form) as in claims 21-23 and their dependent claims. Based on Herrstedt (and the Poli-Bigelli and Hesketh studies it references) POSAs knew 5-HT₃ antagonists such as palonosetron are administered in close proximity with administration of NK₁ antagonists, such as netupitant. EX1039, 3092; EX1037, 4113; EX1009, ¶¶1305-06.

For such drugs administered in close proximity to one another, “there are considerable practical advantages in giving the required drugs in single formulation.” EX1061, 78. A POSA would have recognized that administering a single unit dosage form containing palonosetron and netupitant would “give greater convenience and safety for patient and doctor and reduce the risk of errors in medication,” and would have understood the advantages of such administration to outweigh any potential disadvantages. *Id.*; EX1009, ¶1306; *see also* EX1060, Abstract, 1:48-2:8 (double capsules with multiple actives well known in the art). A POSA would thus have had good reason to formulate a single unit dose with both palonosetron and netupitant, including in the recited dose amounts. EX1009, ¶¶1306-07; *see also Richardson-Vicks Inc. v. Upjohn Co.*, 122 F.3d 1476, 1480-83

(Fed. Cir. 1997) (claim providing single-unit dosage of drugs previously prescribed together separately obvious as a matter of law, regardless of evidence of synergy).

A POSA would also have had good reason to look to Bonadeo when developing a fixed combination dose of palonosetron and netupitant because Bonadeo explains its favorable use in developing a palonosetron capsule. EX1017, 2; *see also id.*, 3 (“Dosage forms of palonosetron, including methods of manufacture, have also been developed with enhanced stability due to their protection from oxygen and oxygen mediated degradation.”); EX1009, ¶1177; *see also supra* §XI (obvious to look to ALOXI). A POSA would also have had a reasonable expected success in the combination, as the recited dosage formats were well-known, predictable options for co-administration of pharmaceuticals. EX1009, ¶¶1308-12.

XV. GROUND 8: CLAIMS 36 AND 45 WERE OBVIOUS OVER HERRSTEDT, BÖS, BONADEO, HARGREAVES, HERRINGTON AND ALOXI

Claims 36 and 45 depend from claims 21 and 35, respectively. As explained in ground 7, claims 36 and 45 were obvious over Herrstedt, Bös, Bonadeo, Hargreaves, Herrington and ALOXI. *Supra* §XIV. Claims 36 and 45 each further recite that “said netupitant occupies at least 70% of said patient’s striatum NK₁ receptors ninety-six hours after said administration.” As further explained in ground 5 for claims 24 and 29, this limitation was obvious over the further

teachings of Hargreaves. *Supra* §XII. For similar reasons, the combination of Herrstedt, Börs, Bonadeo, Hargreaves, Herrington and ALOXI renders claims 36 and 45 obvious, and a POSA would be motivated to arrive at the claimed invention with a reasonable expectation of success. EX1009, ¶¶1315-28.

XVI. NO SECONDARY CONSIDERATIONS

Although Helsinn asserts unexpected properties for netupitant, these properties were present for aprepitant. 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 existence of unexpected properties forecloses a finding of a reasonable expectation of success” because “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 of the application that issued as Trento’826, Helsinn sought to distinguish the new NK₁ antagonist—netupitant—from known NK₁ antagonist—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 [i.e., 0-24 hours] of CINV.” EX1002, 2:12-26.

Trento’826 alleges “it has unexpectedly been discovered that netupitant is active against nausea” *Id.*, 4:37-39. Helsinn also argued during examination that 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 the method using netupitant (in substitution for aprepitant) because “the claimed regimen treats both nausea and vomiting.” *Id.*, 330.

Similarly, during examination of the application that issued as Trento’297 patent, Helsinn alleged unexpected results with the combination of netupitant and palonosetron as compared to aprepitant because, in its selected trials of aprepitant, “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, 331. 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. *Id.*, 331-32. Despite Helsinn’s representations to the examiner, however, experimental data shows that a POSA would have understood aprepitant to be

effective at treating nausea. EX1009, ¶¶1329-32.

The Trento’357 claims are not patentably distinct from the Trento’826 or Trento’297 claims. EX1009, ¶¶33-34, 50-52 (obviousness-type double patenting and terminal disclaimers).

1. Emend label

The common specification reports the Emend label shows that “[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 portions of the Emend label 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. Although statistical significance was not calculated for nausea parameters, the “**complete protection**” value **includes** a lack of significant nausea in its metric. 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, when evaluating whether a patient achieved “**complete protection**,” the Emend label requires (1) **no** emetic episodes; (2) **no** rescue therapy; **and** (3) **no significant nausea**. EX1009, ¶1334. Table 1 of the Emend

label, 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 for 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.

The Emend label shows similar benefits in a second study, which reports “***complete protection***” with statistical significance for ***each of*** the overall, acute phase, and delayed phase timelines. EX1009, ¶1336. The label also reports “In 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 themselves reported a significant improvement on their daily lives due to less nausea and vomiting versus to 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 has an effect on nausea 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 data in Helsinn’s declaration before the examiner 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.

The data in Table 6’s “Palo + Aprep” is not comparable with any of the other columns, and thus cannot show any surprising results or particular benefit for netupitant instead of 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 therapeutic effect for **nausea** and shows it provided significant additive benefit during the acute phase of CINV. EX1009, ¶¶1352; EX1023 (Campos), Abstract, 1763 & Table 4. Campos teaches the 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. *Id.*, 1763. Campos also explains that median nausea scores were lower with the triple therapy in the delayed phase (days 2-5). *Id.*, 1763-1764; EX1009, ¶1353. What Helsinn told the examiner was wrong: the art knew aprepitant provides a beneficial effect for nausea, including specifically providing therapeutic effect to prevent nausea during the acute phase for CINV. EX1009, ¶1354. Post-critical dates add further confirmation. EX1009, ¶¶1355-59.

B. Misrepresentation of data during examination

Helsinn responded to an obviousness rejection with a declaration that exaggerates the difference the triple therapy of netupitant, palonosetron, and dexamethasone versus the prior art. 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 the alterations, 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 and netupitant combination, yet relied on what it represented as its own internal studies. EX1005, 346; EX1009, ¶1365. A POSA would not rely on Helsinn’s purported studies without having access to 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 preventing significant nausea, in MEC patients receiving either aprepitant and ondansetron or netupitant and palonosetron; indeed, during the acute phase, aprepitant showed a slight **improvement** compared to Helsinn’s internal netupitant study. EX1009, ¶1369. This withheld data confirms that 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, even though this parameter requires an evaluation of significant nausea. EX1009, ¶¶1371-72. A POSA would have understood that the **complete protection** value incorporated an evaluation of no significant nausea and was reported with statistical significance. EX1009, ¶1373.

d. Grunberg (Column 6)

The common specification contends aprepitant and 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 its Rule 132 Declaration withheld from its summary substantial and material differences in dosing across cohorts, even though such difference render the Grunberg study incomparable to the Helsinn internal studies, but there are significant differences between the studies that render them non-comparable. EX1009, ¶1374. For example, in Grunberg’s study, participants could receive additional chemotherapy, which would cause additional emesis. EX1035 (Grunberg), 591; EX1009, ¶1375. Grunberg did not administer the normal (FDA-approved) dose of aprepitant on Day 1 (125 mg). EX1013, Table 3; EX1016, 2081; EX1009, ¶1376. Finally, Grunberg administered the dexamethasone only on the first day prior to administration of the chemotherapeutic agent. 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 the antiemetic dexamethasone administered on each of day one, day two, day three, and day four. EX1001, 17:19-64; EX1009, ¶1377. Each of these differences

precludes making a direct comparison between Grunberg's results and the specification's results because such a flawed comparison would overstate the antiemetic effect of netupitant in the combination as compared to aprepitant in the combination. EX1009, ¶1378.

C. No Unexpected Synergy Between Netupitant and Palonosetron

The common patent 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 context of the claims or purported unexpected results. Synergy often means that a combination has a greater benefit than the sum of its distinct parts. EX1009, ¶1381. Yet Helsinn's own declaration data show the combination of palonosetron with **any** NK₁ antagonist had a beneficial effect on nausea. Thus, if a synergistic effect existed, the declaration data shows that such effect is just as applicable to the known combination of palonosetron and aprepitant. 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 if Helsinn’s Table 2 data were accurate (it is hearsay), it 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” specifically with the combination of netupitant and palonosetron. 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 combination of netupitant and palonosetron is substantially the same as the combination of aprepitant and palonosetron, yet the claims do not include aprepitant; indeed, the data indicate a benefit of combining palonosetron and *any* NK₁ antagonist. EX1009, ¶¶1387-88. Moreover, most claims do not specify a dose, yet combinations of palonosetron and aprepitant often outperform combinations with netupitant. 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 that it was

unexpected “that 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 dose of aprepitant is sufficient for treatment of the acute and delayed phases of emesis. EX1009, ¶¶1391-92; EX1016, Abstract, Table 3. From Herrington, a POSA would have expected a single dose of netupitant to also provide therapeutic effect during the acute and delayed phases of emesis. EX1009, ¶1393.

F. Acute Phase Treatment with Netupitant Was Expected

During examination of a related patent, Helsinn argued that it was unexpected “that netupitant also treats emesis during the acute phase”. EX1007, 203. Yet Herrstedt teaches NK₁ antagonists treat emesis during the acute phase. 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 compound known in the prior art—as allegedly unexpected. EX1001, 4:37-51, 5:13-20, Yet Helsinn's purported unexpected discoveries merely recite characteristics of netupitant itself. EX1009, ¶¶1398-1400. Because netupitant was already known in the prior art, any asserted unexpectedness of its characteristics cannot weigh in favor of 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, 5-10, 17-39, and 43-51 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’357.

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:

8,623,826, IPR2025-00945, filed 1 May 2025;

9,186,357, IPR2025-00946 (claims 2-4, 11-16, 40-42, and 52-62), 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

Lead	Richard Torczon, Reg. No. 34,448; rtorczon@wsgr.com
First Backup	Jad A. Mills, Reg. No. 63,344; jmills@wsgr.com
Backup	Michael Rosato, Reg. No. 52,182; mrosato@wsgr.com
	Wendy Devine, Reg. No. 61,309; wdevine@wsgr.com

D. Service Information

Wilson Sonsini Goodrich & Rosati

701 Fifth Avenue, Suite 5100

Seattle, WA 98104-7036

Telephone: 206-883-2554. Facsimile: 206-883-2699.

Please direct all correspondence to the contact information above. Azurity consents to electronic-mail service at the email addresses for counsel listed above and at 4877-8318-2285@mail.vault.netdocuments.com.

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)
1011	T. Hoffmann et al., <i>Design and synthesis of a novel, achiral class of highly potent and selective, orally active neurokinin-1 receptor</i>

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

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

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

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

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

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

Exhibit	Description
1059	P. Li & L. Zhao, <i>Developing Early Formulations: Practice and Perspective</i> , 341 International Journal of Pharmaceutics 1 (2007)
1060	G. Sanso, <i>Double capsule for the administration of active principles in multiple therapies</i> , U.S. Patent 6,350,468 B1 (issued 26 Feb. 2002)
1061	B. Cromie, <i>Drug Combinations</i> , 1(2) Current Medical Research and Opinion 78 (1972)

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 12,190 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, a statement regarding multiple petitions, 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