UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AZURITY PHARMACEUTICALS, INC.,
Petitioner,

v.

HELSINN HEALTHCARE S.A.,
Patent Owner.

Case IPR2025-00947
Patent No. 9,186,357 B2

PATENT OWNER'S PRELIMINARY RESPONSE

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LIST OF EXHIBITS

Exhibit No.	Description	Previously Submitted?
2001	Curran, P. et al., *Aprepitant A Review of its Use in the Prevention of Nausea and Vomiting*, Drugs 2009: 69 (13): 1853-1878	X
2002	EMEND® (aprepitant) FDA Approval Letter, NDA 21-549, dated March 26, 2003, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2003/21-549_Emend_Approv.pdf	X
2003	Ruhlmann, *Casopitant: a novel NK1-receptor antagonist in the prevention of chemotherapy-induced nausea and vomiting*, Therapeutics and Clinical Risk Management 2009:5 375-384	X
2004	Emend IV (fosaprepitant) FDA Approval Letter, NDA 22-023, dated January 25, 2008, available at https://www.accessdata.fda.gov/drugsatfda_docs/NDA/2008/022023s000_Approv.pdf	X
2005	Akynzeo (netupitant/palonosetron) FDA Approval Letter, dated October 10, 2014, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/205718Orig1s000Approv.pdf	X
2006	Global CINV Drugs Market $4.3 Billion by 2031, ihealthcareanalyst, Feb. 3, 2025, available at https://www.ihealthcareanalyst.com/global-chemotherapy-induced-nausea-vomiting-drugs-market/	X
2007	Heron Form 10-K, Feb. 27, 2025	X
2008	Azurity (Aprepitant Injectable Emulsion) FDA Tentative Approval Letter, NDA 218754, dated July 25, 2024, available at https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2024/218754Orig1s000TAltr.pdf	X
2009	U.S. Patent No. 12,097,197 to Dubewar et al.	X

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2010	IDS Statement, Application No. 18/069,204, dated June 29, 2023	X
2011	Press Release – CutisPharma Announces Acquisition of Silvergate Pharmaceuticals, Name Change to Azurity Pharmaceuticals, June 12, 2019, 6:00 ET	X
2012	Press Release – Silvergate Pharmaceuticals Release: FDA Approves XATMEP, The First and Only Ready-To-Use Methotrexate Oral Solution, April 26, 2017	X
2013	GLIADEL® WAFER label	X
2014	Press Release - Azurity Pharmaceuticals Acquires Slayback Pharma, Sept. 27. 2023, available at https://azurity.com/azurity-pharmaceuticals-acquires-slayback-pharma/	X
2015	U.S. Patent Application Publication No. 2024/0156829 A1	X
2016	EMEND® label, March 2003	X
2017	An Efficacy and Safety Study of Oral Netupitant and Palonosetron for the Prevention of Nausea and Vomiting, last updated Nov. 26, 2014, available at https://clinicaltrials.gov/study/NCT01339260	X
2018	A Safety Study of Oral Netupitant and Palonosetron for the Prevention of Nausea and Vomiting, last updated Nov. 17, 2014, available at https://clinicaltrials.gov/study/NCT01376297	X
2019	An Efficacy and Safety Study of Oral and Intravenous Palonosetron for the Prevention of Nausea and Vomiting, last updated Sept. 22, 2021, available at https://clinicaltrials.gov/study/NCT01363479	X

Exhibit No.	Description	Previously Submitted?
2020	FDA Approves Akynzeo for Injection, FDA Approves Intravenous Formulation of Akynzeo (fosnetupitant/palonosetron) for Chemotherapy-Induced Nausea and Vomiting, available at https://www.drugs.com/newdrugs/fda-approves-intravenous-formulation-akynzeo-fosnetupitant-palonosetron-chemotherapy-induced-nausea-4726.html	X
2021	Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, available at https://www.accessdata.fda.gov/scripts/cder/ob/patent_info.cfm?Product_No=002&Appl_No=210493&Appl_type=N	X
2022	Netupitant and Palonosetron Hydrochloride in Preventing Chemotherapy Induced Nausea and Vomiting in Patients With Cancer Undergoing BEAM Conditioning Regimen Before Stem Cell Transplant, last updated Jul 12, 2021, available at https://clinicaltrials.gov/study/NCT03097588	X
2023	PK/ PD Study of Netupitant and Palonosetron in Pediatric Patients for Prevention of Chemotherapy-induced Nausea and Vomiting (CINV), last updated Jun 25, 2024, available at https://clinicaltrials.gov/study/NCT03204279	X
2024	A Study to Assess the Safety and the Efficacy of IV Fosnetupitant/ Palonosetron (260 mg/ 0.25 mg) Combination Compared to Oral Netupitant/ Palonosetron (300 mg/ 0.5 mg) Combination for the Prevention of CINV in AC Chemotherapy in Women With Breast Cancer, last updated Jun 1, 2020, available at https://clinicaltrials.gov/study/NCT03403712	X
2025	Safety and Antiemetic Efficacy of Akynzeo Plus Dexamethasone During Radiotherapy and Concomitant Weekly Cisplatin, last updated Dec. 14, 2021, available at https://clinicaltrials.gov/study/NCT03668639	X
2026	Oral Akynzeo® Vs Standard of Care in Preventing CINV in High-risk MEC Patients (MyRisk) (CINV), last updated Dec. 4, 2024, available at https://clinicaltrials.gov/study/NCT04817189	X

Exhibit No.	Description	Previously Submitted?
2027	A Clinical Trial to Assess Safety and Pharmacokinetics of Fosnetupitant 235mg and Metabolites in Healthy Volunteers, last updated May 4, 2025, available at https://clinicaltrials.gov/study/NCT06840769	X
2028	Prevention of Breakthrough CINV in Patients Receiving Moderately or Highly Emetogenic Chemotherapy, last updated Oct. 10, 2023, available at https://clinicaltrials.gov/study/NCT06065722	X
2029	Study With IV NEPA (Fosnetupitant/ Palonosetron) for the Prevention of Chemotherapy-induced Nausea and Vomiting in Paediatric Cancer Patients Undergoing Highly Emetogenic Chemotherapy (HEC), last updated Jul 28, 2025, available at https://clinicaltrials.gov/study/NCT06904235	X
2030	An Efficacy and Safety Study of Intravenous Palonosetron Administered as an Infusion and as a Bolus for the Prevention of Nausea and Vomiting, last update Jun 20, 2018, available at https://clinicaltrials.gov/study/NCT02557035	X
2031	A Safety Study of Intravenous Pro-Netupitant and Palonosetron Combination for the Prevention of Nausea and Vomiting, last updated Jun 20, 2018, available at https://clinicaltrials.gov/study/NCT02517021	X
2032	U.S. Patent No. 5,202,333 to Berger et al.	X
2033	Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, available at https://www.accessdata.fda.gov/scripts/cder/ob/patent_info.cfm?Product_No=001&Appl_No=210493&Appl_type=N	X
2034	Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, available at https://www.accessdata.fda.gov/scripts/cder/ob/patent_info.cfm?Product_No=001&Appl_No=205718&Appl_type=N	X
2035	AKYNZEO® label	X

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2036	Navari, R.M. Pharmacological Management of Chemotherapy-Induced Nausea and Vomiting. Drugs 69, 515–533 (2009). https://doi.org/10.2165/00003495-200969050-00002 (Published March 2009)	
2037	Ettinger et al., Antiemesis Clinical Practice Guidelines in Oncology, Journal of the National Comprehensive Cancer Network, 7(5): 572-595 (May 2009)	
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2040	Reserved	
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2042	MARINOL® (Dronabinol) label	
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2045	Albert, J.S. et al., "Structural analysis and optimization of NK1 receptor antagonists through modulation of atropisomer interconversion properties." J. Med. Chem. 2004, 47, 519-529.	
2046	Veenstra S.J. et al., "Studies on the active conformation of NK1 antagonist CGP 49823. Part 1. Synthesis of conformationally restricted analogs," Bioorganic & Medicinal Chemistry Letters, 7(3): 347-350 (1997)	
2047	Goldstein D.J. et al., "Lanepitant, an NK-1 antagonist, in migraine prevention," Cephalalgia, 2001 Mar; 21(2):102-6	
2048	George D.T. et al. "Neurokinin 1 Receptor Antagonism as a possible therapy for alcoholism," Science 319: 1536-1539 (2008)	

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2049	Fujii, T. et al., "Pharmacological profile of a high affinity dipeptide NK1 receptor antagonist, FK888," Br. J. Pharmacol. 107:785-789 (1992)	
2050	Diemunsch, Pierre, and Laurent Grélot, "Potential of substance P antagonists as antiemetics," Drugs 60(3): 533-546 (2000)	
2051	Diemunsch, P. et al., "Neurokinin-1 receptor antagonists in the prevention of postoperative nausea and vomiting." British Journal of Anaesthesia, 103(1): 7-13 (2009)	
2052	Rosso, M. et al. "The NK-1 receptor is expressed in human primary gastric and colon adenocarcinomas and is involved in the antitumor action of L-733,060 and the mitogenic action of substance P on human gastrointestinal cancer cell lines." Tumor Biol. 29(4): 245-254 (2008)	
2053	Cascieri, M. et al. "Characterization of the binding and activity of a high affinity, pseudoirreversible morpholino tachykinin NK1 receptor antagonist." European Journal of Pharmacology 325(2-3): 253-26 (1997)	
2054	Sindrup, S. et al., "The NK1-receptor antagonist TKA731 in painful diabetic neuropathy: a randomised, controlled trial." European Journal of Pain 10(6): 567-571 (2006)	
2055	Vendruscolo, F. et al. "Evaluation of the anxiolytic-like effect of NKP608, a NK1-receptor antagonist, in two rat strains that differ in anxiety-related behaviors." Psychopharmacology 170(3): 287-293 (2003)	
2056	Saito, R. et al. "Anti-emetic effects of a novel NK-1 receptor antagonist HSP-117 in ferrets." Neuroscience letters 254(3): 169-172 (1998)	
2057	Ebner, K. et al., "Tachykinin receptors as therapeutic targets in stress-related disorders," Current Pharmaceutical Design 15(14): 1647-1674 (2009)	

Exhibit No.	Description	Previously Submitted?
2058	Shishido, Y. et al. "Discovery and stereoselective synthesis of the novel isochroman neurokinin-1 receptor antagonist 'CJ-17,493'." Bioorganic & Medicinal Chemistry 16(15): 7193-7205 (2008)	
2059	De la Puente-Redondo, V. et al. "The neurokinin-1 antagonist activity of maropitant, an antiemetic drug for dogs, in a gerbil model." Journal of Veterinary Pharmacology and Therapeutics 30(4): 281-287 (2007)	
2060	Rudd, J et al., "Inhibition of emesis by tachykinin NK1 receptor antagonists in Suncus murinus (house musk shrew)." European Journal of Pharmacology 366(2-3): 243-252 (1999)	
2061	Quartara, Laura and Altamura, Maria, "Tachykinin receptors antagonists: from research to clinic." Current Drug Targets 7(8): 975-992 (2006)	
2062	Emonds-Alt, Xavier et al. "SSR240600 [(R)-2-(1-{2-[4-{2-[3, 5-Bis (trifluoromethyl) phenyl] acetyl}-2-(3, 4-dichlorophenyl)-2-morpholinyl] ethyl}-4-piperidinyl)-2-methylpropanamide], a Centrally Active Nonpeptide Antagonist of the Tachykinin Neurokinin-1 Receptor: I. Biochemical and Pharmacological Characterization." The Journal of Pharmacology and Experimental Therapeutics 303(3): 1171-1179 (2002)	
2063	Shue, H. et al. "Cyclic urea derivatives as potent NK1 selective antagonists." Bioorganic & Medicinal Chemistry Letters 15(17): 3896-3899 (2005)	
2064	Araya, I. et al. "Process development and large-scale synthesis of NK1 antagonist." Chemical and Pharmaceutical Bulletin 56(2): 176-180 (2008)	
2065	Hesse, C. et al. "Kinetics and dynamics of the peripheral neurokinin-1 receptor antagonist SLV317 in healthy individuals." *British Journal of Clinical Pharmacology* 61(4): 414-419 (2006)	

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2066	Megens AA, Ashton D, Vermeire JC, Vermote PC, Hens KA, Hillen LC, Fransen JF, Mahieu M, Heylen L, Leysen JE, Jurzak MR, Janssens F. Pharmacological profile of (2R-trans)-4-[1-[3,5-bis(trifluoromethyl)benzoyl]-2-(phenylmethyl)-4-piperidinyl]-N-(2,6-dimethylphenyl)-1-acetamide (S)-Hydroxybutanedioate (R116301), an orally and centrally active neurokinin-1 receptor antagonist. J Pharmacol Exp Ther. 302(2):696-709 (2002 Aug)	
2067	Reserved	
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2069	Reserved	
2070	Reserved	

I. INTRODUCTION

Patent Owner Helsinn Healthcare S.A. ("Helsinn" or "PO") respectfully submits this Preliminary Response to the Petition for *inter partes* review (Paper 1) ("Petition" or "Pet.") filed by Azurity Pharmaceuticals, Inc. ("Azurity" or "Petitioner") against claims 1, 5-10, 17-39, and 43-51 of U.S. Patent No. 9,186,357 ("the '357 patent"). For the reasons explained below, the Petition should be denied under 35 U.S.C. § 314(a) because Azurity has not met its burden of demonstrating a reasonable likelihood of prevailing on any of the challenged claims.

Chemotherapy-induced nausea and vomiting ("CINV") is and has been a major concern for patients undergoing chemotherapy. As of November 2009, the available CINV treatments that had been FDA-approved were known to be effective against vomiting, but did not also allow for the control of nausea. The '357 patent invention offered a CINV treatment that was also effective against nausea and represented a significant, and much-needed, advance in supportive care for cancer patients undergoing chemotherapy. For example, the inventors discovered that administering a combination of two specific chemical compounds, called "netupitant" and "palonosetron," provided "an unanticipated statistically significant effect ***against nausea*** . . . that [had] not previously been observed in

clinical studies."[1] (Ex. 1005 at 345, ¶ 28; Ex. 2068 at ¶¶ 51-57.) This combination of netupitant and palonosetron is recited in independent claim 1 of the '357 patent—the only independent claim challenged in the instant Petition.

Azurity fails to show that this novel, first-of-its-kind treatment would have been obvious to a person of ordinary skill in the art ("POSA") in November 2009. As a preliminary matter, and as explained below (*see infra* Section V.A.), Azurity does not apply the proper legal framework for its obviousness analysis. Instead, Azurity begins with Helsinn's own invention, and then works backwards to stitch together an assertion that the invention would have been obvious to a POSA. But Azurity's approach to the obviousness analysis is legally erroneous. *See Cheese Sys., Inc. v. Tetra Pak Cheese & Powder Sys., Inc.*, 725 F.3d 1341, 1352 (Fed. Cir. 2013) (explaining that "[o]bviousness cannot be based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention"). A proper obviousness inquiry must determine whether there would have been a motivation to combine the prior art with a reasonable expectation of achieving the claimed invention in view of the problem facing a POSA and the potential options the POSA would have

[1] Unless otherwise indicated, all emphasis has been added, and all internal citations and quotations have been omitted.

considered in light of this problem. *See generally Insite Vision Inc. v. Sandoz, Inc.*, 783 F.3d 853, 858-61 (Fed. Cir. 2015). This inquiry is nowhere to be found in Azurity's Petition, which is completely silent regarding the problem facing a POSA and the potential options the POSA would have considered in light of this problem. Azurity's obviousness grounds must fail for that reason alone.

The legal error arising from Azurity's misframing of the obviousness analysis is compounded by its narrow view of the many potential options that were available to a POSA in November 2009. Azurity contends that it would have been obvious for a POSA at the time of the invention to start with a three-drug regimen that included a drug called "aprepitant," and then replace aprepitant with another compound called "netupitant" to arrive at the claimed invention. (*See, e.g.*, Petition at 26, 33 ("A POSA reasonably expected success modifying Herrstedt's antiemetic combination with netupitant because the substituted newer NK_1 antagonist (netupitant for the older aprepitant) would have been expected to act in the same manner to achieve a similar (or better) outcome.").) Azurity's proposed motivation for a POSA to make this specific change directly hinges on its allegation that the prior art recognized netupitant as somehow "improved" over aprepitant. But Azurity ignores that netupitant was just ***one of many*** drugs in the same class as aprepitant that were available in November 2009. Moreover, Azurity's contention that netupitant was "improved" over aprepitant finds no

support in Azurity's cited art, nor does Azurity connect this allegedly "improved" profile to any clinically meaningful results that would have motivated a POSA. (*See infra* Section V.B.) Azurity also fails to demonstrate that a POSA would have had a reasonable expectation as the Petition provides no evidence that a POSA would have reasonably expected the netupitant-based three-drug regimen to be effective at treating both ***nausea*** and vomiting. (*See infra* Section V.C.)

Finally, Azurity fails to address—let alone persuasively challenge—the evidence of unexpected synergy between netupitant and palonosetron in controlling nausea in cancer patients undergoing chemotherapy which was considered by the Patent Office in allowing the claims of the '357 patent's parent patent to issue. This synergy further underscores the nonobviousness of the claimed combination, as the Office recognized in its Notice of Allowance. (*See infra* Section V.D.) Moreover, Azurity's allegation that Helsinn misrepresented certain data during prosecution of the '357 patent's parent patent is demonstrably false, as confirmed by statements in Azurity's own cited art (*e.g.*, Herrington) and the clinical data provided in the FDA-approved labeling for an aprepitant drug product. (*See infra* Section V.E.)

Accordingly, as discussed in more detail below, institution of Azurity's Petition should be denied.

II. BACKGROUND

A. Chemotherapy-Induced Nausea and Vomiting

Chemotherapy-induced nausea and vomiting is a major concern for patients undergoing chemotherapy. (Ex. 2001 at 1856; Ex. 2068 at ¶¶ 23- 27.) Poorly controlled CINV can greatly impact the quality of life of patients with cancer and, in some cases, can be so severe that patients make the difficult decision to discontinue chemotherapy altogether. (Ex. 2001 at 1856; Ex. 2068 at ¶ 24.)

Vomiting (also commonly referred to as emesis)[2] and nausea are two separate adverse events associated with chemotherapy and often need to be treated individually. (Ex. 2068 at ¶ 23.) This distinction between the nausea and vomiting components of CINV is significant, as the nausea arising from chemotherapy has historically been much more difficult to control than vomiting. (*See, e.g.*, Ex. 1010 at 143, 148; Ex. 2068 at ¶¶ 24, 76-82.) As of November 2009, treatments indicated for "CINV" were known to be effective against vomiting, but did not allow for the control of nausea. (Ex. 2068 at ¶¶ 31-42.) A POSA would have thus understood the phrase "CINV" to be somewhat of a misnomer, as treatments for CINV actually did "***not*** need to demonstrate an effect on ***nausea*** to secure approval for

[2] "Emesis" is a term that includes the acts of retching (dry heaving) or vomiting (expulsion of stomach contents) but does not include nausea.

this indication." (Ex. 1005 at 347, ¶ 38; Ex. 2068 at ¶¶ 28-30.) Instead, to receive FDA-approval for the indication of treating CINV, "drug sponsors . . . [were] only required to demonstrate an effect on 'complete response,' defined as no emetic episodes (i.e., vomiting or retching) and no use of rescue therapy during the relevant time period."[3] (Ex. 1005 at 347, ¶ 38; Ex. 2068 at ¶¶ 28-30.)

B. In 2009, Various Options Showed Promise for Controlling Nausea, None of Which Pointed to the Claimed Inventions

As of November 2009, the available CINV treatments that had been FDA-approved were known to be effective against vomiting, but did not also allow for the control of nausea. (Ex. 2068 at ¶¶ 31-42.) And while various drug options had shown promise for controlling nausea, none of the options pointed to the netupitant-based drug regimen described and claimed in the '357 patent.

Clinicians in 2009 had several options for controlling chemotherapy-induced emesis component of CINV, including through various drug products. (Ex. 2068 at ¶¶ 31-41.) For example, at that time, the drug aprepitant had been shown to be effective in clinical trials for controlling emesis, but did not show any statistically

[3] Rescue therapy is when additional treatment beyond the administered prophylactic drugs is required because vomiting and/or nausea occurred within five days of chemotherapy administration. (Ex. 2068 at ¶¶ 27, 27 n. 4.)

significant effect on nausea. (Ex. 1005 at 345-46, ¶¶ 32-34; Ex. 1016 at 2086 ("According to its package insert, aprepitant fails to demonstrate improved efficacy over placebo for the prevention of nausea . . . ."); Ex. 2068 at ¶¶ 104-14.) Aprepitant, which is a member of a family of chemical compounds known as NK-1 receptor antagonists,[4] was typically administered to treat CINV in combination with other drugs, such as 5-HT_3 receptor antagonists and dexamethasone. This three-drug regimen (also referred to as "triple therapy") was found to be effective in treating emesis but did not allow for control of nausea. (Ex. 2068 at ¶¶ 31-40, 42.) As a result, as of November 2009, control of nausea was considered a problem for treating patients for CINV, especially because patients often experience more nausea than vomiting. (Ex. 2068 at ¶¶ 31-40, 75-82.)

While no FDA-approved treatment for CINV that also allowed for the control of nausea was available in 2009, a POSA would have known from the pertinent art that numerous different drugs from various classes showed promise for potentially controlling nausea. (Ex. 2068 at ¶¶ 83-89.) Some exemplary

[4] An "antagonist" is a chemical compound administered to block certain neurotransmitters from binding to receptors. (Ex. 1010 at 144.) For example, a chemical compound that blocks or inhibits activity of an NK-1 receptor is referred to as an "NK-1 receptor antagonist." (Ex. 2068 at ¶25.)

categories of drugs that a POSA could have considered included antipsychotics (*e.g.*, olanzapine), antiepileptics (*e.g.*, gabapentin), and cannabinoids (*e.g.*, dronabinol and nabilone), which had demonstrated encouraging antinausea efficacy as candidates for potential further investigation. (Ex. 2068 at ¶¶ 42-50, 83-89.) None of these options, however, pointed to the claimed inventions of the '357 patent.

Among the numerous drug candidates that were promising at this time, olanzapine was described by one prior art publication as the "most promising" new anti-emetic "with very high complete response rates of both ***nausea*** and vomiting when combined with a 5-HT_3-receptor antagonist and a corticosteroid." (Ex. 2068 at ¶¶ 43-45 (quoting Ex. 1010 at 149), 83-85). The antiepileptic gabapentin was another available option, and further studies had been suggested to determine its potential effects on reducing nausea. (Ex. 2068 at ¶¶ 43, 47-48, 87.) Additionally, cannabinoids had also been suggested for further trials to evaluate their use in the control of nausea. (Ex. 2068 at ¶¶ 49-50, 88-89.) By November 2009, two oral cannabinoid formulations were already FDA-approved for refractory CINV treatments, and cannabinoids were listed in the NCCN guidelines as a potential "breakthrough" CINV treatment. (Ex. 2068 at ¶¶ 50, 89.)

C. The '357 Patent Offered a Much-Needed CINV Treatment That Surprisingly Allowed for Control of Nausea

The invention of the '357 patent offered an improved CINV treatment that was also effective against nausea and represented a significant and much-needed advance in supportive care for cancer patients undergoing chemotherapy. Specifically, the '357 patent inventors discovered an innovative combination of netupitant and palonosetron which provided "an unanticipated statistically significant effect ***against nausea*** . . . that [had] not previously been observed in clinical studies" of other NK-1 receptor antagonists in combination with other 5-HT_3 receptor antagonists. (Ex. 1005 at 345, ¶ 28[5]; Ex. 2068 at ¶¶ 51-52.) Indeed, clinical trials had previously shown that combining the NK-1 receptor antagonist aprepitant with 5-HT_3 receptor antagonists (ondansetron or palonosetron) did not provide significant relief for patients with "nausea" or "significant nausea" that resulted from highly emetogenic chemotherapy ("HEC") or moderately

[5] Exhibit 1005 is the prosecution history of U.S. Patent No 8,623,826 ("the '826 patent") (Ex. 1001), which is the parent of the '357 patent. During prosecution of the '826 patent, Helsinn submitted a Rule 132 declaration of Dr. Giorgia Rossi and Mr. Claudio Pietra submitted by Helsinn (Ex. 1005 at 341-350), which is referenced in this Section and later in Sections V.D. and V.E.

emetogenic chemotherapy ("MEC"). (Ex. 1005 at 345-47, ¶¶ 32-37; *see also* Ex. 2003 at 375 (reporting that "[t]hese drugs [5-HT_3 and NK-1 antiemetics] have had a huge impact in the protection from chemotherapy-induced vomiting, whereas the effect on nausea seems to be limited"); Ex. 2068 at ¶¶ 104-24.)[6]

The inventors hypothesized that this surprising clinical result from combining netupitant and palonosetron (a 5-HT_3 receptor antagonist) was due to an unexpected synergy between the drugs that allowed them to control nausea by inhibiting a naturally occurring substance in the body known as "substance P."[7] (Ex. 1005 at 342, ¶ 12.) These synergistic effects were observed to be far greater than the additive effects of netupitant and palonosetron on "substance P" when administered separately. Through their experiments, the inventors found that, while the "additive effect" of netupitant and palonosetron on inhibition of

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[6] Nausea can be assessed using a Visual-Analog scale (VAS), where patients must identify their feeling of nausea on a scale of 0-100 mm. No nausea is defined as a VAS score of < 5 mm, and no significant nausea is typically defined as a VAS score of < 25 mm. (*See, e.g.*, Ex. 1016 at 2081.)

[7] Substance P binds to NK-1 receptors and plays a key role in triggering nausea. (Ex. 1010 at 146; Ex. 1005 at 342, ¶ 12.)

substance P might be expected to be "66 μM (38 μM for netupitant + 28 μM for palonosetron)," the combination of the drugs unexpectedly resulted in 970 μM, which is a "***nearly 500-fold***" increase on substance P inhibition. (Ex. 1005 at 344, ¶¶ 22-23; Ex. 2068 at ¶¶ 53-57.)[8]

The inventors claimed their synergistic combination of netupitant and palonosetron in, *inter alia*, the '357 patent. The '357 patent is titled "Compositions and Methods for Treating Centrally Mediated Nausea and Vomiting" and claims priority to a November 18, 2009 patent application. (Ex. 1002 at Cover.) Claim 1 of the '357 patent is exemplary and recites:

> A method of treating chemotherapy induced nausea and vomiting (CINV) comprising administering to a subject receiving chemotherapy a regimen of ***palonosetron, netupitant*** and dexamethasone.

(Ex. 1002 at Claim 1.)

III. LEVEL OF ORDINARY SKILL

Azurity proposes the following definition of a POSA at the relevant time:

[8] The "μM" values represent the "EC_{50}" of substance P. An EC_{50} value is used to quantify the relationship between the concentration of a substance and the biological response elicited by that substance.

> A POSA was skilled in one of "clinical medicine, medical oncology, radiation oncology, oncology nursing, statistics, pharmacy, medical policy and decision making, and pharmacology." . . . In 2009, such professionals had advanced degrees in pharmacology, medicine, or allied fields, and would have worked in consultation with other specialists in these fields, and had practical knowledge and experience about metabolism studies, in-vitro and in-vivo testing, formulation, and combination therapy.

(Petition at 8 (citing Ex. 1009 at ¶¶ 1-7, 57-60).) Patent Owner disagrees with Azurity's definition of a POSA to the extent Azurity's POSA definition does not require experience in the field of oncology, including work experience with cancer supportive care medications.

Patent Owner proposes the following definition for a POSA:

> A POSA at the time of the claimed invention was actively involved in the field of oncology and, more specifically, supportive cancer care, which involves a number of disciplines and requires collaborative teamwork among persons with relevant experience. The POSA could have an advanced degree (*e.g.*, Ph.D., M.D., M.S., MSN, DNP, or equivalent) in a relevant field (*e.g.*, oncology) with at least three years of experience in oncology, including the treatment of nausea and vomiting with supportive cancer care medications in cancer patients undergoing

> chemotherapy. More education can substitute for practical experience and *vice versa*.

(Ex. 2068 at ¶ 19.)

Based on the information disclosed in his declaration (Ex. 1009) and *curriculum vitae* (Ex. 1020), Dr. Peroutka appears to lack any substantial experience practicing in the field of oncology during the relevant time period of November 2009.[9] (*See* Ex. 1009 at 1-3, ¶¶ 1-7; Ex. 1020 at 4.) Dr. Peroutka also appears not to have any experience with treating cancer patients or patients suffering from CINV. And while Dr. Peroutka states that his "research includes publications involving chemotherapeutic agents and antiemetic agents, such as 5-hydroxytryptamine-3 ('5-HT_3') receptor inhibitors" (Ex. 1009 at ¶ 5), the most recent of those publications is dated 1989—two decades before the time of invention. (Ex. 1020 at 16.) Accordingly, Dr. Peroutka does not appear to have

[9] During the time that Dr. Peroutka practiced medicine, his practice was limited to the field of neurology. He has not practiced as a clinician in any capacity since about 1990. (Ex. 1020 at 4.) Accordingly, he would have not had an opportunity to prescribe any NK-1 receptor antagonist or palonosetron, as those drugs were not FDA-approved at the time he practiced medicine or for over a decade after that time.

sufficient experience in the field of oncology to accurately opine from the perspective of a POSA in November 2009.

IV. CLAIM CONSTRUCTION

The Board need not construe Azurity's proposed claim terms because construction of those terms is unnecessary to resolve the parties' disputes here. Under any reasonable construction of the claim terms, the prior art fails to disclose or suggest the claimed features. Thus, no claims need be construed here because the Board only construes the claims when necessary to resolve the underlying controversy. *Toyota Motor Corp. v. Cellport Systems, Inc.*, IPR2015-00633, Paper 11 at 16 (Aug. 14, 2015) (citing *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999)).

V. AZURITY HAS NOT ESTABLISHED A REASONABLE LIKELIHOOD THAT ANY CHALLENGED CLAIM WOULD HAVE BEEN OBVIOUS

A. Azurity's Obviousness Analysis Applies the Wrong Legal Framework[10]

In its Petition, Azurity ignores that the obviousness analysis does not begin with the invention, but rather with the problem facing the POSA at the relevant

[10] Helsinn's Preliminary Response focuses on the sole challenged independent claim 1. Azurity's challenges to the dependent claims in each of its grounds, however, fail equally for the same reasons as independent claim 1.

time. Here, Azurity begins with Helsinn's invention, and then works backwards by cobbling together the prior art so as to arrive at the claimed inventions. (*See, e.g.*, Petition at 26, 33 ("A POSA reasonably expected success modifying Herrstedt's antiemetic combination with netupitant because the substituted newer NK_1 antagonist (netupitant for the older aprepitant) would have been expected to act in the same manner to achieve a similar (or better) outcome").) The Federal Circuit has criticized this kind of approach to the obviousness analysis:

> Too often the obviousness analysis is framed as an inquiry into whether a person of skill, with two (and only two) references sitting on the table in front of him, would have been motivated to combine . . . the references in a way that renders the claimed invention obvious. The real question is whether that skilled artisan would have plucked one reference out of the sea of prior art . . . and combined it . . . to address some need present in the field . . . . Whether a skilled artisan would be motivated to make a combination includes whether he would select particular references in order to combine their elements.

WBIP, LLC v. Kohler Co., 829 F.3d 1317, 1337 (Fed. Cir. 2016). Azurity's approach is emblematic of impermissible hindsight and must fail for this reason alone.

Under the proper legal framework, Azurity must show that a POSA at the time of the invention "'would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and . . . would have had a reasonable expectation of success in doing so.'" *Insite*, 783 F.3d at 859; *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Pat. Litig.*, 676 F.3d 1063, 1068-69 (Fed. Cir. 2012). Importantly, the problem facing the POSA provides the foundation for this framework, as "[w]hat matters is the path that the [POSA] would have followed, as evidenced by the pertinent prior art." *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1296 (Fed. Cir. 2012); *WBIP*, 829 F.3d at 1337 ("The real question is whether that skilled artisan would have plucked one reference out of the sea of prior art . . . and combined it . . . to address some need present in the field . . . ."). After the problem facing a POSA is defined, the next step is determining whether a POSA would have "narrow[ed] [their] research focus" in a manner that arrived at the invention. *See Insite*, 783 F.3d at 860.

The Federal Circuit's *Insite* decision is particularly instructive for determining the proper starting point for an obviousness analysis. In *Insite*, the disputed claim recited "a method of treating an ocular infection, comprising topically administering . . . an ocular infection-treating amount of azithromycin." 783 F.3d at 856. There, the district court had defined "the problem facing a [POSA] at the time of the invention as the development of 'improved topical

treatments for ocular infections.'" *Id.* at 857. While affirming the district court's finding on appeal, the Federal Circuit rejected the patent challenger's attempt to narrowly construe the problem facing a POSA and held that the problem "was broader than merely seeking to use azithromycin to treat conjunctivitis." *Id.* at 860.

As explained below, the problem facing a POSA in 2009 was the need for an improved treatment for CINV that allowed for controlling chemotherapy-induced nausea. **(**Ex. 2068 at ¶¶ 70-82.) Rather than analyze the prior art options a POSA would have considered for solving this problem, Azurity impermissibly cherry-picks prior art using the claims as a roadmap. For example, Azurity incorrectly assumed that a POSA would first look to the aprepitant-based triple therapy used to treat CINV, which did not even allow for the treatment of nausea, and then consider swapping the then-gold-standard aprepitant for netupitant to arrive at the claimed invention. (*See, e.g.*, Petition at 26, 33 ("A POSA reasonably expected success modifying Herrstedt's antiemetic combination with netupitant because the substituted newer NK_1 antagonist (netupitant for the older aprepitant) would have been expected to act in the same manner to achieve a similar (or better) outcome").)

Contrary to Azurity's assertions, the obviousness question here cannot be narrowly framed to focus only on whether it would have been obvious to a POSA

substitute netupitant for aprepitant in Herrstedt's three-drug regimen. The obviousness analysis must take into account the many different potential paths that a POSA would have considered to possibly address the problem facing the POSA, and whether any of these paths would have actually led a POSA to the claimed netupitant-based regimen for treating CINV. *See generally Insite*, 783 F.3d at 858-61. Azurity's failure to engage in the requisite analysis is dispositive here.

1. In 2009, the Problem Facing a POSA Was the Need for an Improved Treatment for CINV That Also Controlled Chemotherapy-Induced Nausea

In November 2009, the problem facing a POSA was improving the treatment of CINV to allow for controlling nausea. (Ex. 2068 at ¶¶ 42 (citing Ex. 2036 at 528), 75-82.) The problem facing a POSA in November 2009 is exemplified by the 2009 National Comprehensive Cancer Network ("NCCN") Guidelines (Ex. 2037). These guidelines informed clinicians in 2009 who treated patients suffering from CINV by providing a consensus of expert views on currently accepted approaches to treatment. While NCCN Guidelines recommended administration of the "triple therapy" to reliably control emesis in patients suffering from CINV, the NCCN Guidelines also reported its lack of control of nausea remained a significant problem for patients. (Ex. 2068 at ¶¶ 24, 31-32; Ex. 2037 at 573, 587; Ex. 1010 at 143 ("Today, the majority of patients consider nausea as the main problem."). As discussed above, untreated chemotherapy-induced nausea was a significant patient

concern that affected quality of life for cancer patients, potentially leading to poor compliance with future chemotherapy treatment. (Ex. 2068 at ¶ 24; Ex. 2037 at 572.) Accordingly, framing the problem facing a POSA as improving treatments for CINV to allow for the control of nausea properly reflects the path that a POSA in November 2009 "would have followed, as evidenced by the pertinent prior art." *Otsuka*, 678 F.3d at 1296.

2. A POSA in November 2009 Had Many Potential Pathways for Attempting to Develop an Improved Treatment for CINV That Allowed for Control of Nausea

The prior art that Azurity focuses upon in its Petition, as well as its analysis of what that art would have taught a POSA in November 2009, underscores the hindsight-based nature of Azurity's obviousness analysis. Azurity's Petition relies on Herrstedt as the primary reference across all grounds. (Petition at 2.) Azurity states that Herrstedt discloses a three-drug combination (or "triple therapy") of an NK-1 receptor antagonist aprepitant, a 5-HT_3 receptor antagonist, and the corticosteroid dexamethasone for treating CINV. (*See, e.g.*, *id.* at 17 ("Herrstedt teaches treating highly-emetogenic chemotherapy with a triple-drug combination administered to patients on day 1 including a 5-HT_3 antagonist, an NK_1 antagonist (aprepitant), and dexamethasone.").) By November 2009, this three-drug regimen had been proven effective against vomiting, but did ***not*** successfully control nausea. (Ex. 2068 at ¶¶ 31-40.) Herrstedt even acknowledges this shortcoming, stating that

nausea remained "the main problem[] for the majority of patients," despite the availability of aprepitant and this three-drug dosing regimen. (Ex. 1010 at 148; *see also id.* at 143.) Azurity fails to explain in its obviousness analysis why a POSA would have started with triple therapy when it was not effective in controlling nausea.

But even if the triple therapy in Herrstedt were to be used as a starting point, Azurity's analysis fails to consider the many paths that a POSA in November 2009 would have considered to allow for the treatment of nausea. *See Insite*, 783 F.3d at 859-60 (after the problem facing a POSA is defined, the next step is determining whether a POSA would have "narrow[ed] [their] research focus to lead to the invention"). For example, one possible pathway for a POSA to consider would have been adding a ***fourth*** drug to the existing triple therapy regimen to control nausea instead of substituting for individual drugs (*e.g.*, aprepitant) in that regimen. (Ex. 2068 at ¶¶ 83-89.)

As one possibility, a POSA in 2009 could have explored the addition of olanzapine, a different drug that had already shown potential for controlling nausea, as a fourth drug in the three-drug combination.[11] (Ex. 2068 at ¶¶ 84-85.)

[11] In fact, in subsequent clinical studies carried out in 2016, olanzapine was found to have "significantly improved nausea prevention, as well as the

In fact, Herrstedt itself touts the potential of olanzapine in controlling the nausea component, describing olanzapine as the "most promising" new anti-emetic "with very high complete response rates of both ***nausea*** and vomiting when combined with a 5-HT_3-receptor antagonist and a corticosteroid." (Ex. 2068 at ¶ 85 (quoting Ex. 1010 at 149)).[12] Azurity provides no reason why a POSA would have not considered adding a fourth drug, like olanzapine, to the three-drug combination in Herrstedt, especially given Herrstedt's own statements about the potential benefit of olanzapine. Indeed, "it is impermissible to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art." *In re Wesslau*, 353 F.2d 238, 241 (C.C.P.A. 1965); *see, e.g.*, *Henny Penny Corp. v. Frymaster LLC*, 938 F.3d 1324, 1332 (Fed. Cir. 2019) ("The benefits, *both lost and gained*, should be weighed against one another. That is consistent with the longstanding principle that the prior art must be considered for all its teachings, not selectively.") (citation modified); *Polaris*

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complete-response rate" when added to triple therapy patients receiving highly emetogenic chemotherapy. (Ex. 2068 at ¶ 86 (quoting Ex. 2039 at 134).)

[12] This discussion of the olanzapine regimen in Herrstedt does not even include any mention of an NK-1 receptor antagonist in the regimen.

Indus., Inc. v. Arctic Cat, Inc., 882 F.3d 1056, 1069 (Fed. Cir. 2018) ("[A] reference must be considered for all it taught, disclosures that diverged and taught away from the invention at hand as well as disclosures that pointed towards and taught the invention at hand.").

Azurity also ignores other potential paths that were available to a POSA in November 2009—none of which would lead to the claimed inventions. For example, a POSA could have considered adding other drugs, like gabapentin and cannabinoids, from other, different drug classes to the three-drug regimen for controlling nausea. As Dr. Navari explains, the anti-epileptic gabapentin was one possible option, and further studies had been suggested to determine its potential effects on reducing nausea. (Ex. 2068 at ¶ 87.) Additionally, cannabinoids had also been suggested for further trials to evaluate their use in the control of nausea. (Ex. 2068 at ¶¶ 88-89.) By 2009, two oral cannabinoid formulations were already FDA-approved for refractory CINV treatments, and cannabinoids were listed in the NCCN guidelines as a potential "breakthrough" CINV treatment. (Ex. 2068 at ¶¶ 88-89.)

The prior art, including one of Azurity's own lead references, makes clear that a POSA could have pursued numerous paths to solve the underlying problem of nausea. Again, none of these pathways involve netupitant or point to the claimed netupitant-based CINV treatment. Azurity's lack of consideration of these

alternate paths, coupled with its singular focus on netupitant, underscores that its obviousness analysis is infected by impermissible hindsight. (Ex. 1010 at 149.) Accordingly, for this reason alone, Azurity cannot establish a reasonable likelihood of showing the challenged claims would have been obvious.

B. Even if a POSA Had Focused on NK-1 Receptor Antagonists, Azurity Fails to Show That a POSA Would Have Chosen Netupitant

Azurity's analysis also fails to show a POSA would have focused on using netupitant for a potential CINV treatment over other NK-1 receptor antagonists. As explained below, Azurity's hindsight-based analysis that substituting netupitant for aprepitant in Herrstedt's 3-drug CINV treatment regimen would have been obvious (*see, e.g.,* Petition at 25-26) suffers from a lack of factual support. Indeed, Azurity fails to explain why a POSA would have immediately wanted to "swap out" part of the triple therapy for CINV (aprepitant) that was known to be extremely effective against vomiting. (Ex. 2068 at ¶¶ 90-97.) Moreover, Azurity's bald assertion that netupitant "was known to have favorable qualities as compared to aprepitant" (Petition at 26) is not only unsupported but fails to consider the prior art as a whole.

In November 2009, a POSA would have been aware of numerous NK-1 receptor antagonists. At that time, a long list of NK-1 receptor antagonists were either under investigation or had been investigated, and thus, were at various stages

of development. (Ex. 2068 at ¶¶ 41, 91.) Azurity, however, fails to consider any of these alternative NK-1 receptor antagonists that were known by November 2009—let alone their advantages or shortcomings—and instead contends that a POSA would have zeroed in on netupitant.[13] But a POSA at this time would have considered all of these NK-1 receptor antagonists if they were looking at a potential replacement for aprepitant in the triple-therapy regimen. (Ex. 2068 at ¶ 91.)

Moreover, when the reference that Azurity cites for teaching the NK-1 receptor antagonist netupitant (Bös) is examined, netupitant is one of millions of disclosed compounds.[14] Bös is a U.S. patent directed to 4-phynyl-pyridine

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[13] Azurity's focus on NK-1 receptor antagonists for its obviousness analysis is at odds with its broad definition of a POSA who is not focused on such antagonists.

[14] Azurity injects the "Herrington" reference (Ex. 1016), the "Aloxi® Label" (Ex. 1015), the "Bonadeo" reference (Ex. 1017), and/or the "Hargreaves" reference (Ex. 1012) as tertiary references into one or more grounds of its Petition to address the admitted deficiencies of Herrstedt and Bös. (Petition at 2.) The addition of these references does not resolve the deficiencies with the combination of Azurity's proposed primary and secondary references.

derivatives generally, and netupitant is just one specific derivative that is claimed among millions of compounds. (Ex. 1014 at Cover; Ex. 2068 at ¶¶ 65-68.) Bös also does not include any express language suggesting that netupitant had greater antagonist activity at the NK-1 receptor than any of the other millions of other compounds it disclosed. (Ex. 2068 at ¶¶ 92-97.) Again, Azurity provides no analysis as to why a POSA would have homed in on netupitant to the exclusion of other compounds disclosed in Bös.

Azurity's proposed motivation for a POSA to choose netupitant as the NK-1 receptor antagonist over the millions of other NK-1 receptor antagonists is likewise wholly unsupported. For example, Azurity alleges that netupitant had "favorable qualities as compared to aprepitant" and that would have been a reason that a POSA would select netupitant. (*See, e.g.*, Petition at 26; *see also id.* at 25 (alleging that netupitant was an "improved" NK-1 receptor antagonist).) Azurity also contends that "Bös explains, netupitant was shown to potently and selectively inhibit the NK_1 receptor, and likewise antagonized NK_1 receptor-induced foot tapping after oral administration, which was indicative of successful NK_1 receptor antagonism." (*Id*. at 25.) Bös, however, fails to provide any support for Azurity's contentions regarding netupitant's alleged advantages over aprepitant. (Ex. 2068 at ¶¶ 92-97.)

As a threshold matter, Bös does not include any analysis between aprepitant and netupitant from which a POSA could draw conclusions regarding their comparative clinical efficacy. (Ex. 2068 at ¶ 96.) Bös lacks any human clinical data and only provides data from *in vivo* animal studies and *in vitro* CHO cells (cells derived from hamsters) where human NK-1 receptors were expressed. (Ex. 1014 at 18:42-19:38.) The *in vivo* animal studies were early exploratory studies on, *inter alia*, potential uses for NK-1 receptor antagonists that used animal models for anxiety (gerbil foot tapping), motion sickness (suncus murinus), and emesis (ferrets). (*Id.* at 18:42-19:38.) None of these animal models were used to assess any potential efficacy of netupitant in controlling nausea in humans. (*Id.* at 14:09-30, 18:42-19:38.) Bös's high-level observations regarding netupitant's antagonist activity and CNS penetration fall far short of showing the comparative efficacy of these compounds to aprepitant (or any other NK-1 receptor antagonist) for treating CINV, let alone in treating nausea. (Ex. 2068 at ¶ 96.) In fact, CNS penetration is a trait common to NK-1 receptor antagonists generally, including aprepitant, and is associated with potential treatment of numerous different conditions, including depression, anxiety, Parkinson's disease, and Alzheimer's disease. (Ex. 2068 at ¶ 94.)

Bös therefore does not show netupitant was in any way "improved" over aprepitant, or that a POSA would have been motivated to substitute netupitant for

aprepitant due to netupitant's purportedly "improved" profile. Without any valid data or analysis, there would have been no reason for a POSA to believe that netupitant offered any properties beyond what aprepitant already possessed. Thus, Azurity has failed to demonstrate the requisite motivation for a POSA, and each of its grounds fail for this reason alone.

C. Azurity Fails to Demonstrate Any Reasonable Expectation of Success by a POSA

Azurity also fails to provide sufficient evidence from which the Board can find that a POSA would have had a reasonable expectation of success in arriving at the claimed invention. Specifically, claim 1 of the '357 patent requires that the claimed method would treat ***both nausea*** and vomiting. (Ex. 1002 at Claim 1 ("A method of treating chemotherapy induced nausea and vomiting (CINV) . . . .").) But Azurity provides no evidence that a POSA would have reasonably expected the netupitant-based three-drug regimen to be effective at treating ***nausea*** and vomiting.

For example, Azurity broadly argues that "[a] POSA reasonably expected success modifying Herrstedt's antiemetic combination with netupitant because the substituted newer NK_1 antagonist (netupitant for the older aprepitant) would have been expected to act in the same manner to achieve a similar (or better) outcome." (Petition at 26, 33.) But Azurity fails to demonstrate that a POSA would have had

a reasonable expectation of success ***in treating nausea*** with this regimen, as required by the claims. (Ex. 2068 at ¶¶ 98-100.) In fact, the triple therapy Herrstedt failed to treat nausea (*supra* Section V.A.2.), and Azurity offers no evidence that incorporating netupitant in place of aprepitant would have provided a different result. Azurity's conclusory allegations regarding a reasonable expectation of success are insufficient as a matter of law, and based on this deficiency alone, a reasonable likelihood of success cannot be found.

D. Helsinn's Evidence of Unexpected Synergy Further Confirms Nonobviousness

Azurity has also failed to overcome, much less meaningfully address, the evidence of objective indicia of nonobviousness that Helsinn submitted during prosecution of the '826 patent. This evidence demonstrates the unexpected results of the administration of netupitant/palonosetron in combination, which was shown to reduce nausea at level far greater than observed when these two drugs were administered individually. As discussed above in Section II.C., the claimed invention of the '357 patent combines netupitant and palonosetron for administration to a patient suffering from CINV. This novel combination exhibited "an unanticipated statistically significant effect ***against nausea*** . . . not previously been observed in clinical studies" of other NK-1 receptor antagonists in combination with other 5-HT_3 receptor antagonists. (Ex. 1005 at 345, ¶ 28.)

This unexpected clinical result of the control of nausea in patients suffering from CINV appears to stem from the unexpected synergy between netupitant and palonosetron on "substance P," which is found naturally in the human body and plays a key role in triggering nausea. (Ex. 1010 at 146; Ex. 1005 at 342, ¶ 12.) As the Rule 132 declaration submitted by Helsinn during prosecution of the '826 patent explains, at "concentrations where neither individual molecule [*i.e.*, 1 nM netupitant and 0.2 nM palonosetron] increased the EC_{50} of substance P, the combination of molecules increased the EC_{50} of substance-P from 2 μM to 120 μM, a ***sixty-fold increase*** in the EC_{50} of substance-P. The additive increase ***should have been zero.***" (Ex. 1005 at 344, ¶ 21.) Additionally, for concentrations of 30 nM netupitant and 6 nM palonosetron, Helsinn "observed an increase in EC50 [of substance P] to 970 μM, ***nearly 500-fold***," when the increase ***should have been zero***. (*Id.*, ¶ 23.)

The data upon which Helsinn relies in support of these statements is expressly set forth in Table 1 below, which was also included in the Rule 132 declaration:

TABLE 1

Inhibition of SP response in NG108-15 cells by netupitant (netu) and palonosetron (palo).

SP + Antagonist(s)	EC_{50} (μM) ± S.E.M.	n
SP only	2 ± 0.2	38
Plus netu (1 nM)	2 ± 0.3	3
Plus netu (3 nM)	5 ± 3	3
Plus netu (10 nM)	10 ± 0.9	3
Plus netu (30 nM)	40 ± 10[a]	6
Plus palo (0.2 nM)	2 ± 0.1	3
Plus palo (0.6 nM)	3 ± 0.6	3
Plus palo (2 nM)	10 ± 2	3
Plus palo (6 nM)	30 ± 6[a]	5
Plus net (1 nM) plus palo (0.2 nM)	120 ± 20[b]	7
Plus net (30 nM) plus palo (6 nM)	970 ± 150[c]	5

(*Id.* at 343, ¶ 17.) This data shows that the combination of netupitant and palonosetron had a greater effect on the EC_{50} of substance P, which indicates a greater clinical impact on control of nausea, when administered together than the sum of their effects when administered separately. The Office noted this evidence of unexpected synergy in its Notice of Allowance for the '826 patent. (Ex. 1005 at 369.)

Azurity does not appear to dispute the unexpected impact of the netupitant-palonosetron combination on substance P activity. (Ex. 2068 at ¶¶ 101-03.) Instead, Azurity baldly asserts that combination of netupitant and palonosetron had no better effect on nausea as compared to other known combinations of 5-HT3 receptor antagonists and NK-1 receptor antagonists

(*e.g.*, palonosetron with aprepitant). (Petition at 59-60.) Azurity further claims, without evidence, that palonosetron has this synergistic effect with NK-1 antagonists generally. (*Id*.)

Azurity is incorrect. *First*, Azurity does not provide any scientific evidence or data for its contention that "palonosetron has this 'synergistic' effect with NK_1 antagonists generally." For example, Azurity does not submit any evidence showing that palonosetron combined with other NK-1 receptor antagonists had the same impact on substance-P activity as the netupitant-palonosetron combination. *Second*, the undisputed evidence shows that palonosetron combined with another NK-1 receptor antagonist (aprepitant) does not, in fact, have the same or better impact on nausea as the netupitant-palonosetron combination. (Ex. 2068 at ¶¶ 115- 21.) For example, controlled clinical trials showed that aprepitant administered in combination with 5-HT_3 receptor antagonists (ondansetron or palonosetron) did ***not*** provide statistically significant relief for "nausea" or "significant nausea", as compared to standard therapy, for patients receiving highly emetogenic chemotherapy ("HEC") or moderately emetogenic chemotherapy ("MEC"). (Ex. 2068 at ¶¶ 109-18; *see also* Ex. 1005 at 345-47, ¶¶ 32-37; Ex. 2003 at 375 (reporting that "[t]hese drugs [5-HT_3 and NK-1 antiemetics] have had a huge impact in the protection from chemotherapy-induced vomiting, whereas the effect on nausea seems to be limited").) The evidence submitted by Helsinn

further demonstrates that the specific combination of netupitant and palonosetron "interacted in an unpredictable or unexpected way" which provides additional support for the nonobviousness of the '357 patent claims. *See ModernaTx, Inc. v. Arbutus Biopharma Corp.,* 18 F.4th 1364, 1375 (Fed. Cir. 2021) ("[W]e have held that evidence that the components 'interacted in an unpredictable or unexpected way could render the combination nonobvious.'").

E. Helsinn Did Not Misrepresent Any Data During Prosecution

In an apparent attempt to distract from the deficiencies in its analysis, Azurity contends that Helsinn allegedly misrepresented certain data during prosecution to "exaggerate[] the differences between its triple therapy of netupitant, palonosetron, and dexamethasone versus the prior art combination" and purportedly manufactured an argument for unexpected synergistic effects of the combination of netupitant and palonosetron. (Petition at 55-60.) But as explained below, Helsinn's submissions during prosecution accurately characterized the underlying data that demonstrate these unexpected synergistic effects. Importantly, the majority of this data was ***readily available for the Office to review through the same public documents*** that were cited in the Rule 132 declaration (Ex. 1005 at 341-350). "[T]he Examiner was free to reach his own conclusions and accept or reject [the Rule 132 declaration's] arguments." *Young v. Lumenis, Inc.*, 492 F.3d 1336, 1349 (Fed. Cir. 2007) (holding that a patentee's

"interpretation" of prior art before the Examiner fails to "constitute affirmative misrepresentations of material fact"). The only misrepresentations here come from Azurity.

Azurity contends that, contrary to Helsinn's statements, "aprepitant has a substantial effect on nausea." (Petition at 56.) But as explained by Dr. Navari, Azurity is wrong. (Ex. 2068 at ¶¶ 104-24.) The Rule 132 declaration stated that "we generated unexpectedly superior results when using netupitant against CINV instead of aprepitant" and "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 ondansetron or aprepitant with palonosetron." (Ex. 1005 at 345, ¶ 28.) In support of this statement, the Rule 132 declaration cited two tables copied directly from the FDA-approved labeling for Emend® (aprepitant), which are reproduced below and show the results of a clinical study in patients receiving highly emetogenic chemotherapy. (*Id.* at 345-46, ¶ 32 (TABLE 2 referring to Ref. E), 350 (describing Ref. E as the March 27, 2003 Emend® label); *see also* Ex. 2016; Ex. 1030.)[15] These tables plainly demonstrate that the effect of an aprepitant

[15] Azurity and its expert, Dr. Peroutka, cite to the Emend® label from 2008. (*See, e.g.*, Ex. 1009 at ¶ 1334 (citing Ex. 1030).) But during examination, Helsinn

regimen on nausea or significant nausea were found ***not*** to be statistically significant in this clinical study, as compared to standard therapy and indicated by the "NS**" that appears in the p-Value column on the right-hand side:

Table 1

Percent of Patients Receiving Highly Emetogenic Chemotherapy Responding by Treatment Group and Phase for Study 1 — Cycle 1

ENDPOINTS	Aprepitant Regimen (N = 260)[†] %	Standard Therapy (N = 261)[†] %	p-Value
* * * *			
No Nausea			
Overall	48	44	NS**
Delayed phase	51	48	NS**
No Significant Nausea			
Overall	73	66	NS**
Delayed phase	75	69	NS**

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

referenced the Emend® label from 2003 (*see, e.g.,* Ex. 1005 at 346, ¶ 32 (TABLE 2 referring to Ref. E), 350 (describing Ref. E as the March 27, 2003 Emend® label)), which is Exhibit 2016 in this proceeding. For the purposes of this proceeding, Patent Owner references Exhibit 1030 cited by Dr. Peroutka and Azurity because the underlying data is the same.

Table 2

Percent of Patients Receiving Highly Emetogenic Chemotherapy Responding by Treatment Group and Phase for Study 2 — Cycle 1

ENDPOINTS	Aprepitant Regimen (N = 261)† %	Standard Therapy (N = 263)† %	p-Value
* * * *			
No Nausea			
Overall	49	39	NS*
Delayed phase	53	40	NS*
No Significant Nausea			
Overall	71	64	NS**
Delayed phase	73	65	NS**

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

(*Compare* Ex. 1005 at 330, *with* Ex. 1030 at 4-5 (annotations added).)

Industry publications, including Azurity's own cited Herrington reference (Ex. 1016), support the Rule 132 declaration's interpretation of this data. Herrington expressly cites the Emend® (aprepitant) labeling in stating that, "[a]ccording to its package insert, ***aprepitant fails to demonstrate*** improved efficacy over placebo for the prevention of nausea . . . ." (Ex. 1016 at 2086.) Yeo 2009 (Ex. 1048), another publication cited by Azurity, states that aprepitant makes "no difference in the nausea domain." (Ex. 2068 at ¶ 109; Ex. 1048 at 534.)

Rather than address lack of statistical significance for aprepitant's treatment of "nausea" and "significant nausea" that is shown in Emend® label, Azurity

focuses on the "complete protection" data that is provided elsewhere in that label. (Petition at 52-53.) Azurity asserts that "'complete protection' includes a lack of significant nausea" and "a POSA would have recognized improved [] treatment of nausea, particularly significant nausea" in view of the complete protection data that is provided. (*Id.*) As Dr. Navari explains, however, "complete protection" is not the correct metric by which to measure a drug's effect on nausea, as complete protection is a composite that represents a combination of data from three separately measured endpoints (*i.e.*, no emesis, no use of rescue antiemetics, and no significant nausea). (Ex. 2068 at ¶¶ 111-14.) The only information in the Emend® label that specifically provides information on aprepitant's impact on nausea unequivocally stated that aprepitant had no statistically significant impact. (*See* Ex. 2068 at ¶ 114; Ex. 1030 at 4-5.)

Turning back to the Rule 132 declaration, Azurity further asserts that the data presented in Table 2 of that declaration was "lacking." (Petition at 56-59.) For example, Azurity alleges that the declaration never provided the Office with the "underlying data for any palonosetron-netupitant combination." (*Id.* at 56.) But as can be seen in Columns 1 and 3 of Table 2 (reproduced below), the Rule 132 declaration did provide Helsinn's internal data for the netupitant/palonosetron combination. Moreover, the Rule 132 declaration cited specific internal studies (NETU-07-07 and NETU-08-18) as the source of the data in Table 2. (*See* Ex.

1005 at 345-46, ¶ 32.) If the Office had wanted to further evaluate the underlying data, they could have simply asked Helsinn to provide it, and Helsinn would have obliged without issue.

TABLE 2

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

*Statistically Significant ($p < 0.05$)
[nr] Data Not Reported
[ncs] Non-Comparative Study; statistical significance not evaluated
[a] Helsinn Study NETU-07-07
[b] Helsinn Study NETU-08-18
[c] Warr *et al.* (2005) (Ref. D)
[c1] FDA-Approved Prescribing Information for Emend® (aprepitant) (results of two studies reported) (Ref. E)
[d] Herrington *et al.* (2008) (Ref. F)
[e] Grunberg *et al.* (2008) (Ref. G)
[f] Yeo *et al.* (2009) (Ref. H)
[g] Longo *et al.* (2012) (Ref. I)

(Ex. 1005 at 345-46, ¶ 32.)

Azurity also argues that Columns 4 and 7 in Table 2 "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.'" (Petition at 57 (citing Ex. 1009 at ¶¶ 1367-68).) Columns 4 and 7 set forth data from two publicly available documents, Warr (Ex. 1034) and Yeo (Ex. 1048), and expressly cite those documents within the table. These publications were thus before the Office. Moreover, the data provided in these two publications is consistent with statements in the Rule 132 declaration that there was not a statistically significant effect of aprepitant on nausea. (Ex. 2068 at ¶¶ 121-22.)

Azurity further asserts that Column 4a in the Rule 132 declaration "[did] not include Emend's 'complete protection' data, even though this parameter requires an evaluation of significant nausea." (Petition at 57.) As discussed above, complete protection is a composite metric, and not a specific or appropriate measure of nausea. Moreover, data about complete protection does not inform a POSA about whether aprepitant has a specific effect on nausea. (Ex. 2068 at ¶ 114.)

For at least these reasons, and as further supported by Dr. Navari's declaration, Helsinn did not misrepresent any data during prosecution.

VI. CONCLUSION

For at least these reasons, Helsinn respectfully requests that the Board deny

the Petition for *inter partes* review of the '357 patent.[16]

Respectfully submitted,

Dated: September 4, 2025

By: /Eric W. Dittmann/
Eric W. Dittmann (Reg. No. 51,188)
Counsel for Patent Owner

[16] If trial is instituted, Helsinn reserves the right to raise additional arguments as to why Azurity has failed to carry its burden and why the challenged claims should be confirmed.

CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(d), the undersigned certifies that the foregoing Patent Owner's Preliminary Response contains, as measured by the word-processing system used to prepare this paper, 7,902 words. This word count does not include the items excluded by 37 C.F.R. § 42.24.

Respectfully submitted,

Dated: September 4, 2025

By: /Eric W. Dittmann/
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CERTIFICATE OF SERVICE

I hereby certify that on September 4, 2025, I caused a true and correct copy of the foregoing Patent Owner's Preliminary Response to be served via email on Petitioner at the following addresses:

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