

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 IPR2025-00948
Patent US 9,943,515 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 1-23 of U.S. Patent 9,943,515 (“Trento’515”, EX1003), assigned to Patent Owner (Helsinn). This petition covers 23 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, and materially-flawed testimony. As this petition and accompanying exhibits with expert testimony show, these claims were never patentable.

II. STANDING CERTIFICATIONS

Trento’515 is available for IPR. Azurity is not barred or estopped from requesting IPR on these grounds.

III. CHALLENGES AND PRECISE RELIEF REQUESTED

Claims 1-23 should be cancelled as unpatentable under 35 U.S.C. §103¹ on these grounds:

¹ All references to 35 U.S.C. §§102 and 103 are to the pre-AIA versions.

Ground	Claims	Obvious from the Combined Teachings of
1	11-17 & 19-23	Herrstedt ² (EX1010), Bös ³ (EX1014) & optionally Herrington ⁴ (EX1017)
2	1-10 & 18	Herrstedt, Bös, Hargreaves ⁵ (EX1012) & Herrington

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

IV. TRENTO'515 PATENT

Trento'515 is entitled "Compositions and methods for treating centrally mediated nausea and vomiting", claims priority to a provisional filed on November

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

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

18, 2009, and purports to provide “compositions and methods for treating or preventing nausea and vomiting in patients undergoing chemotherapy, radiotherapy, or surgery.” EX1003, cover.

A. Specification

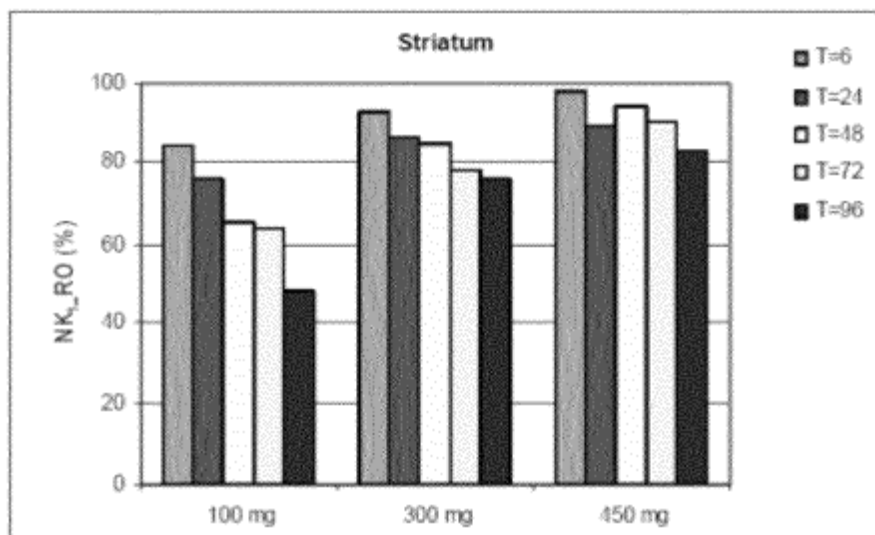
The specification “relates to the use of centrally acting NK₁ antagonists to treat nausea and vomiting, particular[ly] nausea and vomiting induced by highly emetogenic chemotherapy, and to the treatment of such nausea and vomiting over multiple consecutive days. The present invention also relates to combined oral dosage forms of palonosetron and netupitant.” EX1003, 1:25-31. 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.” EX1003, 1:42-45. Indeed, “[p]alonosetron hydrochloride ha[d] recently emerged as a highly efficacious anti-nauseant and anti-emetic agent.” EX1003, 1:50-51.

NK₁ antagonists aprepitant and casopitant had been tested—FDA had even approved aprepitant “for the prevention of nausea and vomiting”—but Trento’515 reported neither was effective. EX1003, 2:29-34. (Actually, Helsinn reported similar or better results for the standard “Aprepitant Regimen” versus netupitant regimens. EX1003, 19:Table 6; EX1009, ¶24.) Nevertheless, Trento’515 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.” EX1003, 3:60-4:9. Trento’515 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. EX1003, 4:55-5:40.

Example 4 in Trento’515 discloses the results of 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 in subjects receiving a single oral dose of 300 mg or more. 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). EX1003, 17:4-28.



B. Challenged Claims

Trento'515 has 23 claims; two (1, 11) are independent. Claim 11 relates to treating acute- or delayed-phase nausea and vomiting for 5 days with a single dose of netupitant. Claim 1 relates to treating acute- or delayed-phase nausea and vomiting for 5 days by administering day-one netupitant. EX1003, 22:2-19, 23:1-14.

C. Prosecution History

Trento'515 issued from application 15/003,327 (EX1007), filed 19 May 2016, which claims priority to PCT/IB2010/003106⁶ and to provisionals 61/382,709⁷ and 61/262,470.⁸ Its earliest possible effective filing date is 18 November 2009; however, the earlier provisional never discloses co-administering dexamethasone, so claims encompassing dexamethasone are not entitled to priority before 14 September 2010.

During examination, the examiner rejected claims over Reddy,⁹ which

⁶ EX1055, filed 18 November 2010.

⁷ EX1056, at 154-190, filed 14 September 2010.

⁸ EX1057, at 192-219, filed 18 November 2009.

⁹ 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).

taught treating CINV by administering an 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 treating chemotherapy-induced nausea and vomiting (CINV) with an NK₁ antagonist, a 5-HT₃ antagonist, and dexamethasone, where the NK₁ antagonist could be aprepitant or netupitant. The examiner also rejected the claims for double patenting over Helsinn’s 8,623,826 (EX1001) and 9,186,357 (EX1002) patents.¹⁰ EX1007; EX1009, ¶¶36-37. The examiner found netupitant’s NK₁-receptor occupancy in the striatum of at least 80% was an inherent property. EX1007, 150; EX1009, ¶38.

In response, Helsinn amended its independent claims and argued “Reddy does not anticipate or render obvious independent claims 16 and 54 because Reddy does not teach or suggest the prevention of emesis during the acute phase by netupitant” because aprepitant allegedly had a lesser effect based on Table 6 of the applicant’s specification. EX1007, 196, 201-02. Helsinn also argued Reddy “does not describe or suggest the administration of a single dose of netupitant over a five-

¹⁰ The objects of IPR2025-00945 and IPR2025-00946 and -00947, respectively.

day period” and asserted “[a] tremendous amount of work was required to discover [the] dosing limitations” of the claims. *Id.*, 200-02. Helsinn then argued treating acute and delayed CINV with a single netupitant dose, especially its acute-phase effectiveness, were unexpected results. *Id.*, 203; EX1009, ¶39. Helsinn did not contest the inherency of netupitant’s receptor occupancy; instead, Helsinn relied on this inherency to support its claim to an unexpected result. *Id.*, 203; EX1009, ¶40.

In a final Office action, the examiner maintained the rejection over Reddy. EX1007, 211-213. The examiner found (1) “[t]he familiarity of working with an NK-1 antagonist and its intended use make obvious the administration of netupitant, as claimed, based on the administration of other NK-1 antagonists, e.g. aprepitant” made it “obvious to administer netupitant on day one of five consecutive days;” (2) the specification’s Table 5 failed “to distinguish over aprepitant, especially since numbers were fairly similar;” (3) the “binding habit of netupitant is *an inherent property* of netupitant” and the other purported benefits were known in the art; and (4) Helsinn failed to establish unexpected results and that “administration of a single dose...may also be construed as *an inherent property* of netupitant especially since the prior art teaches administration to patients for treatment of chemotherapy-induced nausea and vomiting.” *Id.*, 215-18; EX1009, ¶40. In response, Helsinn canceled claims and amended then-pending independent claims to require a single dose of netupitant. EX1007, 281-82. Helsinn

argued the single-dose requirement without further doses to treat delayed nausea distinguished over the prior art. *Id.*, 286-87. Helsinn also continued to argue that “Netupitant’s efficacy during the acute phase is unexpected.” *Id.*, 288-89. Helsinn did not contest the examiner’s finding that the claimed features of netupitant were inherent. EX1009, ¶41.

Following the after-final rejection response, the examiner issued an advisory action, stating that the amendments would raise new issues and thus the amendments would not be entered. EX1007, 312. The applicant then filed a Request for Continued Examination and amended the independent claims to recite “no further netupitant or pharmaceutically acceptable salt thereof is administered during said five consecutive days, and said single dose of netupitant or pharmaceutically acceptable salt thereof if [sic] effective to treat said nausea and vomiting for said five consecutive days.” *Id.*, 324, 326. The applicant also reiterated that its “position is that it is unexpected that a single dose of netupitant would be effective against nausea and vomiting during the acute and delayed phases of emesis.” *Id.*, 328-29. Following after-final prosecution to enter amendments and terminal disclaimers, the examiner allowed the claims without further substantive examination. EX1009, ¶¶41-49.

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’515 itself notes the high level of skill in the art. For example, “[t]he skilled artisan will be able to determine appropriate dosages[.]” EX1003, 8:17-19. Similarly, the art can determine the “suitable dosing regimen”. EX1003, 10:37-40. *Cf. Immunogen, Inc. v. Stewart*, No. 23-1762, slip 10 (Fed. Cir. 2025) (affirming obviousness where art showed physicians could determine the claimed dose).

VI. CLAIM CONSTRUCTION

Trento’515 provides definitions of claim terms. EX1003, 7:26-8:31.

The phrase ***therapeutically effective amount***¹¹ means “an amount sufficient to elicit the desired biological response.” EX1003, 8:13-15.

The word ***if*** in claims 1 and 11 appears from context to mean “is”. *Ex parte Tanksley*, 26 USPQ2d 1384, 1387 (BPAI 1991) (reaching merits where claim

¹¹ Bold-italicized text indicates added emphasis.

meaning was sufficiently clear to apply the prior art).

The phrase *minimum effective dose of dexamethasone* means 20 mg on day-one and on subsequent days 16 mg for HEC and 0 mg for MEC. EX1003, 8:20-30 (“The minimum effective dose of dexamethasone, when used to treat CINV induced by [HEC], has been demonstrated to be 20 mg. administered orally or by injection on day one, and sixteen mg. administered orally or by injection on days two, three and four. * * * When used to treat CINV induced by [MEC], the minimum effective dose of dexamethasone is 20 mg. administered orally or by injection on day one, and zero mg. on days two, three and four.”); EX1009, ¶635.

For claim element 1[b], the plain and ordinary meaning of “*which*” in the phrase beginning “which enters...” is that the functions following “which” describe inherent properties rather than therapeutic effects that might further restrict a therapeutically-effective amount. *In re Hyatt*, 708 F.2d 712, 714 (Fed. Cir. 1983) (“A claim must be read in accordance with the precepts of English grammar.”); EX1009, ¶¶614-17 (explaining the prior art identifies these functions as inherent in a therapeutic amount).

VII. PRIOR ART

All the applied and background references were publicly available over one year before the critical date and are thus 35 U.S.C. 102(b) prior art. No ground reference was applied in a rejection during examination.

A. Herrstedt

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. 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.

D. 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.

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 11-17 AND 19-23 WERE OBVIOUS OVER HERRSTEDT, BÖS, AND HERRINGTON

These claims were unpatentably obvious variants on a then-state-of-the-art professional recommended 3-drug regimen with a newer NK₁ antagonist (netupitant) substituted for an older NK₁ antagonist (aprepitant), with routine choices about dosage form, amount, and timing. Herrstedt teaches methods of treating both nausea and vomiting for five consecutive days after chemotherapy. EX1010, 143, 146. Herrstedt teaches administering a day-one NK₁ antagonist (aprepitant) in a therapeutically effective amount. *Id.*, 146. Herrstedt describes that the above steps are effective to treat both nausea and vomiting during a 5-day period. *Id.*, 146. EX1009, ¶¶504-06.

Bös teaches its “Formula Ib” is an improved NK₁ antagonist. EX1014, 14:31-38 (“The compound of formula Ib and its salts is also characterized by *valuable therapeutic properties* as a *highly selective* antagonist of the Neurokinin 1 (NK-1, substance P)”), 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.”). A POSA would have known Bös formula Ib was netupitant. EX1009, ¶507 (comparing structures).

Herrington teaches administering an NK₁ antagonist (aprepitant) on day one—and only on day one—of a five-day treatment period was effective at

preventing nausea and vomiting from chemotherapy-induced emesis. EX1017, Abstract; EX1009, ¶508.

A. Claim 11 is an obvious modification of the prior art

- 1. [preamble]: “A method of treating nausea and vomiting in response to an emesis-inducing event for a period of five consecutive days in a patient in need thereof, comprising”**

To the extent the preamble is limiting, Herrstedt teaches it. Herrstedt teaches methods for treating “[c]hemotherapy-induced *nausea and vomiting*” in a patient. EX1010, 143. Herrstedt explains chemotherapy is an emesis-inducing event. *Id.* (“emesis is a natural consequence of treatment with most cancer chemotherapy.”). Herrstedt’s primary therapeutic endpoint was no emesis for five consecutive days following administration of the chemotherapeutic agent (e.g., 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, ¶¶509-10.

- 2. [a]: “administering to said patient netupitant or a pharmaceutically acceptable salt thereof, in a therapeutically effective amount which is effective to treat nausea and vomiting during the acute and delayed phases of emesis,”**

Herrstedt reports studies treating highly-emetogenic chemotherapy patients with a triple-drug combination including an NK₁ antagonist (aprepitant). EX1010,

146 (“Two of the HEC studies used an identical design...ondansetron, dexamethasone and *aprepitant* day 1 followed by dexamethasone days 2-4 plus *aprepitant* days 2-3.”). Herrstedt teaches the NK₁ antagonist is administered in a therapeutically effective amount, providing benefits to patients receiving the antiemetic combination. *Id.* (“a complete response of 72.7% in the *aprepitant* arm versus 52.3% in the control arm” and “complete response rates were 62.7% versus 43.3%” in another study); *id.* (“Again a statistical[] benefit favouring *aprepitant* was seen, resulting in a complete response in the *aprepitant* arm of 72.0% versus 60.6% in the control arm.”). EX1009, ¶¶511-12.

Herrstedt teaches a therapeutically-effective amount of NK₁ antagonist treats nausea and vomiting during both acute and delayed emesis. NK₁ antagonist treatment in Herrstedt “increase[d] the effect of a serotonin₃-receptor antagonist plus a corticosteroid against *acute emesis* induced by highly or moderately emetogenic chemotherapy” and also was “active in the protection against *delayed* emesis.” EX1010, Abstract, 148-149 & Table 4. EX1009, ¶513.

A POSA additionally would have understood Herrstedt’s antiemetic therapy treated nausea and vomiting during the acute and delayed phases of emesis because it provided a “complete response,” which covers both acute and delayed phases following chemotherapy. EX1010, 146 (“Complete response, defined as ‘no emesis and no rescue therapy on days 1-5 postcisplatin’, was the primary end-point

in all studies.”). A POSA would have known the acute phase means the first 24 hours following chemotherapy and the delayed phase means the period 24 to 120 hours after chemotherapy. *Id.*, 143; EX1009, ¶¶514-15.

Although Herrstedt reports administering the NK₁ antagonist aprepitant, Herrstedt teaches that aprepitant was merely “the first drug” in this class of selective NK₁ antagonists. Herrstedt, Abstract. Bös not only discloses netupitant (“formula Ib”) as a potent and selective NK₁ antagonist, but also recommends use of an effective amount of netupitant for treating emesis. EX1014, 14:31-38 (“The compound of formula Ib [netupitant] and its salts is also characterized by *valuable therapeutic properties* as a *highly selective* antagonist of the Neurokinin 1 (NK-1, substance P”), 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.”). Indeed, “[T]he most preferred indications” identified in Bös “are those which include *disorders of the central nervous system*, for example indications for the treatment or prevention of certain depressive disorders, anxiety or *emesis by the administration of NK-1 receptor antagonists.*” *Id.*, 4:15-24. Bös teaches “pharmacological activity of the compounds of this invention as NK-1 receptor antagonists ... is correlated with treatment of” CNS disorders. *Id.*, 39:42-48, 9:22-29 (“particularly useful for

treating CNS disorders, such as ... emesis.”), 19:10-30 (netupitant effective for treatment of emesis). EX1009, ¶516.

Bös teaches a therapeutically effective amount of its NK₁ antagonists (including netupitant) to be within 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.”). Thus, Bös discloses netupitant as a potent and selective NK₁ antagonist and teaches administering from a dosing range of about 10 to 1000 mg for a therapeutically effective amount. EX1009, ¶517. A POSA thus had good reason to replace Herrstedt’s aprepitant with Bös’ newer netupitant with a reasonable expectation of successfully determining a therapeutic dose. EX1009, ¶¶518-19.

3. [b]: “wherein said therapeutically effective amount of netupitant or pharmaceutically acceptable salt thereof is administered on day one of said five consecutive days, no further netupitant or pharmaceutically acceptable salt thereof is administered during said five consecutive days, and said single dose of netupitant or pharmaceutically acceptable salt thereof if [sic, is] effective to treat said nausea and vomiting for said five consecutive days.”

Herrstedt teaches administering a single dose of NK₁ antagonist (aprepitant)

on the first of said five consecutive days, then administering more aprepitant on days one, two, and three. EX1010, 146 (“Two of the HEC studies used an identical design comparing ondansetron, dexamethasone and placebo day 1 followed by dexamethasone plus placebo days 2-4 with ondansetron, dexamethasone and *aprepitant day 1* followed by dexamethasone days 2-4 plus aprepitant days 2-3...”); EX1009, ¶¶520-21.

The combined teachings of Herrstedt and Bös suggest a single dose of netupitant is administered on the first of said five consecutive days, with no further netupitant during the five consecutive days, would be effective to treat nausea and vomiting for the five-day period because netupitant was known to have a large half-life value, thus providing reason to omit subsequent NK₁-antagonist dosing. Bös, 19:3-10 (functional half-life of 30 hours). EX1009, ¶522. Herrington confirms the suggestion that a single dose of NK₁ antagonist on day 1 renders further doses in the 5-day period unnecessary because Herrington teaches a single dose of aprepitant provided similar effectiveness as compared to Herrstedt’s protocol of dosing aprepitant three times. EX1017, 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.*”). Thus, a POSA would have reasonably expected a single dose of an NK₁ antagonist on day 1 would be as successful as dosing the NK₁ antagonist on multiple days. EX1009, ¶523; *id.*, 2081 (“The primary efficacy endpoint was the proportion of patients with emesis in the acute (Day 1) and delayed (Days 2-5) phases after chemotherapy.”), Abstract (“There were no significant differences between Arms A [3-day aprepitant] and B [single day-1 dose aprepitant] for emesis, nausea, or the use of break-through antiemetics. In *Arms A and B, 93% of patients were emesis-free from Days 1-5* compared with only 50% in Arm C [control group].”), 2086 (“The control of nausea was achieved in similar fashion between the 2 aprepitant arms.”). Although Herrington identified “a trend toward better significant nausea on Days 4-5 with the 3-day Arm A versus the single dose” the mean severity of nausea for the single dose of aprepitant was lower than the control test group across all five days. *Id.*, 2086, 2084 & Table 4; EX1009, ¶523. A POSA would have been motivated to use a single dose of aprepitant as disclosed by Herrington in Herrstedt’s therapeutic combination for increased simplicity and ease of patient compliance. EX1009, ¶¶524-26.

B. Claim 12: “The method of claim 11, comprising orally administering from about 200 to about 400 mg of netupitant as the free base.”

Building on the obviousness of claim 11, Bös teaches orally administering a therapeutically-effective amount of NK1 antagonists—including netupitant—in a range that includes from about 200 mg to about 400 mg as the free base. EX1014, 2:1-65, 14:9-20, 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.”). Bös teaches its NK₁ antagonists (e.g., netupitant) are useful “for treatment induced vomiting” including “the reduction of cisplatin-induced emesis by a selective neurokinin-1-receptor antagonist.” EX1014, 1:60-64, 14:9-15:20 (Formula Ib is netupitant), 14:32-38 (netupitant “is also characterized by valuable therapeutic properties as a highly selective antagonist of the Neurokinin 1 (NK-1, substance P)”), 18:42-19:38 (favorable in vitro and in vivo studies as well as oral bioavailability and half-life results); EX1009, ¶¶527-30.

A POSA would have recognized Bös’ range spanning (about 10 to 1000 mg) as a favorable starting point for identifying optimal therapeutic dose amounts, with good reason to optimize within Bös’ range to determine a therapeutically-effective

amount of netupitant, and with a reasonable expectation of success in attaining a therapeutically-effective dose. EX1009, ¶531; *In re Urbanski*, 809 F.3d 1237, 1242 (Fed. Cir. 2016) (routine to optimize result-effective variable). Dose determination is routine in the art, as Trento’515 contemplates for its own claims. EX1003, 8:13-19, 10:37-40; EX1009, ¶¶532-33.

C. Claim 13: “The method of claim 11, comprising orally administering about 300 mg of netupitant as the free base.”

Building on the obviousness of claim 11, Bös teaches orally administering therapeutically-effective amounts of NK₁ antagonists—including netupitant—in a range including about 300 mg of netupitant as a free base. EX1014, 42:5-11 (“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.”). A dose of 300 mg falls squarely within the disclosed range, near its midpoint. EX1009, ¶534-36. A POSA would have recognized a range spanning two orders of magnitude to be a common starting point when determining therapeutic-dose amounts, and would have been routine to have arrived at about 300 mg as a therapeutically-effective dose through typical optimization. *Id.*, ¶¶537-38; EX1003, 8:13-19 (dose determination is routine); *Urbanski*, 809 F.3d at 1242. Trento’515 itself does not ascribe any criticality or unexpected results to a 300 mg dose of netupitant. EX1009, ¶¶539-40.

D. Claim 14: “The method of claim 11, wherein when said emesis inducing event comprises highly emetic chemotherapy, and the chemotherapy is selected from the group consisting of carmustine, *cisplatin*, cyclophosphamide ≥ 1500 mg/m², dacarbazine, dactinomycin, mechlorethamine, streptozotocin and combinations thereof.”

Building on the obviousness of claim 11, Herrstedt teaches HEC is an emesis-inducing event that may be treated with an antiemetic-drug combination to combat CINV. EX1010, Abstract (efficacy of the drug combination on “emesis induced by *highly ... emetogenic chemotherapy*”). Herrstedt specifically teaches the chemotherapy could be cisplatin. EX1010, 146 (“Four phase III trials have investigated the use of aprepitant in patients receiving *cisplatin-based, highly emetogenic chemotherapy* or a combination of cyclophosphamide plus an anthracycline. Complete response, defined as ‘no emesis and no rescue therapy on days 1–5 *postcisplatin*’, was the primary end-point in all studies.”). Moreover, Herrstedt teaches treating CINV in response not only to cisplatin, but broadly treating CINV. EX1010, Abstract (explaining NK₁ antagonist “increases the effect of a serotonin₃-receptor antagonist plus a corticosteroid against acute emesis induced by *highly or moderately emetogenic chemotherapy...*”). Herrstedt describes such HEC includes cisplatin, mechlorethamine, streptozocin, dacarbazine, and cyclophosphamide > 1500 mg/m². *Id.*, Table 1; EX1009, ¶¶541-46.

E. Claim 15: “The method of claim 11, wherein when said emesis inducing event comprises moderately emetic chemotherapy, and the chemotherapy is selected from the group consisting of carboplatin, cyclophosphamide<1500 mg/m², cytarabine>1 mg/m², daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, oxaliplatin and combinations thereof.”

Building on the obviousness of claim 11, Herrstedt teaches MEC is an emesis-inducing event that may be treated with Herrstedt’s antiemetic drug combination. EX1rstedt, Abstract (efficacy of the drug combination on “emesis induced by ... *moderately emetogenic chemotherapy*”). While Herrstedt reports treating CINV after HEC (cisplatin) (Herrstedt), Herrstedt suggests using NK₁ antagonists more broadly. EX1010, 146, Abstract (NK₁ antagonist “increases the effect of a serotonin₃-receptor antagonist plus a corticosteroid against acute emesis induced by *highly or moderately emetogenic chemotherapy*...”) Herrstedt teaches MEC includes carboplatin, cyclophosphamide<1500 mg/m², cytarabine>1000 mg/m² (which includes cytarabine>1 mg/m²), daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, and oxaliplatin. *Id.*, Table 1; EX1009, ¶¶547-51.

F. Claim 16: “The method of claim 11, wherein said emesis inducing event comprises chemotherapy selected from the group consisting of carboplatin, cyclophosphamide, cytarabine >1 mg/m², daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, carmustine, *cisplatin*, dacarbazine, dactinomycin, mechlorethamine, streptozotocin, oxaliplatin and combinations thereof.”

Building on the obviousness of claims 11 and 14 (which claims treating cisplatin-induced emesis), claim 16 was obvious for the reasons claims 11 and 14 were obvious. EX1009, ¶¶552-56.

G. Claim 17: “The method of claim 11, for the treatment of CINV defined as no emetic episodes and no use of rescue medication following chemotherapy.”

Building on the obviousness of claim 11, Herrstedt defines treatment of CINV as no emetic episodes and no use of rescue medication following chemotherapy, also called a “complete response”. EX1010, 146 (“[c]omplete response, *defined as ‘no emesis and no rescue therapy on days 1-5 postcisplatin’*, was the *primary end-point in all studies.*”); EX1009, ¶¶559-60. Herrstedt teaches treating CINV with a therapeutically-effective amount of an NK₁ antagonist. EX1010, 146; EX1009, ¶¶557-62.

H. Claim 19: “The method of claim 11, wherein said emesis inducing event is highly emetogenic chemotherapy, and said regimen is effective to prevent or reduce the severity of nausea during the acute and delayed phases.”

Building on the obviousness of claim 11, Herrstedt teaches treating CINV from HEC. EX1010, 146 (“cisplatin-based, highly emetogenic chemotherapy”).

Herrstedt specifically teaches the NK₁ antagonist is “also active in the protection against delayed emesis.” *Id.*, Abstract, 146; EX1009, ¶¶563-65.

A POSA would have understood Herrstedt to teach an antiemetic therapy effective to achieve a “complete response”, i.e., to prevent or reduce the severity of nausea during the acute and delayed phases. EX1010, 146 (“Complete response, defined as ‘no emesis and no rescue therapy on days 1-5 postcisplatin’, was the primary end-point in all studies.”). A POSA knew *acute phase* means the first 24 hours following chemotherapy and *delayed phase* means the period 24 to 120 hours after chemotherapy. *Id.*, 143. Hence, a POSA would have expected Herrstedt’s combination with netupitant as the NK₁ antagonist to treat both acute and delayed emesis. EX1009, ¶¶566-68.

I. Claim 20: “The method of claim 11, wherein said emesis inducing event is moderately emetogenic chemotherapy, and said regimen is effective to prevent or reduce the severity of nausea during the acute and delayed phases.”

Building on the obviousness of claim 11, Herrstedt suggests treating CINV after MEC with an antiemetic drug combination. Herrstedt, Abstract (efficacy of the drug combination on “emesis induced by highly or *moderately emetogenic chemotherapy*”). Although Herrstedt reports studies for preventing CINV after HEC (cisplatin) (EX1010, 146), Herrstedt teaches using NK₁ antagonists more broadly to treat MEC-induced nausea and vomiting. The NK₁ antagonist “increases the effect of a serotonin₃-receptor antagonist plus a corticosteroid against acute

emesis induced by highly or *moderately emetogenic chemotherapy*....” EX1010, Abstract, Table 1. Thus, a POSA would have understood Herrstedt to teach administering its antiemetic drug combination to treat MEC-induced CINV. EX1009, ¶¶569-73.

Herrstedt also teaches its combination therapy achieves a “complete response,” which means treating *both acute and delayed phases* CINV following chemotherapy. Herrstedt, 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, ¶¶574-75. A POSA had good reason to administer Herrstedt’s combination, substituting Bös’ netupitant, with a reasonable expectation of success in achieving a complete response (both acute and delayed) for MEC-induced CINV. EX1009, ¶¶576-77.

J. Claim 21: “The method of claim 11, wherein said emesis inducing event comprises *cisplatin*.”

K. Claim 22: “The method of claim 11, wherein said emesis inducing event comprises carboplatin, *cisplatin*, oxaliplatin, or doxorubicin.”

Building on the obviousness of claims 11 and 14, claims 21 and 22 both define the emesis-inducing event as comprising treatment with cisplatin, in the case of claim 22, as one of four options. Claims 21 and 22 are obvious for the reasons given for claim 14.

EX1009, ¶¶578-82.

L. Claim 23: “The method of claim 11, wherein said emesis inducing event comprises cyclophosphamide.”

Building on the obviousness of claim 11, Herrstedt teaches the emesis-inducing event comprises HEC or MEC, both of which can be treated with Herrstedt’s antiemetic drug combination. EX1010, Abstract (efficacy of the drug combination on “emesis induced by *highly or moderately emetogenic chemotherapy*”). Herrstedt teaches cyclophosphamide is an emetogenic chemotherapy, classified as highly emetogenic or moderately emetogenic depending on its dose. *Id.*, Table 1 (reproduced below). A POSA would have understood Herrstedt to suggest that its antiemetic drug combination treats MEC-inducing CINV, where the MEC is cyclophosphamide. EX1009, ¶¶583-88.

M. Reasons 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 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 increase patient compliance and ease of administration for both

provider and patient. EX1009, ¶¶589-92.

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 act in the same manner to achieve a similar (or better) outcome. EX1009, ¶593. Similarly, a POSA would have reasonably expected a single therapeutically-effective dose of netupitant (having an even longer half-life) to work for 5-days, just as the older aprepitant that it replaced did. EX1009, ¶¶594-95.

X. GROUND 2: CLAIMS 1-10 AND 18 WERE OBVIOUS OVER HERRSTEDT, BÖS, HARGREAVES, AND HERRINGTON

A. Claim 1

The combination of Herrstedt, Bös, Hargreaves, and optionally Herrington discloses each and every element of each of claims 1-10 and 18. A POSA had good reason to combine these references in a manner that satisfies each claim as a whole with a reasonable expectation of success. Herrstedt teaches treating both nausea and vomiting for five consecutive days. EX1010, 143, 146. Herrstedt also teaches administering an NK₁ antagonist (aprepitant) in a therapeutically-effective amount on day 1. EX1010, 146. Using an NK₁ antagonist required administering a lower day-1 dose of dexamethasone in a lower dose than what would typically be given (i.e., ineffective against CINV when administered alone) but was effective when administered in combination. EX1010, 146-147. EX1009, ¶¶596-98.

Bös teaches its “Formula Ib” is an improved NK₁ antagonist. EX1014, 14:31-38 (“The compound of formula Ib and its salts is also characterized by *valuable therapeutic properties* as a *highly selective* antagonist of the Neurokinin 1 (NK-1, substance P)”). A POSA would have understood Bös’ formula Ib to be netupitant. EX1009, ¶599. Bös teaches formula Ib is “a potent and selective antagonist.” EX1014, 17:61-18:48, 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.”). A POSA had good reason to substitute Bös’ newer NK₁ antagonist (netupitant) for the existing NK₁ antagonist aprepitant in Herrstedt’s combination and reasonably expect the combination to work as well or better. EX1009, ¶599.

Hargreaves correlates therapeutically-effective doses of NK₁ antagonist with NK₁ receptor occupancy greater than 75%. EX1012, Abstract, 23, Fig. 6B. Hargreaves teaches measuring NK₁-receptor occupancy in the striatum. A POSA had good reason to choose a therapeutically-effective netupitant dose that would occupy at least 70% of NK₁ receptors in the striatum 72 hours after administration. EX1009, ¶600.

Herrington teaches administering an NK₁ antagonist (aprepitant) on day 1 of a 5-day treatment period to prevent CINV. EX1017, Abstract. Herrington identified “no statistically significant differences” between patients treated with a

single day-1 dose of aprepitant and patients receiving “the traditional 3-day regimen”. *Id.*, 2084 & Fig. 2; EX1009, ¶¶601-02.

1. [preamble]: “A method of treating nausea and vomiting from an emesis-inducing event for a period of five consecutive days in a patient in need thereof, comprising”

To the extent the preamble is limiting, Herrstedt teaches it. Herrstedt teaches methods for prophylactically treating “[c]hemotherapy-induced *nausea and vomiting*”. EX1010, 143. Chemotherapy is an emesis-inducing event. *Id.* (“emesis is a natural consequence of treatment with most cancer chemotherapy.”). Herrstedt reports its primary therapeutic endpoint was no emesis for a period of five consecutive days following administration of the chemotherapeutic agent (e.g., 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, ¶603.

2. [a]: “administering to said patient netupitant or a pharmaceutically acceptable salt thereof, in a therapeutically effective amount which is effective to treat nausea and vomiting during the acute and delayed phases of emesis,”

Herrstedt reports studies treating HEC-induced acute and delayed emesis with a triple-drug combination including an NK₁ antagonist (aprepitant). EX1010, 146 (“Two of the HEC studies used an identical design ... ondansetron,

dexamethasone and *aprepitant* day 1 followed by dexamethasone days 2-4 plus aprepitant days 2-3.”). Herrstedt teaches administering the NK₁ antagonist in a therapeutically-effective amount, providing antiemetic benefits. *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), (“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 explains the therapeutically-effective amount of NK₁ antagonist prevents both acute and delayed emesis. EX1010, Abstract (NK₁ antagonist “increases the effect of a serotonin₃-receptor antagonist plus a corticosteroid against *acute emesis* induced by highly or moderately emetogenic chemotherapy” and “is also active in the protection against *delayed* emesis.”). Herrstedt reports using an NK₁ antagonist is effective to treat nausea and vomiting during the acute and delayed phases. Herrstedt, 148-149 & Table 4. EX1009, ¶¶604-08.

Although Herrstedt’s NK₁ antagonist was aprepitant, Herrstedt teaches aprepitant was merely “the first drug” in a class of selective NK₁ antagonists. EX1010, Abstract. Bös not only discloses netupitant (“formula Ib”) as a potent and selective NK₁ antagonist, but also recommends using an effective amount of netupitant for treating emesis. EX1014, 14:31-38 (“The compound of formula Ib [netupitant] and its salts is also characterized by *valuable therapeutic properties* as

a *highly selective* antagonist of the Neurokinin 1 (NK-1, substance P”)), 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.”). Bös reports “the most preferred indications in accordance with the present invention are those which include *disorders of the central nervous system*, for example indications for the treatment or prevention of certain depressive disorders, anxiety or *emesis by the administration of NK-1 receptor antagonists.*” *Id.*, 4:15-24. “[P]harmacological activity of the compounds of this invention as NK-1 receptor antagonists ... is correlated with treatment of” CNS disorders. EX1014, 42-48, 9:22-29 (“particularly useful for treating CNS disorders, such as depression, anxiety or emesis.”), 19:10-30 (netupitant effective for treatment of emesis). EX1009, ¶609.

Bös teaches “[t]he *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.” EX1014, 42:5-11. A POSA had good reason to replace Herrstedt’s older NK₁ antagonist (aprepitant) with Bös’ new NK₁ antagonist (netupitant) because, for example,

excellent CNS penetration was highly desirable in NK₁ antagonists to permit the drug to reach CNS NK₁ receptors to prevent emesis following emetogenic therapy. EX1009, ¶¶610-12.

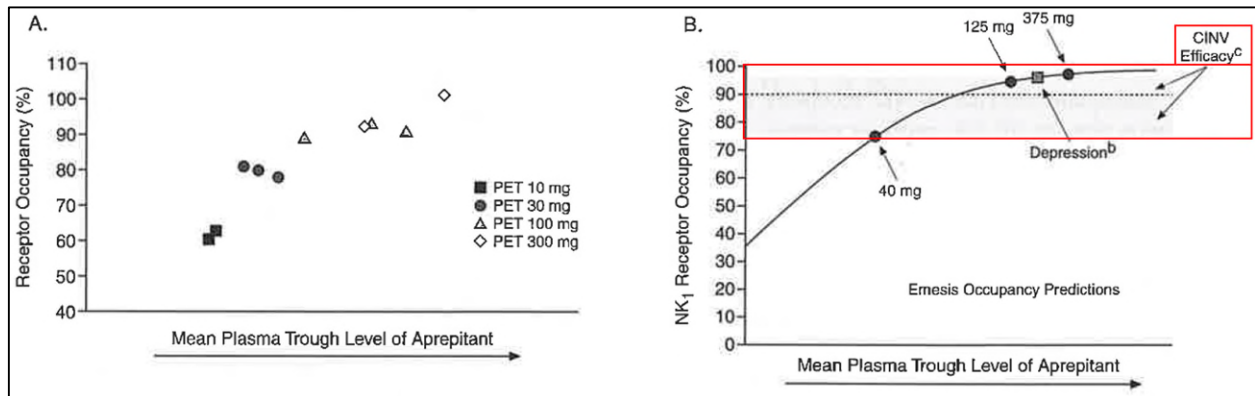
3. [b]: “and which enters the systemic circulation, crosses the blood brain barrier and occupies 70% or more of NK₁ receptors in the striatum seventy-two hours after said administration,”

Bös teaches netupitant belongs to a family of orally-administered compounds. EX1014, 42:5-11 (“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”). Orally-administered netupitant must reach CNS NK₁ receptors and, to do so, it must enter systemic circulation after administration and cross the blood brain barrier in order to arrive at the striatum. EX1009, ¶¶613-14.

Hargreaves teaches or suggests a therapeutically-effective amount of NK₁ antagonist occupies at least about 75% (i.e., more than 70%) of NK₁ receptors in the striatum. The striatum is the densest location of NK₁ receptors. EX1012, Fig. 4(A); EX1009, ¶615. Hargreaves associates NK₁-receptor occupancy in the striatum and antiemetic therapeutic effectiveness. EX1012, 23:

On the basis of these findings, a plasma concentration vs. receptor occupancy relationship was established (Figure 6A [below]). 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 [below, annotated]), whereas **the initial 40-mg dose used in the study of emesis resulted in lower (75%) receptor occupancy (Figure 6B)**.



EX1009, ¶616. As Dr. Peroutka explains (*id.*), Fig. 6B shows “CINV Efficacy” for antiemetic therapy beginning at approximately 75% of NK₁-receptor occupancy, corresponding to a 40 mg dose, which would have suggested to a POSA that prophylactically administering a therapeutically-effective amount of NK₁ antagonist (e.g., netupitant) occupying 75% (at least 70%) of NK₁ receptors in the striatum seventy-two hours after administration would be very likely to be efficacious for treating CINV.

This “at least 70%” occupancy limitation covers the “at least 75%” occupancy threshold Hargreaves teaches naturally accompanied administration of a therapeutically-effective amount of an NK₁ antagonist for treating emesis. Indeed, the examiner during examination of a related application found (without rebuttal) that the claimed occupancy was an inherent property of administering a therapeutically-effective amount of netupitant. EX1009, ¶¶617-18. Seventy-two hours falls squarely within the 5-day therapeutic period and reflects the known prolonged half-life of netupitant. *Id.*, citing EX1014, 19:7-38; EX1003, 4:55-5:3 (Trento’515 admitting “netupitant binds to NK₁ receptors in the striatum in a long-lasting manner, and [] less than 20 or 30% of netupitant is released from striatum NK₁ receptors even ninety-six hours after administration.”). Accordingly, from Hargreaves, a POSA would have considered it obvious to use therapeutically-effective doses of netupitant occupying at least 70% of NK₁ receptors in the striatum seventy-two hours after administration.

4. [c]: “wherein a single dose of netupitant or pharmaceutically acceptable salt thereof is administered on day one of said five consecutive days, no further netupitant or pharmaceutically acceptable salt thereof is administered during said five consecutive days, and said single dose of netupitant or pharmaceutically acceptable salt thereof if [sic, is] effective to treat said nausea and vomiting for said five consecutive days.”

Herrstedt teaches administering a dose of NK₁ antagonist on day 1 of the 5-

day treatment period, although its aprepitant NK₁ antagonist is also administered on days one, two, and three. EX1010, 146 (“Two of the HEC studies used an identical design comparing ondansetron, dexamethasone and placebo day 1 followed by dexamethasone plus placebo days 2-4 with ondansetron, dexamethasone and *aprepitant day 1* followed by dexamethasone days 2-4 plus aprepitant days 2-3”). The combination of Herrstedt and Bös suggests administering a single netupitant dose on day-1 of the 5-day treatment period with no further netupitant during the remaining days because a single dose of netupitant is effective to treat nausea and vomiting for five consecutive days. EX1009, ¶¶619-21. Netupitant was known to have a large half-life value, thus providing reason to omit subsequent netupitant doses. *Id.*; EX1014, 19:3-10 (functional half-life of 30 hours).

Herrington confirms a single dose of NK₁ antagonist administered on day 1 of the five consecutive days, where no further NK₁ antagonist is administered during said five consecutive days, is effective to treat nausea and vomiting for the five consecutive days. EX1017, 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,

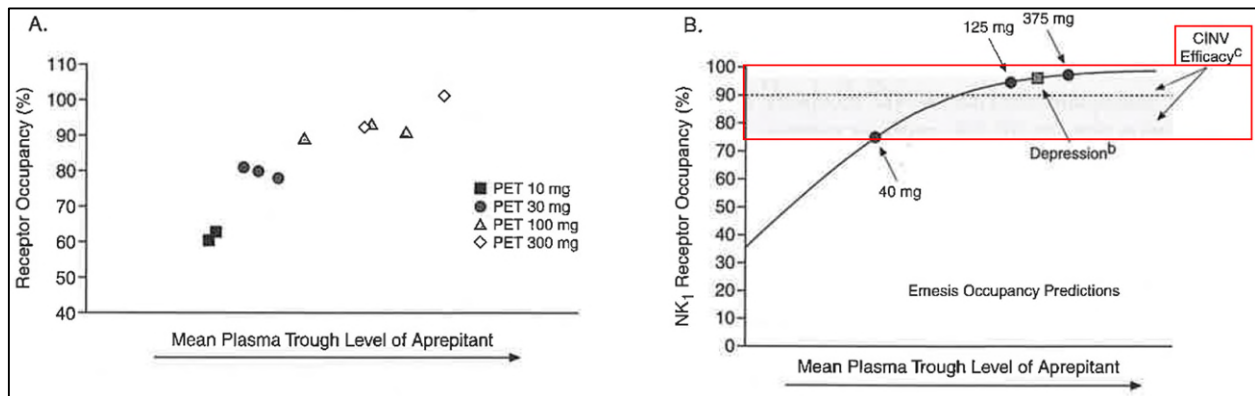
a single dose of aprepitant displayed similar effectiveness compared with 3-day aprepitant.”), EX1009, ¶622. Herrington reports this efficacy for treating CINV evaluated across the 5-day treatment period. EX1017, 2081 (“The primary efficacy endpoint was the proportion of patients with emesis in the acute (Day 1) and delayed (Days 2-5) phases after chemotherapy.”), Abstract (“There were no significant differences between Arms A [3-day aprepitant] and B [single day-1 dose aprepitant] for emesis, nausea, or the use of break-through antiemetics. In *Arms A and B, 93% of patients were emesis-free from Days 1-5* compared with only 50% in Arm C [control group].”), 2086 (“The control of nausea was achieved in similar fashion between the 2 aprepitant arms.”). Although Herrington identified “a trend toward better significant nausea on Days 4-5 with the 3-day Arm A versus the single dose” the mean severity of nausea for the single aprepitant dose was lower than the control test group for all five days. *Id.*, 2086, 2084 & Table 4. A POSA had good reason to use a single dose of aprepitant in Herrstedt’s therapeutic combination for increased simplicity and ease of patient compliance. EX1009, ¶¶623-25.

B. Claim 2: “The method of claim 1, wherein said netupitant occupies 80% or more of NK₁ receptors in the striatum seventy-two hours after said administration.”

Building on the obviousness of claim 1, Hargreaves teaches NK₁ antagonists occupy at least 80% of NK receptors in the striatum. Hargreaves correlates NK₁-

receptor occupancy in the striatum and antiemetic effects for CINV. EX1012, 23:

On the basis of these findings, a plasma concentration vs. receptor occupancy relationship was established (Figure 6A). The data suggest that a trough concentration following treatment with the 10-mg dose of aprepitant corresponds to approximately 60% receptor occupancy, whereas *the occupancy of $\geq 90\%$ of NK_1 receptors* requires aprepitant doses ≥ 100 mg. Curve fitting to the plasma concentration—receptor occupancy curves showed that *high levels of NK_1 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 NK_1 receptors* in the CNS (Figure 6B), whereas *the* initial 40-mg dose used in the study of emesis resulted in lower (75%) receptor occupancy (Figure 6B [below, annotated]).



Hargreaves Fig. 6B shows “CINV Efficacy” for antiemetic therapy in the shaded region beginning at approximately 75% of NK_1 -receptor occupancy and teaches therapeutically-effective amounts of an NK_1 antagonist are those occupying high

levels of NK₁ receptors (e.g., greater than 75% and preferably greater than 90%) in the striatum. EX1009, ¶626-28.

As previously explained (§IX.A.2 above), from Hargreaves, a POSA would have considered it obvious to use therapeutically-effective doses of netupitant occupying at least 70% of NK₁ receptors in the striatum seventy-two hours after administration. The “at least 80%” occupancy limitation is substantially similar to the “at least 75%” occupancy threshold that the prior art taught naturally accompanied administration of therapeutically-effective amounts of NK₁ antagonist for treating emesis. Hargreaves, 23 & Fig. 6. Indeed, the examiner’s (unrebutted) finding was that the claimed “at least 80%” occupancy is an inherent property of administering a therapeutically-effective amount of netupitant.

EX1009, ¶629. Seventy-two hours falls within the 5-day therapeutic period and reflects netupitant’s known prolonged half-life. Bös, 19:7-38. Trento’515 admits this is a characteristic of netupitant itself: “netupitant binds to NK₁ receptors in the striatum in a long-lasting manner, and [] less than 20 or 30% of netupitant is released from striatum NK₁ receptors even ninety-six hours after administration.”

EX1003, 4:62-65. Helsinn’s admissions and lack of dispute on inherency with the examiner are consistent with a POSA’s understanding. EX1009, ¶¶629-31.

C. Claim 3: “The method of claim 1, further comprising:”

Claim 1 was obvious for the reasons provided in §X.A above. EX1009,

¶¶632-33.

1. **“a)[1] administering to said patient on day one a first dose of dexamethasone which is ineffective against nausea and vomiting when administered alone, but effective against nausea and vomiting when administered in combination with said netupitant,”**

The specification defines 20 mg as the standard effective first dose of dexamethasone, below which it is ineffective when administered alone. EX1003, 8:20-30; EX1009, ¶¶634-35; §VI above. Herrstedt teaches administering a single, sub-20 mg day-1 dose of dexamethasone for the treatment of MEC-induced CINV. EX1010, 145-147. In contrast to the standard 20 mg day-1 dose, Herrstedt teaches the day-1 dexamethasone should be reduced—about 25% to 50% less than the 20 mg standard dose—because metabolic interactions of corticosteroids (e.g., dexamethasone or methylprednisolone) and the NK₁ antagonist (e.g., aprepitant) doubles the corticosteroids’ effect. *Id.*, 147 (“Dexamethasone and methylprednisolone are sensitive to substrates of CYP3A4. The combination of aprepitant and oral dexamethasone results in a *two-time increase in the AUC of dexamethasone indicating an inhibition of aprepitant on dexamethasone metabolism*. When methylprednisolone is given in combination with aprepitant the intravenous dose can be *reduced by 25%* and *the oral dose by 50%* to obtain the same exposure of methylprednisolone, when given without concomitant administration of aprepitant.”), 246 (“During the development of aprepitant, *it*

became clear that the dose of oral (and to a minor degree intravenous) *corticosteroids had to be reduced* due to interaction at the cytochrome P450 (CYP) 3A4 enzyme system between corticosteroids and aprepitant.”). The reduced metabolism of dexamethasone when co-administered with netupitant is a property that necessarily and naturally flows from the combination, so a POSA performing routine metabolism studies on the combination therapy would reasonably expect to reduce the dexamethasone dose below the 20 mg standard dose. EX1009, ¶¶636-40.

2. a)[2] “wherein said first dose comprises from 50 to 70% of a minimum effective dose when administered alone; and”

Herrstedt teaches:

Dexamethasone and methylprednisolone are sensitive to substrates of CYP3A4. The combination of aprepitant and oral dexamethasone results in a *two-time increase in the AUC of dexamethasone indicating an inhibition of aprepitant on dexamethasone metabolism*. When methylprednisolone is given in combination with aprepitant the intravenous dose can be *reduced by 25%* and *the oral dose by 50%* to obtain the same exposure of methylprednisolone, when given without concomitant administration of aprepitant.

EX1010, 147, 146 (“During the development of aprepitant, *it became clear that the dose of oral* (and to a minor degree intravenous) *corticosteroids had to be reduced* due to interaction at the cytochrome P450 (CYP) 3A4 enzyme system

between corticosteroids and aprepitant.”). Herrstedt thus teaches reducing the day-1 dose of oral dexamethasone, when administered with an NK₁ antagonist, by about 50% of the minimum effective dose when administered alone in order to achieve the same effective AUC concentration. EX1009, ¶¶641-43.

3. **“b) if said patient is subject to highly emetogenic chemotherapy, administering to said patient, on days two, three and four, a second dose of dexamethasone which is ineffective against nausea and vomiting when administered alone, but effective against nausea and vomiting when administered in combination with said netupitant, wherein said second dose comprises from 40 to 60% of a minimum effective dose when administered alone.”**

Herrstedt teaches administering dexamethasone after HEC on days two, three, and four, including studies having such dosing:

Two of the *HEC [highly emetogenic chemotherapy]* studies used an identical design comparing ondansetron, dexamethasone and placebo day 1 followed by *dexamethasone* plus placebo *days 2–4* with ondansetron, dexamethasone and aprepitant day 1 followed by *dexamethasone days 2–4* plus aprepitant days 2–3.... The most recently published *HEC* study used the same design, except that ondansetron was included in the control arm for delayed protection days 2–4.

Herrstedt, 146 (studies involved “patients receiving *cisplatin-based, highly emetogenic chemotherapy*”). Herrstedt suggests the days 2-4 doses of dexamethasone are ineffective against CINV when administered alone, but

effective when administered with an NK₁ antagonist because Herrstedt teaches a lower dose of corticosteroids, such as dexamethasone, should be used when administered with an NK₁ antagonist. Herrstedt, 147-148; EX1009, ¶¶644-46. Herrstedt also suggests the second dose is 40%-60% of a minimum effective dose when administered alone. Herrstedt, 146-147 (reducing corticosteroid orally administered with NK₁ antagonist “by 50% to obtain the same exposure.”). A POSA thus had good reason to administer doses of dexamethasone on days two, three, and four in an amount reduced about 50% to account for increased AUC exposure based on the continued presence of the NK₁ antagonist. EX1009, ¶¶647-50.

D. Claim 4: “The method of claim 1 wherein:

Claim 1 was obvious for the reasons provided in §X.A above. EX1009, ¶¶651-52.

- 1. a) only one dose of netupitant is administered during said five days on day one, comprising about 300 mg. of netupitant as the free base; and**

As discussed for claim 1 (§X.A.4 above), the combination of Herrstedt, Bös, Hargreaves, and optionally Herrington teaches or suggests only one dose of netupitant on day 1 of the 5-day treatment. EX1009, ¶¶653-55. Bös suggests a 300 mg dose of netupitant as the free base. Bös discloses a therapeutically effective amount of NK₁ antagonists (including netupitant) comprises a range including

about 300 mg of netupitant as a free base. EX1014, 42:5-11 (“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.”). A 300 mg dose falls within the disclosed range, near its midpoint. A POSA would have recognized this range as a good starting point and it would have arrived at an about 300 mg as a therapeutically-acceptable dose through routine optimization. EX1009, ¶¶656-58; *Urbanski*, 809 F.3d at 1242. Note that Trento’515 ascribes no criticality or unexpected result to a 300 mg netupitant dose. EX1009, ¶¶659-60.

2. b) administering about 12 mg. of dexamethasone on day one; and

Herrstedt teaches administering dexamethasone with a NK₁ antagonist, including in two studies. EX1010, 146. A POSA would have known (by reviewing the underlying studies) that 12 mg of dexamethasone was administered on day 1 in both studies. EX1009, ¶¶661-62; *In re Baxter Travenol*, 952 F.2d 388, 390 (Fed. Cir. 1991) (“[E]xtrinsic evidence may be considered when it is used to explain, but not expand, the meaning of a reference.”). A POSA had good reason to administer about 12 mg of dexamethasone on day 1 with a reasonable expectation of success that it would provide relief from emesis. EX1009, ¶¶662-63.

3. c) if said patient is undergoing highly emetogenic chemotherapy, administering about 8 mg. of dexamethasone on days two, three and four.”

Herrstedt teaches administering dexamethasone an NK₁ antagonist after HEC, summarizing two studies employing a triple anti-emetic drug combination. EX1010, 146 (investigating an NK₁ antagonist “in patients receiving *cisplatin-based, highly emetogenic chemotherapy*.”). A POSA (reviewing the underlying studies) would have understood that in Herrstedt, 8 mg dexamethasone was administered on days two, three and four after HEC. EX1009, ¶¶664-65; *Baxter Travenol*, 952 F.2d at 390. A POSA thus had good reason to orally administer about 8 mg of dexamethasone on days two, three and four after HEC with a reasonable expectation of success that this dosing would provide relief from emesis. EX1009, ¶¶665-67.

E. Claim 5: “The method of claim 1 wherein said nausea and vomiting is chemotherapy induced nausea and vomiting (‘CINV’), radiation therapy induced nausea and vomiting (‘RINV’), or post-operative nausea and vomiting (‘PONV’).”

Building on the obviousness of claim 1, Herrstedt teaches using a combination therapy to treat CINV. EX1010, 146 (“Four phase III trials have investigated the use of aprepitant in patients receiving *cisplatin-based, highly emetogenic chemotherapy* or a combination of cyclophosphamide plus an anthracycline. Complete response, defined as ‘*no emesis and no rescue therapy* on

days 1–5 postcisplatin’, was the primary end-point in all studies.”), Abstract (reporting on “treatment of nausea and vomiting from chemotherapy.”). EX1009, ¶¶668-71.

F. Claim 6: “The method of claim 1 wherein said nausea and vomiting is induced by moderately or highly emetogenic chemotherapy.”

Building on the obviousness of claim 1, Herrstedt teaches treating CINV after MEC and HEC. EX1010, Abstract (“emesis induced by *highly or moderately emetogenic chemotherapy*.”), 146 (“Four phase III trials have investigated the use of aprepitant in patients receiving *cisplatin-based, highly emetogenic chemotherapy* or a combination of *cyclophosphamide plus an anthracycline*. Complete response, defined as ‘no emesis and no rescue therapy on days 1–5 *postcisplatin*’, was the primary end-point in all studies.”), Table 1 (classifying cisplatin as HEC and the cyclophosphamide and anthracycline combination chemotherapy as between highly emetogenic and moderately emetogenic). Thus, the studies described in Herrstedt evaluated the antiemetic combination to treat CINV induced by MEC or HEC. Herrstedt, 146; EX1009, ¶¶672-75.

G. Claim 7: “The method of claim 1 comprising administering moderately or highly emetogenic chemotherapy within from about one hour to about two hours of said administration of said netupitant or pharmaceutically acceptable salt thereof.”

Building on the obviousness of claim 1, Herrstedt teaches administering

MEC or HEC with an antiemetic NK₁ antagonist, reporting two studies employing the triple anti-emetic drug combination. A POSA would have known (from reviewing the underlying studies) that the chemotherapy in the studies was administered within from about one hour to about two hours of the NK₁ antagonist, consistent with routine practice, and thus had good reason to administer MEC or HEC within from about one hour to about two hours of the administration of netupitant with a reasonable expectation of success that this dosing would provide relief from emesis. EX1009, ¶¶676-80.

H. Claim 8: “The method of claim 1 comprising treating nausea and vomiting in response to highly emetogenic chemotherapy during the acute phase, or in response to highly emetogenic chemotherapy during the delayed phase, or in response to moderately emetogenic chemotherapy during the acute phase, or in response to moderately emetogenic chemotherapy during the delayed phase.”

Building on the obviousness of claim 1, Herrstedt teaches treating CINV from HEC during the entire 5-day treatment period. EX1010, 146 (“cisplatin-based, highly emetogenic chemotherapy”). In particular, the NK₁ antagonist is “also active in the protection against delayed emesis.” *Id.*, Abstract. Herrstedt teaches a *complete response*, which would require preventing CINV in both the acute and delayed phases. EX1010, 146 (“Complete response, defined as ‘no emesis and no rescue therapy on days 1-5 postcisplatin’, was the primary end-point in all studies.”). A POSA had good reason to administer Herrstedt’s drug

combination, substituting Bös' netupitant, with a reasonable expectation of success that this dosing would treat CINV after HEC with a complete response (preventing during both the acute and delayed phases). EX1009, ¶¶681-85.

I. Claim 9: “The method of claim 1, comprising administering from about 200 to about 400 mg of netupitant as the free base.”

Building on the obviousness of claim 1, Bös teaches administering a therapeutically effective amount of NK₁ antagonists, including netupitant as the free base. EX1014, 2:1-65, 14:9-20, 1:60-64 (“for treatment induced vomiting” including “the reduction of cisplatin-induced emesis by a selective neurokinin-1-receptor antagonist.”). Bös discloses a dose range for its NK₁ antagonists (including netupitant) that covers the claimed range from about 200 to about 400 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.”). A POSA would have recognized Bös' range as a favorable starting point for identifying optimal therapeutic-dose amounts using routine dose determination with a reasonable expectation of success in achieving the desired therapeutic effect administering that dose because Bös teaches this to be an appropriate dose for the oral administration of the family of NK₁ antagonists to which

netupitant belongs. EX1009, ¶¶686-90; *Baxter Travenol*, 952 F.2d at 390. Indeed, Trento’515 admits such dose determination would be routine. EX1003, 8:13-19 (“*The skilled artisan will be able to determine appropriate dosages depending on these and other factors* in addition to the present disclosure.”); EX1009, ¶¶691-92.

J. Claim 10: “The method of claim 1, comprising orally administering about 300 mg of netupitant as the free base.”

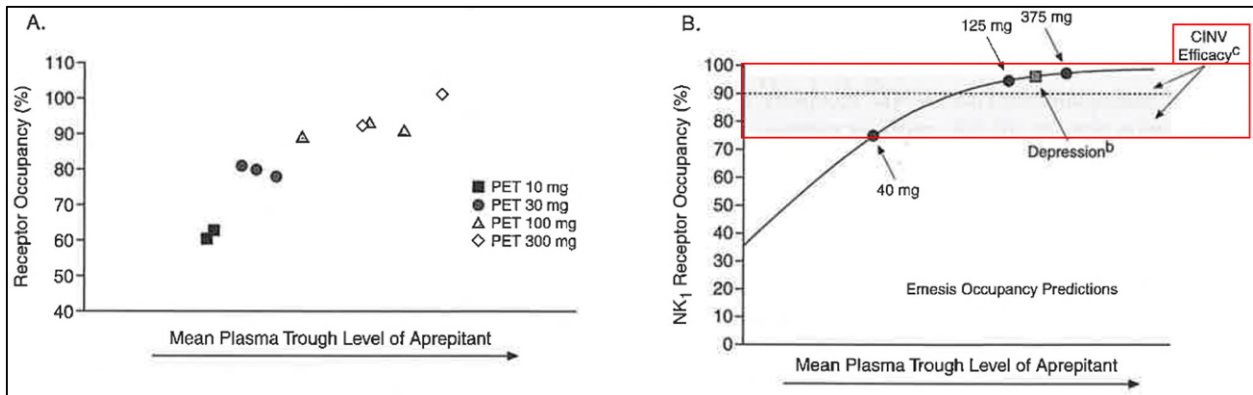
Building on the obviousness of claims 1 and 9, A POSA would have found it routine to arrive at 300 mg as a therapeutic netupitant dose with a reasonable expectation of success in achieving the desired therapeutic effect with this dose. EX1009, ¶¶693-97. Note Trento’515 itself does not ascribe any criticality or unexpected results to a 300 mg dose of netupitant; although the netupitant-dexamethasone drug interaction study (*id.*, 16:34-17:2) shows increasing dexamethasone bioavailability with each of 100 mg, 300 mg, and 450 mg doses, the 300 mg dose did not provide any particular benefits. *Id.*, Fig. 4. Indeed, in an NK₁-receptor occupancy study of netupitant (*id.*, 17:4-29), the highest dose group (again, 450 mg) achieved the greatest duration of blockade of NK₁ receptors because “the decline over time was dose dependent.” *Id.*, Fig. 5. The 300 mg dose was merely the highest dose evaluated in a clinical efficacy study (*id.*, Example 5) but even that study only showed the expected iterative increase of efficacy with increased dose amount. Hence, the 300 mg dose lacks any disclosed criticality. EX1009, ¶¶698-99.

K. Claim 18: “The method of claim 17, wherein said netupitant occupies at least 70% of said patient's striatum NK₁ receptors ninety-six hours after said administration.”

Building on the obviousness of claim 17 (see §IX.G above), Hargreaves associates therapeutically-effective doses of NK₁ antagonist to NK₁-receptor occupancy in 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. Bös teaches netupitant has high affinity for the NK₁ receptor (EX1014, 18:42-48) and belongs to a family of compounds that are therapeutically effective when administered. EX1014, 42:5-11 (“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”), 18:64-19:30 (in vivo testing confirming efficacy). Hargreaves teaches aprepitant passes into the CNS and binds to CNS NK₁ receptors, including in the striatum. EX1009, ¶¶700-05; EX1012, 23:

On the basis of these findings, a plasma concentration vs. receptor occupancy relationship was established (Figure 6A). The data suggest that a trough concentration following treatment with the 10-mg dose of aprepitant corresponds to approximately 60% receptor occupancy, whereas the occupancy of $\geq 90\%$ 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 [below, annotated])*.



Hargreaves suggests therapeutically-effective netupitant dose would occupy at least 70% of said patient's striatum NK₁ receptors after administration and a POSA would have expected that a therapeutically-effective dose of netupitant would occupy at least 75% (i.e., more than 70%) of neurokinin-1 (NK₁) receptors in the striatum ninety-six hours after administration. EX1009, ¶¶705-06. Indeed, the examiner in a related examination found (without rebuttal) that NK₁-receptor occupancy was an inherent property of administering a therapeutically-effective amount of netupitant that satisfies the "at least 70%" occupancy limitation. EX1009, ¶706; EX1003, 4:55-5:3 (admitting "netupitant binds to NK₁ receptors in the striatum in a long-lasting manner, and [] less than 20 or 30% of netupitant is

released from striatum NK₁ receptors *even ninety-six hours* after administration.”). Moreover, seventy-two and ninety-six hours (3 and 4 days, respectively) falls within the 5-day therapeutic period and reflects the known prolonged half-life of netupitant. EX1014, 19:7-38. Helsinn’s admissions and lack of dispute on inherency with the examiner support inherency. EX1009, ¶¶706-07.

L. Reason to Combine and Reasonably Expect Success

By November 2009, a POSA had good reason to treat the acute and delayed phases of CINV from MEC or HEC with Herrstedt’s antiemetic combination, substituting therapeutically effective amounts of Bös’ newer NK₁ antagonist, including by pre-administering the day-1 netupitant an hour or two before MEC or HEC. EX1009, ¶¶708-12. Because Herrstedt’s and Bös’ NK₁ antagonists share the same mechanistic pathway—e.g., antagonism of the NK₁ receptor—a POSA had good reason to make the substitution and reasonably expect it to provide the same or better therapeutic effect. The claimed netupitant doses fall within the prior-art range and would have been identified as therapeutically-effective amounts using routine dose-determination techniques; none of the claimed doses has been shown to be critical or provide unexpected results. Similarly, a POSA would have understood from Hargreaves that an effective dose of NK₁ antagonist correlates to at least about 75% of NK₁-receptor occupancy in the striatum, with larger doses correlating to greater occupancy (in excess of about 90%). EX1009, ¶¶708-12.

Thus, the POSA had good reason to similarly use NK₁-receptor occupancy to determine therapeutically effective dose amounts of other NK₁ antagonists, such as netupitant.

A POSA had good reason to expect Bös' newer NK₁ antagonist (netupitant) to work in the same manner as Herrstedt's older NK₁ antagonist (aprepitant) to achieve a similar (or better) outcome. Herrington provides a reasonable expectation that using just a single, day-1 dose of netupitant would provide a complete result for the entire 5-day treatment period. EX1009, ¶¶713-16. The inherent properties of netupitant assure success. *Cytiva*, 122 F.4th at 886-87.

XI. NO SECONDARY CONSIDERATIONS

Although Helsinn asserts unexpected properties for netupitant, aprepitant had these properties. An expected result is the opposite of an unexpected result. *In re Skoll*, 523 F.2d 1392, 1397 (CCPA 1975) ("Expected beneficial results are evidence of obviousness of a claimed invention, just as unexpected beneficial results are evidence of unobviousness."). In any case, "the expected properties of a claimed compound may be sufficient to lead to a reasonable expectation of success in modifying a prior art compound to make that claimed compound." *Bristol-Myers Squibb v. Teva Pharms.*, 752 F.3d 967, 976 (Fed. Cir. 2014).

A. Aprepitant Shows Efficacy for Nausea

During examination for Trento'826, Helsinn sought to distinguish netupitant

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

Similarly, during examination for Trento’297 patent, Helsinn alleged unexpected results for a netupitant-palonosetron combination versus aprepitant because, in its selected aprepitant trials, “in none of these trials was aprepitant able to demonstrate a statistically significant effect against nausea or significant nausea. This was true throughout the acute and delayed phases of emesis, and it was true regardless of whether moderately emetogenic chemotherapy (MEC) or highly emetogenic chemotherapy (HEC) was administered.” EX1008, 181. Helsinn asserted a POSA “would not have had a reasonable expectation of successfully treating nausea from the combination of netupitant and palonosetron” because aprepitant allegedly did not provide such effect. *Id.*, 181-182. Despite Helsinn’s representations to the examiner, however, experimental data shows a POSA knew

aprepitant treats nausea effectively. EX1009, ¶¶1329-32.

The Trento'515 claims are not patentably distinct from the Trento'826 or Trento'297 claims. EX1009, ¶¶37, 41, 47, 50-52 (obviousness-type double patenting and terminal disclaimers).

1. Emend label

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

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

Emend shows similar benefits in a second study, which reports “*complete protection*” with statistical significance for *each of* the overall, acute phase, and delayed phases. EX1009, ¶1336. Emend also reports “[i]n each of the 2 studies, a higher proportion of patients receiving the aprepitant regimen reported minimal or no impact of nausea and vomiting on daily life (Study 1: 74% versus 64%; Study 2: 75% versus 64%).” EX1030, 6. Patients reported significant improvement in their daily lives due to less nausea and vomiting versus 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’s effect on nausea is comparable to netupitant. Data in Table 6 corresponds to columns 1, 2, and 6 of Table 2 from Helsinn’s Rule 132 Declaration and shows Helsinn misleadingly excised information from Table 6’s larger data

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

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

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

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

3. Campos

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

B. Data misrepresented during examination

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

1. Differences Between the Declaration and Helsinn's Arguments

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

2. Helsinn's Data During Examination Was Lacking

a. Internal Helsinn Studies (Columns 1-3)

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

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

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

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

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

d. Grunberg (Column 6)

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

C. No Unexpected Synergy Between Netupitant and Palonosetron

The common specification contends “palonosetron is much more effective in

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

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

D. No Nexus Between Alleged Synergy and Claimed Effect

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

E. Single Dose of Netupitant Was Expected

During examination of Trento'515, Helsinn argued unexpectedly "only a single dose of netupitant is required during the acute and delayed phases of emesis." EX1007, 203. The common specification makes a similar claim. EX1001, 4:38-42 ("unexpectedly been discovered...a single dose of netupitant is able to treat nausea and vomiting in response to highly and moderately emetogenic chemotherapy for five consecutive days"). Yet Herrington describes a single aprepitant dose is sufficient to treat acute- and delayed-phase emesis. EX1009,

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

F. Acute-Phase Treatment with Netupitant Was Expected

During examination of Trento’515, Helsinn argued unexpectedly “netupitant also treats emesis during the acute phase”. EX1007, 203. Yet Herrstedt teaches NK₁ antagonists treat acute-phase emesis. EX1010, Abstract (“Aprepitant increases the effect of a serotonin₃-receptor antagonist plus a corticosteroid against *acute emesis* induced by highly or moderately emetogenic chemotherapy.”). Similarly, Hargreaves reports NK₁ antagonists “were recently shown to block emesis in animal models and to *prevent acute* and delayed chemotherapy-induced *nausea and vomiting* (CINV) in the clinic.” EX1012, 18. Other prior art shows the same. EX1009, ¶¶1395-96. From Bös, a POSA would have expected similar results for netupitant, a new NK₁ antagonist in the same class as aprepitant. EX1009, ¶1397.

G. Characteristics of Netupitant Were Expected

Helsinn’s patents present properties of netupitant—a prior-art compound—as allegedly unexpected. EX1001, 4:37-51, 5:13-20; EX1009, ¶¶1398-1400. Because netupitant was 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.”).

XII. CONCLUSION

Claims 1-23 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.

XIII. 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.

XIV. 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’515.

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 and IPR2025-00947, filed 1 May 2025; and

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

C. Lead and Back-up Counsel

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XV. EXHIBIT LIST - §42.63(e)

Exhibit No.	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 <i>Basic & Clinical Pharmacology & Toxicology</i> 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 antagonists</i> , 16 <i>Bioorganic & Medicinal Chemistry Letters</i> 1362-1365 (2006)
1012	R. Hargreaves, <i>Imaging Substance P Receptors (NK₁) in the Living Human Brain Using Positron Emission Tomography</i> , 63(11) <i>J.</i>

	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)
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</i>

	<i>emetogenic chemotherapy</i> , 17 <i>Annals of Oncology</i> 1441-49 (2006)
1023	D. Campos et al., <i>Prevention of cisplatin-induced emesis by the oral neurokinin-1 antagonist, MK-869, in combination with granisetron and dexamethasone or with dexamethasone alone</i> , 19(6) <i>Journal of Clinical Oncology</i> , 1759 (2001)
1024	A.E. Chang et al., eds., <i>Oncology: An Evidence-Based Approach</i> (2006)
1025	S.P. Chawla et al., <i>Establishing the Dose of the Oral NK₁ Antagonist Aprepitant for the Prevention of Chemotherapy-Induced Nausea and Vomiting</i> , 97 <i>Cancer</i> 2290 (2003).
1026	S.P. Chawla et al., <i>Establishing the Dose of the Oral NK₁ Antagonist Aprepitant for the Prevention of Chemotherapy-Induced Nausea and Vomiting</i> , 37th Annual Meeting of the American Society of Clinical Oncology, in 20 <i>Proceedings of ASCO</i> 383a (2001)
1027	A. De Leon, <i>Palonosetron (Aloxi): a second-generation 5-HT₃ receptor antagonist for chemotherapy-induced nausea and vomiting</i> , in 19(4) <i>Baylor University Medical Center Proceedings</i> 413 (2006)
1028	R.A. Duffy, <i>Potential therapeutic targets for neurokinin-1 receptor antagonists</i> , 9(1) <i>Expert opinion on emerging drugs</i> , 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, <i>General Considerations for the Clinical Evaluation of Drugs</i> (1978)
1033	U.S. Food and Drug Administration, <i>Q3A Impurities in New Drug Substances</i> (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) <i>Journal of Clinical Oncology</i> 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 <i>Supportive Care in Cancer</i> 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-on-regulatory-filings-for-zunrisarezonic/
1037	P.J. Hesketh et al., <i>The Oral Neurokinin-1 Antagonist Aprepitant for the Prevention of Chemotherapy-Induced Nausea and Vomiting: A Multinational, Randomized, Double-Blind, Placebo-Controlled Trial in Patients Receiving High-Dose Cisplatin—The Aprepitant Protocol 052 Study Group</i> , 21(22) <i>Journal of Clinical Oncology</i> 4112 (2003)
1038	G.S. Paulekuhn et al., <i>Trends in active pharmaceutical ingredient salt selection based on analysis of the orange book database</i> , 50(26) <i>Journal of Medicinal Chemistry</i> 6665 (2007)
1039	S. Poli-Bigelli et al., <i>Addition of the neurokinin 1 receptor antagonist aprepitant to standard antiemetic therapy improves control of chemotherapy-induced nausea and vomiting: Results from a randomized, double-blind, placebo-controlled trial in Latin America</i> , 97(12) <i>Cancer</i> 3090 (2003)
1040	T. Qiu et al., <i>Antiemetic regimen with aprepitant in the prevention of chemotherapy-induced nausea and vomiting</i> , 99(33) <i>Medicine</i> e21559 (2020)
1041	C. Rojas, <i>The antiemetic 5-HT₃ receptor antagonist Palonosetron inhibits substance P-mediated responses in vitro and in vivo</i> , 335(2) <i>The Journal of Pharmacology and Experimental Therapeutics</i> 362 (2010)

1042	C. Ruhlmann & J. Herrstedt, <i>Casopitant: a novel NK1-receptor antagonist in the prevention of chemotherapy-induced nausea and vomiting</i> , 5 Therapeutics and Clinical Risk Management 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) Journal of Pharmacological Sciences 87 (2003)
1044	Ronald D. Schoenwald, <i>Pharmacokinetics in Drug Discovery and Development</i> (2002)
1045	A.G. Thomas, <i>Netupitant and palonosetron trigger NK1 receptor internalization in NG108-15 cells</i> , 232 Experimental Brain Research 2637 (2014)
1046	K.E. Thummel, <i>Gut instincts: CYP3A4 and intestinal drug metabolism</i> , 117(11) Journal of Clinical Investigation 3173 (2007)
1047	D.S. Wang, <i>Effect of aprepitant for the prevention of chemotherapy-induced nausea and vomiting in women: a randomized clinical trial</i> , 4(4) JAMA Network Open e215250 (2021)
1048	W. Yeo et al., <i>A randomized study of aprepitant, ondansetron and dexamethasone for chemotherapy-induced nausea and vomiting in Chinese breast cancer patients receiving moderately emetogenic chemotherapy</i> , 113 Breast Cancer Research and Treatment 529 (2009)
1049	S.F. Zhou, <i>Drugs Behave as Substrates, Inhibitors and Inducers of Human Cytochrome P450 3A4</i> , 9(4) Current Drug Metabolism 310 (2008)
1050	<i>Parenteral</i> , Merriam-Webster, https://www.merriam-webster.com/dictionary/parenterally
1051	NK1 receptor antagonist by Roche, <i>Advances in Drug Discovery</i> (Feb. 23, 2006), https://web.archive.org/web/20080215091703/http://leaddiscovery.blogspot.com/2006/02/nk1-receptor-antagonist-by-roche.html (archived Feb. 15, 2008)

1052	RxList, ALOXI (palonosetron HCl) Capsules, https://web.archive.org/web/20080924091503/http://www.rxlist.com:80/script/main/hp.asp (archived Oct. 24, 2008)
1053	DailyMed excerpts relating to ALOXI (palonosetron HCl) Capsules, downloaded from https://dailymed.nlm.nih.gov/dailymed/index.cfm , https://dailymed.nlm.nih.gov/dailymed/dailymed-announcements-details.cfm?date=2015-10-08 , https://dailymed.nlm.nih.gov/dailymed/archives/index.cfm?query=palonosetron&date=10%2F30%2F2008 , & https://dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archiveid=9092
1054	DailyMed excerpts relating to Aloxi (palonosetron HCl) Capsules, as archived at https://web.archive.org/web/20081112024512/http://dailymed.nlm.nih.gov/dailymed/about.cfm (archived Nov. 12, 2008), https://web.archive.org/web/20090117151926/http://dailymed.nlm.nih.gov/dailymed/drugList.cfm?startswith=P (archived Jan. 17, 2009), and https://web.archive.org/web/20090521131758/http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=8295 (archived May 21, 2009)
1055	PCT Publication WO 2011/061622, filed 18 November 2010
1056	Provisional Patent Appl. 61/382,709, filed 14 September 2010
1057	Provisional Patent Appl. 61/262,470, filed 18 November 2009
1058	Drugs@FDA: FDA-Approved Drugs, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=022233
1059	P. Li & L. Zhao, <i>Developing Early Formulations: Practice and Perspective</i> , 341 <i>International Journal of Pharmaceutics</i> 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) <i>Current Medical Research and Opinion</i> 78 (1972)

XVI. CERTIFICATIONS

A. Rule 42.24(d) Certification

Pursuant to 37 C.F.R. §42.24(d), the undersigned certifies that this Petition complies with the type-volume limitation of 37 C.F.R. §42.24(a). The word count application of the word processing program used to prepare this Petition indicates that the Petition contains 13,520 words, excluding the parts of the brief exempted by 37 C.F.R. §42.24(a).

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

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

Sullivan IP Solutions
PO Box 4452
New York, NY 10163

C. Declaration

All statements in this certificate of service made of my own knowledge are true and all statements made on information and belief are believed to be true. I acknowledge that willful false statements and the like are punishable by fine or imprisonment, or both (18 U.S.C. §1001) and may jeopardize the validity of this proceeding.

Dated: 1 May 2025

/Yawen Wang /
Yawen Wang