UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AZURITY PHARMACEUTICALS, INC.,
Petitioner,

v.

HELSINN HEALTHCARE S.A.,
Patent Owner.

Case IPR2025-00946
Patent 9,186,357

PATENT OWNER'S RESPONSE

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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

Exhibit No.	Description	Previously Submitted
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

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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

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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

Exhibit No.	Description	Previously Submitted
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)	X
2037	Ettinger et al., Antiemesis Clinical Practice Guidelines in Oncology, Journal of the National Comprehensive Cancer Network, 7(5): 572-595 (May 2009)	X
2038	Reserved	
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2040	Reserved	
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2042	MARINOL® (Dronabinol) label	X
2043	CESAMET™ (Nabilone) label	X
2044	Navari CV	X
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.	X
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)	X
2047	Goldstein D.J. et al., "Lanepitant, an NK-1 antagonist, in migraine prevention," Cephalalgia, 2001 Mar; 21(2):102-6	X
2048	George D.T. et al. "Neurokinin 1 Receptor Antagonism as a possible therapy for alcoholism," Science 319: 1536-1539 (2008)	X

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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)	X
2050	Diemunsch, Pierre, and Laurent Grélot, "Potential of substance P antagonists as antiemetics," Drugs 60(3): 533-546 (2000)	X
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)	X
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)	X
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)	X
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)	X
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)	X
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)	X
2057	Ebner, K. et al., "Tachykinin receptors as therapeutic targets in stress-related disorders," Current Pharmaceutical Design 15(14): 1647-1674 (2009)	X

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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)	X
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)	X
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)	X
2061	Quartara, Laura and Altamura, Maria, "Tachykinin receptors antagonists: from research to clinic." Current Drug Targets 7(8): 975-992 (2006)	X
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)	X
2063	Shue, H. et al. "Cyclic urea derivatives as potent NK1 selective antagonists." Bioorganic & Medicinal Chemistry Letters 15(17): 3896-3899 (2005)	X
2064	Araya, I. et al. "Process development and large-scale synthesis of NK1 antagonist." Chemical and Pharmaceutical Bulletin 56(2): 176-180 (2008)	X
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)	X

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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)	X
2067	Reserved	
2068	IPR2025-00946; IPR2025-00947: Declaration of Rudolph Modesto Navari, M.D., Ph.D, F.A.C.P.	X
2069	Reserved	
2070	Reserved	
2071	Declaration of Melanie Rupert in Support of Motion for Pro Hac Vice	X
2072	Declaration of Justin T. Fleischacker in Support of Motion for Pro Hac Vice	X
2073	Schmoll, H.J. et al., *Comparison of an aprepitant regimen with a multiple-day ondansetron regimen, both with dexamethasone, for antiemetic efficacy in high-dose cisplatin treatment*, Annals of Oncology 17:1000-1006 (2006)	
2074	*Emesis*, *Vomiting*, Black's Medical Dictionary (41st ed. 2005)	
2075	Bloechl-Daum, B. et al., *Delayed Nausea and Vomiting Continue to Reduce Patients' Quality of Life After Highly and Moderately Emetogenic Chemotherapy Despite Antiemetic Treatment*, J. Clin. Oncol. 24:4472-4478 (2006)	
2076	Guidance for Industry, E9 Statistical Principles for Clinical Trials (Sept. 1998)	
2077	Press Release – GSK provides update on regulatory filings for Zunrisa/Rezonic, September 27, 2009	

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2078	Hamik, A. and Peroutka, S., *Differential interactions of traditional and novel antiemetics with dopamine D_2 and 5-hydroxytryptamine$_3$ receptors*, Cancer Chemother Pharmacol 24:307-310 (1989)	
2079	Ison. P. and Peroutka, S., *Neurotransmitter Receptor Binding Studies Predict Antiemetic Efficacy and Side Effects*, Cancer Treatment Reports Vol. 70, No. 5, 637-641 (May 1986)	
2080	January - March 2018 | Potential Signals of Serious Risks/New Safety Information Identified from the FDA Adverse Event Reporting System (FAERS)	
2081	Jordan, K. et al., *Chemotherapy-induced nausea and vomiting: current and new standards in the antiemetic prophylaxis and treatment*, European Journal of Cancer, 41 (2005) 199-205	
2082	O'Brien, M.E.R. et al., *The role of metoclopramide in acute and delayed chemotherapy induced emesis: a randomised double blind trial*, Br. J. Cancer, 60 (1989) 759-763	
2083	Peroutka, S., *Combination Antiemetics*, Cancer Treatment Reports, Vol. 66, No. 6, (June 1982) 1449	
2084	Peroutka, S., *Chemotherapeutic agents do not interact with neurotransmitter receptors*, Cancer Cheother Pharmocol 19:131-132 (1987)	
2085	Guidance for Industry, Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products (May 1998)	
2086	Deposition transcript of Stephen J. Peroutka, taken on January 13, 2026	
2087	Eric Roeland, MD, FASCO, FAAHPM Curriculum Vitae	
2088	RESERVED	
2089	IPR2025-00946, -00947 - Declaration of Eric Roeland, MD, FASCO, FAAHPM	

Exhibit No.	Description	Previously Submitted
2090	RESERVED	
2091	RESERVED	
2092	Peroutka, S., *Neurogenic Inflammation and Migraine: Implications for Therapeutics*, 5 Molecular Interventions 3:304-311 (Oct. 2005)	
2093	COMPAZINE® (prochlorperazine) label	
2094	PHENERGAN® (promethazine) label	
2095	Arpornwirat, W., M.D. et al., *Phase 2 Trial Results With the Novel Neurokinin-1 Receptor Antagonist Casopitant in Combination With Ondansetron and Dexamethasone for the Prevention of Chemotherapy-Induced Nausea and Vomiting in Cancer Patients Receiving Moderately Emetogenic Chemotherapy*, Cancer: 5807-5816 (Dec. 15, 2009)	
2096	MacCoss, M. and Baillie, T.A., *Organic Chemistry in Drug Discovery*, Science 303:1810-1813 (Mar. 19, 2004)	
2097	REGFAN® (metoclopramide) label	
2098	ZYPREXA® (olanzapine) label	
2099	NEURONTIN® (gabapentin) label	
2100	Park, Y. et al., *Nausea and vomiting in an evolving anticancer treatment landscape: long-delayed and emetogenic antibody-drug conjugates*, Future Oncology, Vol. 21, No. 10, 1261-1272 (2025)	
2101	Stahis, M. et al., *Inhibition of substance P-mediated responses to NG108-15 cells by netupitant and palonosetron exhibit synergistic effects*, Eur. J. of Pharmacology 689 (2012) 25-30	
2102	DOXIL® (doxorubicin) label	
2103	de Boer-Dennert, M., *Patient perceptions of the side-effects of chemotherapy: the influence of 5HT3 antagonists*, British Journal of Cancer 76(8) 1055-1061 (1997)	

I. Introduction

Patent Owner Helsinn Healthcare S.A. ("Helsinn" or "PO") respectfully submits this Response in accordance with 37 C.F.R. § 42.120, responding to the Board's decision to institute *inter partes* review (Paper 13) ("Institution Decision" or "Decision") and to the Petition for *inter partes* review (Paper 2) ("Petition") filed by Azurity Pharmaceuticals, Inc. ("Azurity"). The Board instituted review of claims 2-4, 11-16, 40-42, and 52-62 of U.S. Patent No. 9,186,357 ("the '357 patent") based on the Petition, which raises only obviousness grounds. Helsinn respectfully maintains that Azurity has not shown and cannot show that any of these claims would have been obvious.

Chemotherapy-induced nausea and vomiting ("CINV") is a major concern for patients undergoing chemotherapy. As of November 2009, the available CINV treatments approved by the FDA were known to be effective against vomiting, but did not effectively control nausea.[1] The invention of the '357 patent addressed this need for cancer patients by providing a statistically significant and clinically meaningful improvement in nausea control that had not previously been observed. (*Infra* Section II.) This innovative method of treatment, as recited in, for example,

[1] The '357 patent claims priority to a November 18, 2009 patent application. (Ex. 1002, Cover.)

independent claim 4 of the ’357 patent, includes administering a combination of the drug substances netupitant (an NK-1 receptor antagonist) and palonosetron (a 5-HT_3 receptor antagonist) to cancer patients undergoing chemotherapy.

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 explained below (*see infra* Section V.A), Azurity ignored the problem of chemotherapy-induced nausea and did not demonstrate that the claims would have been obvious ***given this problem*** (or any other problem known to a POSA). As confirmed by its own expert, Azurity did not identify a problem with the prior art and instead, cobbled together its obviousness positions using the claims as a roadmap. All of Azurity’s grounds fail for that reason alone. *See Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1354 (Fed. Cir. 2013) (“[o]nly after recognizing the existence of [a] problem would an artisan *then* turn to the prior art and attempt to develop a new formulation . . . .”) (emphasis in original).

Irrespective of Azurity’s improper framework, its obviousness analysis fails for multiple ***independently dispositive*** reasons. (*See infra* Sections V.B, V.C, VI.) Azurity has not shown that a POSA would have expected that replacing aprepitant (an NK-1 receptor antagonist) in the prior art “triple therapy” regimen with netupitant would have provided a similar or better patient outcome. (*Infra* Section V.B.) As admitted by Azurity’s own expert, this failure dooms Azurity’s

motivation to combine argument. (*Id*. (citing Ex. 2086, 293:19-294:10).) Netupitant's alleged pharmacological properties (*e.g.*, NK-1 receptor selectivity) (based solely on animal data) also do not provide a reason to combine the prior art because Azurity does not compare them with aprepitant's properties. (*Infra* Section V.B.) Azurity has also not demonstrated that a POSA would have reasonably expected that the treatment regimen resulting from Azurity's modifications to triple therapy treats CINV, as required by independent claims 2 and 4, and prevents or reduces the severity of nausea (especially delayed nausea), as required by dependent claims 58 and 59. (*Infra* Section V.C.) Moreover, even if the prior art was combined, Azurity fails to show that all claim limitations are disclosed by the prior art. (*Infra* Section VI.)

Finally, certain objective indicia support the nonobviousness of the claimed invention. Namely, Helsinn's innovative combination of netupitant and palonosetron provided unexpected benefits in treating nausea despite the prior art's skepticism that an NK-1 receptor antagonist could control nausea at all. (*See infra* Section VII.)

Accordingly, as discussed in more detail below, the challenged claims are not unpatentable and should be confirmed.

II. Background

A. The Nausea and the Vomiting that Result from Chemotherapy Are Separate Events

As explained by Patent Owner's expert Dr. Eric Roeland, supportive cancer care focuses on alleviating the physical and emotional burdens of cancer and its treatment.[2] The ultimate goal of supportive cancer care is to help patients endure cancer treatment while preserving their dignity and quality of life.[3] (Ex. 2089, ¶¶1, 5 n.2; *see infra* Section III.) Among the most debilitating side effects of chemotherapy are nausea and vomiting. (Ex. 2089, ¶¶30-39.) They can be severe, persistent, and profoundly demoralizing, and often exacerbate fatigue, fear, and loss of appetite. (*Id.*, ¶¶34-42.) For many patients, these symptoms are not merely uncomfortable, but overwhelming. (*Id.*, ¶¶34-42.) Some patients delay, reduce, or abandon potentially life-saving chemotherapy, and choose to accept disease progression (and eventual death) rather than continue treatment. (*Id.*, ¶35; Ex. 2001, 1856.)

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[2] As detailed in his declaration, Dr. Roeland is a practicing oncologist and palliative care specialist. (Ex. 2089, ¶¶1-20.)

[3] Dr. Eric Roeland is Patent Owner's expert in this proceeding. Helsinn expressly withdraws (and no longer relies upon) the declaration of Dr. Navari (Ex. 2068) submitted with the Preliminary Response.

"Delayed nausea" (which spans days 2 to 5 after chemotherapy) poses a particularly stubborn challenge for cancer patients.[4] (Ex. 2089, ¶¶37-42, *see also id.*, ¶¶36, 43-44.) Delayed nausea is harder to predict, harder to treat, and can quietly erode a patient's willingness to continue therapy over repeated cycles. (*Id.*) Therefore, even modest improvement in the control of delayed nausea represents a major advance, offering patients renewed tolerance for chemotherapy and giving clinicians a powerful tool to help patients stay the course with treatment that may ultimately extend or save their lives. (*Id.*)

Within the field of cancer research and treatment, the nausea and vomiting components of CINV are viewed as two ***separate*** events, with patients often experiencing more nausea than vomiting. (Ex. 2086, 39:12-15; Ex. 2089, ¶¶30-33, 36-38.)[5] Different factors can impact nausea and vomiting (Ex. 2089, ¶¶32-33, 64-69), so a treatment that controls vomiting after chemotherapy will not necessarily also control nausea. (*Id.*; Ex. 2086, 39:25-40:3, 42:2-5.)

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[4] In contrast, "acute nausea" occurs within a few minutes to several hours after administering chemotherapy and commonly resolves within the first 24 hours. (Ex. 2037, 585.)

[5] Vomiting is also referred to as "emesis." (Ex. 2086, 39:22-24 (agreeing that "a POSA understands . . . emesis is vomiting").)

B. The "Standard of Care" in 2009 Failed to Control Nausea after Chemotherapy

In November 2009, the treatment dubbed the "standard of care" for treating CINV was a three-drug regimen commonly referred to as "triple therapy" that consisted of aprepitant, a 5-HT_3 antagonist, and dexamethasone.[6] (Ex. 2086, 62:12-24, 63:25-64:20.) Triple therapy was recommended in guidelines promulgated in 2005 by the Multinational Association of Supportive Care in Cancer ("MASCC")[7] and in 2009 by the National Comprehensive Cancer Network ("NCCN"),[8] based on evaluation in several human clinical trials. (Ex. 2089, ¶¶62-

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[6] Aprepitant is an NK-1 receptor antagonist. In this context, an "antagonist" is a compound that is administered to block certain neurotransmitters from binding to their receptors. (Ex. 1010, 144.) A compound that blocks or inhibits activity of an NK-1 receptor is referred to as an "NK-1 receptor antagonist." (Ex. 2089, ¶36 n.4.)

[7] The MASCC included "representatives from nine different organizations, including the American Society for Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO)." (Ex. 1010, 148.)

[8] The NCCN guidelines provided a consensus of expert views on then-accepted approaches to CINV treatment in 2009. (Ex. 2089, ¶38 (citing Ex. 2037).)

63, 90-92.) But while triple therapy was proven to be effective in preventing vomiting after chemotherapy, it failed to provide meaningful control of nausea, including delayed nausea. (*See, e.g.*, Ex. 1010, 143, 148; Ex. 2089, ¶¶37-38, 62-63, 88; *see also id.*, ¶¶87-148; *infra* Section V.C.)[9]

The MASCC guidelines and Herrstedt made clear that the underlying clinical trials supporting its recommendation for triple therapy were based on the effectiveness of triple therapy against ***only*** emesis (*i.e.*, vomiting). (Ex. 2089, ¶¶90-95; Ex. 2086, 140:20-141:7; Ex. 1013.) These clinical trials showed that, while triple therapy had a statistically significant effect in reducing emesis as compared to standard therapy (*i.e.*, a 5-HT_3 receptor antagonist and

[9] Even through triple therapy was recommended as a treatment for "CINV," a POSA would have understood that triple therapy did not have specific efficacy in controlling nausea. (Ex. 2089, ¶¶62-63, 88; *see also id.*, ¶¶49-56, 87-148.)

dexamethasone),[10] no such effect was seen for nausea.[11] (Ex. 2089, ¶¶132-142; *see also id.*, ¶¶96-118.) Indeed, as of November 2009, the prior art repeatedly acknowledged that triple therapy was effective against ***vomiting, but not nausea***, and nausea remained a significant problem for most patients. (*See, e.g.*, Ex. 1010, 148; Ex. 1048, 534 ("aprepitant-based anti-emetic regimen improves patients' quality of life, especially on aspects of control of vomiting, while there was no difference in the nausea domain"); Ex. 2036, 522 ("The control of nausea was not improved with the use of aprepitant."); Ex. 2001, 1874 ("The control of nausea in patients receiving MEC or HEC remains a significant problem."); Ex. 2089, ¶¶88, 192-194; *see infra* Section V.C.)

Accordingly, as of November 2009, effective control of nausea remained a major problem for patients undergoing chemotherapy.

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10 Before the advent of triple therapy, "standard therapy" was considered the standard treatment for CINV in cancer patients and is frequently used in clinical trials of potential new CINV drugs as the baseline treatment. (Ex. 2089, ¶¶57-61.)

11 As explained below in Section IV.A, clinical data must show a "statistically significant effect" to confirm that "the effect is real" and not "due to random chance." (Ex. 2086, 24:9-16; Ex. 2089, ¶¶ 56, 174-175.)

C. The ’357 Patent Invention Provided a Surprising Improvement in Nausea Control for Cancer Patients

The invention of the ’357 patent offered an improved treatment to cancer patients undergoing chemotherapy that was ***effective against both nausea and vomiting***, and represented a significant and much-needed advance in supportive cancer care. The inventors discovered that, along with preventing emesis, the innovative combination of a specific NK-1 receptor antagonist (netupitant) and a specific 5-HT_3 receptor antagonist (palonosetron) provided “an unanticipated statistically significant effect ***against nausea*** . . . that [had] not previously been observed in clinical studies” of other NK-1 receptor antagonists. (Ex. 1005, 345, ¶ 28.)[12]

The inventors claimed their innovative combination of netupitant and palonosetron in, *inter alia*, the ’357 patent. (*See, e.g.,* Ex. 1002, claim 4.) In the ’357 patent specification, the inventors disclosed specific clinical data supporting the surprising clinical effects of their innovative treatment regimen. As shown in Table 6 (reproduced below), in a “multicenter, randomized, double-blind” study (Ex. 1002, 17:12-64), administration of 200 mg and 300 mg of netupitant in combination with palonosetron and dexamethasone to patients undergoing

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

chemotherapy demonstrated a statistically significant effect (p-value < 0.05) in controlling nausea when compared to standard therapy of palonosetron and dexamethasone:

TABLE 6

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

Efficacy endpoint	Palo alone (n = 136)	Palo + Netu 100 mg (n = 135)	Palo + Netu 200 mg (n = 137)	Palo + Netu 300 mg (n = 135)	Aprepitant Regimen (N = 134)	Palo + Aprep 285 mg (N = 41)**
No Nausea						
Overall	50.7	54.8	62.0	61.5	58.2	32
Acute	75.0	72.6	77.4	80.0	77.6	59
Delayed	53.7	59.3	65.0	68.1*	60.4	41
No Significant Nausea						
Overall	79.4	80.0	86.1	89.6*	85.8	56
Acute	93.4	94.1	94.2	98.5*	94.0	79
Delayed	80.9	81.5	89.8*	90.4*	88.1	59

*p-value < 0.05 compared with palonosetron-alone; aprepitant comparisons p-values calculated by post-hoc analysis

**As reported by Grunberg et al., Support Cancer Care (2009) 17: 589-594

(Ex. 1002, 19:1-40 (Table 6 (annotated)); *see also* Ex. 2089, ¶¶243-247.)[13] As seen in Table 6, the administration of 300 mg of netupitant in combination with

[13] Table 6 does not expressly mention dexamethasone, but the specification confirms that "palo alone" refers to palonosetron and dexamethasone and each

palonosetron and dexamethasone provided a statistically significant improvement in "no nausea" in the delayed phase following chemotherapy,[14] and "no significant nausea" in the overall, acute, and delayed phases, compared to standard therapy.[15] (Ex. 1002, 16:59-18:24, 18:60-19:40.) The 200 mg netupitant dose also showed a statistically significant improvement in "no significant nausea" in the delayed phase following chemotherapy, compared to standard therapy. (*Id.*)

As explained by Dr. Roeland, this data is clinically meaningful. "Significant" nausea can easily escalate into a major problem and only gets worse if it continues past 24 hours. (Ex. 2089, ¶¶37-42.) The improvement in the

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patient group received dexamethasone as part of their treatment. (Ex. 1002, 17:12-18:3.)

14 This statistically significant improvement in "no nausea" and "no significant nausea" over control can be attributed to the use of netupitant at the 300 mg dose, given that the addition of netupitant was the only difference in the dosing regimen between Groups 1 and 4. (Ex. 1002, 17:1-30, Ex. 2089, ¶¶239-242.)

15 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, 2081.)

"delayed" phase (days 2-5 following chemotherapy) was thus particularly meaningful for patients and clinicians because, while standard therapy could be effective against nausea in the acute phase, standard therapy overwhelmingly failed to control nausea during the delayed phase. (*Id.*; *supra* Section II.A (discussing delayed nausea as a particularly stubborn challenge).)

The inventors hypothesized that this surprising clinical result of controlling nausea arose from an unexpected synergy when netupitant and palonosetron are combined. Together, this innovative combination of netupitant and palonosetron had an unexpected impact on "substance P," a naturally occurring substance in the body that binds to the NK-1 receptor. (Ex. 1005, 342, ¶ 12; Ex. 1010, 146.) Through their experiments, the inventors found that, while the "additive effect" of netupitant and palonosetron on inhibition of 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, 344, ¶¶ 21-24; Ex. 2089, ¶255.)[16]

III. Level of Ordinary Skill in the Art

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[16] 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.

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.*, supportive cancer care) with at least three years of experience in supportive cancer care, 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*.

(*See* Ex. 2089, ¶25.) In its Decision, the Board did "not agree with Patent Owner that the POSA needs specific clinical experience in the field of oncology" on the basis that the "claimed subject matter relates to the treatment of a side-effect associated with cancer therapy (CINV), and not the cancer itself." (Decision, 10.) Patent Owner respectfully submits and maintains that clinical experience in ***supportive cancer care*** is necessary for a POSA. Without such experience, a POSA would not have a true appreciation of issues at the heart of the '357 patent, namely drug regimens for treating the side-effects of chemotherapy, like nausea and vomiting. (Ex. 2089, ¶¶24-26; *see also id.*, ¶¶27-29.)

Azurity's expert Dr. Peroutka lacks any relevant clinical experience, and Patent Owner respectfully submits that he is thus not "qualified to testify from the perspective of a POSA in this proceeding." (*Contra* Decision, 10.) For example, a key issue here is whether a POSA would have been motivated to replace aprepitant with netupitant in triple therapy and administer the modified regimen to cancer patients undergoing chemotherapy. To opine on the issue of motivation, an "expert" necessarily needs to understand the standard-of-care at the time of the invention in November 2009, the types of challenges and shortcomings associated with that standard of care, and what solutions a POSA would have considered for solving those problems.

Dr. Peroutka does not have the experience (clinical or otherwise) to opine on what a POSA would have done when facing these challenges at the relevant time (November 2009). Dr. Peroutka's most recent research into CINV "was in the 1980s," which is also the last time he published on that issue. (Ex. 2086, 16:14-17, 33:16-21.) Moreover, his CINV publications solely concerned *in vitro* receptor binding studies carried out in cell lines or rat brains, not in human patients (Ex. 2078, Ex. 2079, Ex. 2084), as well as a one-page letter summarizing others' work on combination antiemetics (Ex. 2083). He has also never treated patients for CINV, let alone by prescribing any 5-HT_3 receptor antagonists or NK-1 receptor antagonists. (Ex. 2086, 16:18-22, 18:12-20.) His experience reading ***unspecified***

"studies" published since 2000 on CINV is simply insufficient to educate him on the effects of 5-HT_3 receptor antagonists and NK-1 receptor antagonists on patients (Ex. 2086, 20:9-22:2), which is a key issue in this IPR.

This lack of expertise is reflected in Dr. Peroutka's deposition testimony discussed throughout this response, which is demonstrably inconsistent with the contemporaneous scientific literature. For example, he incorrectly testified that as of November 2009, there were only "around 10" NK-1 receptor antagonists (Ex. 2086, 123:15-19), whereas his own reference (Hoffman) disclosed 31 NK-1 receptor antagonists. (*Id.*, 271:2-10; Ex. 1011). He similarly testified that not a single NK-1 receptor antagonist had failed before November 2009, which ignores the late-stage failure of casopitant. (*See infra* Section V.B (citing Ex. 2086, 89:17-90:12.) His lack of experience here is especially significant given the claims at issue are method-of-treatment claims, and concern the effects of 5-HT_3 receptor antagonists and NK-1 receptor antagonists on patients. All of this explains why Dr. Peroutka needed to resort to the use of hindsight. (*See* Section V.A.4, *infra*.)

Unlike Dr. Peroutka, Patent Owner's expert Dr. Eric Roeland is a practicing medical oncologist and palliative care specialist, with experience caring for patients with cancer with poorly controlled symptoms. (Ex. 2089, ¶¶1, 8-20 (citing Ex. 2087).) He has administered the classes of drugs at issue in this matter to patients receiving chemotherapy. (Ex. 2089, ¶12.) He has also served on the

major antiemesis guidelines that instruct clinicians on how to best care for their patients who experience nausea and vomiting because of chemotherapy. (Ex. 2089, ¶17-18.) Furthermore, his research focuses on "symptom science," a clinical research program dedicated to promoting the discovery, validation, and accessibility of innovative approaches to improving the quality of life of people with cancer that is guided by rigorous, evidence-based, collaborative research. (Ex. 2089, ¶1.)

But no matter which definition of a POSA is used, Azurity has failed to show that the challenged claims are unpatentable.

IV. Claim Construction

The Board applies the claim construction standard set forth in *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005) (en banc) in IPR proceedings. *See* 83 Fed. Reg. 51,340 (Oct. 11, 2018). Under *Phillips*, claim terms are typically given their ordinary and customary meanings as would have been understood by a POSA at the time of the invention and who had taken into consideration the language of the claims, the specification, and the prosecution history of record. *Phillips*, 415 F.3d at 1313; *see also id.* at 1312-16.

Here, the following terms warrant construction.

A. "Treating CINV," "Prevent Nausea," "Reduce Nausea"

Independent claims 2 and 4 recite a "method of treating . . . (CINV)." (Ex. 1002, claims 2 and 4.)[17] Dependent claims 58 and 59 further recite that the claimed regimen is "effective to prevent or reduce the severity of nausea" in the patient. (*Id*., claims 58 and 59.) "Treating" and "effective to prevent or reduce the severity of nausea" should be construed to require that the claimed regimen achieves an improvement in the desired effect (treating CINV and preventing or reducing the severity of nausea, as applicable) to a ***statistically significant degree***, as compared to a baseline.

This construction reflects a POSA's natural reading of the claim because, especially in the medical field, a treatment regimen that fails to show statistical significance relative to a baseline cannot be trusted to result in the intended clinical treatment effect. (Ex. 2089, ¶176.) At his deposition, Dr. Peroutka admitted that clinical data must show a "statistically significant effect" to confirm that "the effect is real" and not "due to random chance." (Ex. 2086, 24:9-16; Ex. 2089, ¶¶174-175.) He also acknowledged that if, for example, nausea was not improved by a statistically significant degree as compared to the baseline, any observed

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[17] Azurity, the party with the burden of proof, does not demonstrate that the preamble is not limiting.

superior effect could only be attributed to chance. (Ex. 2089, ¶¶174-175; Ex. 2086, 24:9-16, 25:13-18, 29:8-16, 183:17-184:3.) In fact, all of the clinical studies on triple therapy cited by Dr. Peroutka evaluated statistical significance (*see, e.g.*, Ex. 1034; 1037; 1039), which is also consistent with what the FDA requires as part of its drug-approval process. (Ex. 2089, ¶175; Ex. 2086, 28:16-23, 29:8-16, 32:5-33:1.)

The '357 patent specification confirms this well-understood requirement by expressly stating that, "when a ***treatment*** is described herein, it will be understood that the treatment shows efficacy to a ***degree of statistical significance***." (Ex. 1002, 8:32-34.)[18] In the context of the '357 patent, a method of preventing or reducing the severity of nausea is a method of treatment. (*Id*., 8:5-23.) The specification further states that "[w]hen a measurable result or effect is expressed or identified herein, it will be understood that the result or effect is evaluated based

[18] The specification makes clear the terms "treatment" and "treating" are synonymous by providing the same definition for both quoted terms (*id.* at 8:5-8), a "strong indication" of lexicography. *See, e.g.*, *Sinorgchem Co., Shandong v. Int'l Trade Comm'n*, 511 F.3d 1132, 1138 (Fed. Cir. 2007); *cf. Edwards Lifesciences LLC v. Cook Inc.*, 582 F.3d 1322, 1329 (Fed. Cir. 2009) ("The interchangeable use of the two terms is akin to a definition equating the two.").

upon its statistical significance relative to a baseline." (*Id.*, 8:28-31; *see also id.*, 8:54-59.) Accordingly, and consistent with the ordinary and customary meaning of treating, preventing, or reducing the severity of a medical condition, a POSA would have understood the '357 patent inventors acted as lexicographers to define "treating," "preventing," and "reducing" as requiring a treatment that shows efficacy to a degree of statistical significance. *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1051-52 (Fed. Cir. 2010) ("[T]he specification may reveal a special definition given to a claim term by the patentee that differs from the meaning it would otherwise possess. In such cases, the inventor's lexicography governs.").

This construction is further supported by other disclosures in the '357 patent specification. For example, Table 6 provides a direct comparison between the innovative three-drug regimen of netupitant/palonosetron/dexamethasone with the baseline of palonosetron and dexamethasone. (Ex. 1002, 19:1-40 (Table 6).) Table 6 shows that, at 200 mg and 300 mg doses of netupitant, the three-drug regimen had a statistically significant effect on both nausea and vomiting compared to baseline. (*Id.*) The '357 patent specification also provides guidance on how a given clinical result was evaluated for statistical significance. The specification expressly states that "[u]nless otherwise specified, the level of statistical significance is $p<0.05$." (Ex. 1002, 8:27-28.) This p-value shows the

odds that this result occurred by chance were just 1 in 20. (Ex. 2089, ¶175; Ex. 2086, 28:16-23, 29:9-16, 32:5-33:1.)

For all of these reasons, "treating CINV," "effective to prevent nausea or reduce the severity of nausea," should be construed to require that the claimed regimen achieves these effects following chemotherapy to a statistically significant degree ($p<0.05$), as compared to baseline.

V. Azurity Fails to Show Motivation to Combine with a Reasonable Expectation of Success in Arriving at the Claimed Invention

Azurity contends that it would have been obvious for a POSA in November 2009 to begin with Herrstedt's aprepitant-based triple therapy as a starting point, and then replace aprepitant with netupitant. (*See, e.g.,* Petition, 18 ("Bös provides ample reason to replace Herrstedt's NK_1 antagonist aprepitant with a therapeutically-effective amount of Bös' new and improved NK_1 antagonist netupitant."), 27-28; Decision, 28-29.)[19] But Azurity's obviousness analysis does not apply the proper legal framework, and is based wholly on impermissible hindsight. (*See infra* Section V.A.) Even setting aside this legal error, and applying Azurity's improper framework, the claims still would not have been obvious to a POSA due to lack of motivation to combine Azurity's cited prior art

[19] Azurity's failures outlined in Section V apply to all grounds.

(Sections V.B) and lack of reasonable expectation of success in achieving the claimed invention (Section V.C).

A. Azurity's Obviousness Analysis Applies an Incorrect 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 . . . ." *Insite Vision Inc. v. Sandoz, Inc.*, 783 F.3d 853, 859 (Fed. Cir. 2015). 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. Ltd. v. Sandoz, Inc.*, 678 F.3d 1280, 1296 (Fed. Cir. 2012); *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1337 (Fed. Cir. 2016) ("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*** . . . ."). Indeed, "[o]nly after recognizing the existence of [a] problem would an artisan *then* turn to the prior art and attempt to develop a new formulation . . . ." *Leo Pharm. Prods.*, 726 F.3d at 1354 (emphasis in original). 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. Azurity has failed to apply this legal framework.

1. Azurity Did Not Consider the Problem of Nausea

As discussed above in Section II.B, nausea induced by chemotherapy was not being adequately controlled in cancer patients by using aprepitant-based triple therapy, which was considered in 2009 to be the standard of care. (Ex. 2089, ¶¶190-194.) According to the NCCN Guidelines (Ex. 2037), the subset of patients who still experienced significant nausea despite administration of triple therapy with aprepitant or standard therapy without aprepitant was 40%. (Ex. 2037, 587.) Therefore, a POSA in 2009 would have been faced with the problem of uncontrolled nausea in patients who were receiving chemotherapy.[20] Framing the problem facing a POSA in this manner 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.

But neither Azurity nor its expert identified ***any*** problem with triple therapy.[21] Nor did they show that the claims would have been obvious ***in view of***

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[20] As explained above in Section II.B, aprepitant triple therapy was efficacious against vomiting, leaving nausea as the problem. (Ex. 2089, ¶¶192-193.)

[21] To the contrary, they allege that aprepitant-based triple therapy was effective at treating both nausea and vomiting arising from chemotherapy. (*See* Petition, 14.)

the above-identified problem facing a POSA in 2009. All of Azurity's grounds fail for that reason alone. *See Leo Pharm. Prods.*, 726 F.3d at 1354. Here, Dr. Peroutka "first focused on the standard of care [i.e., triple therapy], then [he] looked at the claims and . . . was iterating . . . with the patent claims, and trying to integrate all that to see what a POSA would think of the claims of 2009." (Ex. 2086, 107:17-25.) When questioned about whether a POSA was faced with any problem at the relevant time, Dr. Peroutka stated "your words are not making sense to me, in the sense that, you know, problem to be solved, I'm just not understanding what you mean by that." (Ex. 2086, 108:4-10.) As Dr. Peroutka did not understand the words "problem to be solved," he did not understand the proper starting point for his obviousness analysis. And without a proper starting for obviousness, the entire foundation of his analysis gives way.

Dr. Peroutka and Azurity's analysis, which wholly ignores the problem facing a POSA, is textbook impermissible hindsight: starting with Helsinn's claimed invention, and working backwards by picking and choosing different pieces of the prior art arrive at that invention. Dr. Peroutka even admitted that he focused on netupitant because it was "the subject of this patent dispute." (Ex. 2086, 127:5-10.) Under the correct legal framework, where obviousness is considered in view of the problem facing a POSA, Azurity has not shown that POSA would have a motivation to swap aprepitant for netupitant. (*See infra*

Section V.A.2.) In fact, given the problem of uncontrolled nausea, a POSA would have been led towards other solutions – *e.g.*, adding a fourth drug with a different mechanism of action to triple therapy. (*See infra* Section V.A.3.)

The problem with Azurity's analysis is not that the Petition analyzes *only* whether the claimed invention would have been obvious and not whether *other* methods of treating CINV that are not covered by the challenged claims also would have been obvious as the Board suggested in related IPR2025-00945. Instead, the issue is that Azurity did not identify a problem with the prior art, nor show that the claim would have been an obvious solution ***given*** the problem facing a POSA.

2. Aprepitant and Netupitant Were Not Interchangeable

Instead of explaining why a POSA would have looked to swap aprepitant for netupitant given the problem of nausea (or another problem known in the prior art), Azurity and the Board assumed that a motivation would have existed because aprepitant and netupitant are allegedly interchangeable. (*See, e.g.*, Petition, 18 (touting netupitant as a "new and improved" NK1-receptor antagonist); *see also* Decision, 29-30.) But Azurity points to no evidence demonstrating that these two molecules are interchangeable or equivalent.

Bös, the reference relied upon by Azurity as disclosing netupitant, does not include any comparative analysis between aprepitant and netupitant from which a POSA could draw conclusions regarding their comparative clinical efficacy in

treating nausea and vomiting. (Ex. 2089, ¶¶206-207; *see also id.*, ¶¶205-216.) Bös lacks human clinical data, and instead provides data from only exploratory *in vivo* animal models for anxiety (gerbil foot tapping) and *in vitro* CHO cells (non-CNS cells derived from hamster ovaries) where NK-1 receptor antagonists were introduced. (Ex. 1014, 18:42-19:38.)

Bös does not contain, and Azurity has not provided, any evidence comparing aprepitant and netupitant's physical, chemical, or pharmacological properties or how those may impact the affinity with the NK-1 receptor. (Ex. 2086, 240:25-241:3, 242:25-243:5, 253:7-255:15.) Just because two molecules are in the same class (*e.g.*, NK-1 receptor antagonists) does not mean they will be equivalent in the sense of clinical efficacy. (Ex. 2089, ¶208; *see also id.*, ¶152.) If that were the case, aprepitant could be substituted with each one of the potentially millions of NK-1 receptor antagonists, and that the efficacy and safety of the replacement would be identical.[22] Given the well-established unpredictability in the drug

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[22] In Hoffmann, netupitant was one of 31 NK-1 receptor antagonists. (Ex. 1011, 1364; Ex. 2089, ¶217.) In Bös, netupitant is just one specific derivative that is claimed among millions of compounds. (Ex. 1014, Cover; Ex. 2089, ¶159.) But the universe of potential NK-1 receptor antagonists was much larger. As explained

development field, this clearly cannot be the case. (Ex. 2089, ¶¶45-48, 149-151, 178.)

Furthermore, Azurity has pointed to no contemporaneous evidence suggesting that a POSA would have looked to netupitant as a potential solution to problem of uncontrolled nausea. In fact, a POSA would have been skeptical of any such claim because contemporaneous scientific literature hypothesized that NK-1 receptor antagonists are unlikely to have the desired effect on nausea. (Ex. 2089, ¶¶248-249; Ex. 2073, 1005 ("neurokinin-1 receptor antagonists may have less impact on the nausea component of chemotherapy-induced nausea and vomiting."); Ex. 1034, 2829 ("***other neurotransmitters may also be involved*** in the pathogenesis of these symptoms***, especially nausea***."); *see also infra* Section V.C.)

3. A POSA Faced with the Problem of Treating Uncontrolled Nausea Would Have Looked to Other Treatment Regimens

It is a "longstanding principle that the prior art must be considered for all its teachings, not selectively." *Henny Penny Corp. v. Frymaster LLC*, 938 F.3d 1324, 1331-32 (Fed. Cir. 2019). Here, the prior art ***as a whole*** suggested to a POSA that aprepitant triple therapy was effective against vomiting, but failed to treat nausea.

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by Dr. Roeland, there were many other NK-1 receptor antagonists that had promising clinical data. (Ex. 2089, ¶¶217-220.)

(Ex. 2089, ¶¶195-203; *see also id.*, ¶¶72-86.) Given the problem of uncontrolled nausea from chemotherapy (*supra* Section V.A.), a POSA would have looked at contemporaneous treatment options that were ***known*** or deemed ***promising*** for solving this problem.[23] None of those contemporaneous options suggested replacing aprepitant with another NK-1 receptor antagonist (such as netupitant) to control nausea. (Ex. 2089, ¶¶195-203 (citing, for example, Ex. 2036, Ex. 2001, Ex. 1010, Ex. 1019).) In fact, because aprepitant had shown efficacy against ***vomiting***, dropping it from triple therapy in favor of another NK-1 receptor antagonist to solve the problem for nausea would have made no sense to a POSA. (Ex. 2089, ¶196.)

Instead, a POSA would have looked at adding a ***fourth*** drug that acted on different receptors (*e.g.*, dopamine receptor antagonists, olanzapine, gabapentin, and cannabinoids) to the clinically proven aprepitant-based triple therapy. (Ex. 2089, ¶¶195-203; *see also id.*, ¶¶72-86.) Dr. Peroutka acknowledged that

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[23] As Dr. Peroutka acknowledged, a POSA could look for new drugs with new mechanisms of action, new treatment regimens, and new formulations. (Ex. 2086, 60:10-61:22; 100:16-23, 101:21-102:1.) Dr. Peroutka did not engage in such analysis (*id.*, 97:7-24), but a POSA would have. (Ex. 2089, ¶190-191; *see also id.*, ¶¶191-203.)

dopamine receptor antagonists, olanzapine, gabapentin, and cannabinoids had all shown promise for treating chemotherapy-induced nausea. (Ex. 2086, 130:11-137:1.) For instance, Herrstedt (Azurity's own cited reference) touts the potential of olanzapine in controlling the nausea, 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. 2089, ¶197 (quoting Ex. 1010, 149); *see also* Ex. 2089, ¶198).[24] Accordingly, adding olanzapine to aprepitant-based triple therapy would have been a plausible option for a POSA seeking a treatment for chemotherapy-induced nausea.

In addition to olanzapine, the antiepileptic gabapentin was another possible option, and by November 2009, further studies had been suggested to determine its potential effects on reducing nausea in cancer patients. (Ex. 2089, ¶199.) Additionally, cannabinoids had also been suggested for further trials to evaluate their use in the control of nausea. (Ex. 2089, ¶¶200-201.) By 2009, two oral cannabinoid formulations were already FDA approved for refractory CINV

[24] This discussion of the olanzapine regimen in Herrstedt does not even include any mention of an NK-1 receptor antagonist (including aprepitant) in the regimen.

treatments, and cannabinoids were listed in the NCCN guidelines as a potential "breakthrough" CINV treatment. (Ex. 2089, ¶¶201.)

Azurity and Dr. Peroutka did not consider whether a POSA would have pursued any of these alternative paths to solve the problem of uncontrolled nausea following chemotherapy. But notably, none of these paths would have led a POSA to netupitant. (Ex. 2089, ¶203.) This underscores the legal error in Azurity's analysis. While it is true that, as the Board stated in the related -00945 IPR Institution Decision, that multiple solutions may have been obvious, Azurity has not shown that the claimed invention is one of those obvious solutions.

4. Dr. Peroutka's Reasoning for Choosing Netupitant Highlights His Use of Impermissible Hindsight

Dr. Peroutka's deposition confirmed that Azurity's obviousness analysis used the claims themselves as his starting point. Dr. Peroutka initially testified that a POSA looking for a regimen for treating a cancer patient for nausea and vomiting induced by chemotherapy would consider the NK-1 receptor antagonists that were known in the art as of 2009. (Ex. 2086, 83:5-84:18.) Dr. Peroutka also agreed it would have been reasonable for a POSA to evaluate the other NK-1 receptor antagonists that were known as of 2009. (*Id.*, 84:15-18.) But Dr. Peroutka did not actually conduct this analysis.

Dr. Peroutka purportedly evaluated only four NK-1 receptor antagonists: aprepitant, fosaprepitant, netupitant, and casopitant. (Ex. 2086, 122:20-123:2.) Of

these four NK-1 receptor antagonists, three of them (aprepitant, fosaprepitant, and casopitant) all had human clinical trial data, while one of them (netupitant) did not. (Ex. 2086, 122:20-123:13; Ex. 1011; Ex. 1014.) Dr. Peroutka testified that he selected netupitant as his fourth compound to evaluate based on its "CNS penetration, [its] oral bioavailability, [and] the NK-1 antagonism." (Ex. 2086, 251:13-23.) But under that reasoning, at least 38 of other NK-1 receptor antagonists could have been considered by a POSA, and yet ***none*** of those were considered by Dr. Peroutka. (Ex. 2089, ¶¶217-218.) For example, Hoffmann alone provides 31 other NK-1 receptor antagonists that Dr. Peroutka admitted he could have, but ultimately did not, evaluate. (Ex. 2086, 271:14-273:17.) Even outside of Hoffmann, which there is no reason to focus exclusively on, the class of NK-1 receptor antagonists had many other candidates with promising preclinical data, which again Dr. Peroutka failed to evaluate. (Ex. 2089, ¶¶217-220.)

Hindsight is thus the only explanation for Dr. Peroutka's failure to consider NK-1 receptor antagonists other than netupitant. Azurity's obviousness grounds fail for this additional reason.

B. Azurity Fails to Demonstrate that Replacing Aprepitant with Netupitant Would Have Provided a Similar or Better Clinical Outcome

Even if the Board were to overlook Azurity's dispositive legal failure to consider obviousness from the vantage point of the problem facing a POSA,

Azurity still cannot prevail because its analysis cannot meet the ***threshold*** for motivation to combine laid out by its own expert. Azurity's primary reference (Herrstedt) describes numerous clinical studies of aprepitant-based triple therapy disclosed in Herrstedt, which was widely considered the standard of care for patients suffering from CINV as of November 2009. (Ex. 2089, ¶¶62-63, 90-95.) Numerous clinical studies in humans generated data confirming that aprepitant-based triple therapy significantly improved patient outcomes for ***vomiting*** arising from chemotherapy. (*See, e.g.*, Ex. 1010, 146 (citing Exs. 1034, 1037, 1039, 2073); *supra* Section II.B.) Azurity contends that a POSA in November 2009 would have been motivated to alter this standard-of-care regimen by replacing aprepitant with netupitant. (*See, e.g.,* Petition, 18.) But as Dr. Peroutka admitted, a POSA would have no motivation to swap aprepitant for netupitant unless the POSA expected "that the change would provide similar or better patient outcomes" compared to the combination of aprepitant, a 5-HT_3 inhibitor, and dexamethasone:

> Q. . . .You would agree with me that a POSA would not be changing the aprepitant triple therapy unless they believe that the change would provide similar or better patient outcomes, correct?
> THE DEPONENT: Correct.

(Ex. 2086, 293:19-294:10 (objection omitted).) Dr. Peroutka also acknowledged that a POSA would not alter aprepitant-based triple therapy unless the POSA

expected "a high chance of success that the resulting therapy would match or exceed the existing standard of care, which was aprepitant in triple therapy." (*Id.*, 295:4-296:14; *see also* Ex. 1009, ¶¶136 (opining, albeit incorrectly, that a POSA would have good reason to alter triple therapy to "achieve similar or better efficacy in CINV"), 175 (same).) Dr. Roeland agrees. (Ex. 2089, ¶205.)

Azurity, however, offers no evidence demonstrating that a POSA would have expected that replacing aprepitant with netupitant in the standard-of-care triple therapy would result in a treatment that has similar or better patient outcomes. (Ex. 2089, ¶¶205-216; *supra* Section V.A.2.) As explained above in Section V.A.2, neither Azurity nor its cited references contain data comparing netupitant with aprepitant, and Azurity's expert has offered none. (Ex. 2086, 240:25-241:3, 242:25-243:5, 253:7-255:15, 280:21-281:19; *see also* Decision, 29-30 (recognizing lack of comparative analysis between netupitant and aprepitant).) Dr. Peroutka's testimony thus undercuts the Decision's finding that such comparative data "is not necessary to provide the requisite reason to combine." (Decision, 29-30.)

Moreover, the preclinical animal data in Azurity's cited reference (Bös) is limited to netupitant's effect on emesis. (Ex. 2089, ¶¶206-207; *see also id.*, ¶¶158-163; *supra* Section V.A.2.) Azurity has provided no data ***at all*** on netupitant's effect on nausea. And even if there were such preclinical data, that would not have

been sufficient for a POSA to conclude whether a netupitant three-drug regimen would have the same or better clinical outcome than aprepitant triple therapy. Preclinical data in animals would not necessarily translate to efficacy in humans, especially with difficult-to-model conditions like the nausea and vomiting induced by chemotherapy. (Ex. 2089, ¶¶207, 213-216; Ex. 2086 at 37:6-11.) Dr. Peroutka's own prior work confirms this fact. Specifically, Dr. Peroutka published a paper noting that of NK-1 receptor antagonists "hypothesized to be highly effective in the acute treatment of migraine because they selectively inhibited trigeminal-induced PPE in rodent models," these same antagonists proved ineffective in humans. (Ex. 2092, 307.) As confirmed by Dr. Peroutka, animal models studying CNS penetration of a drug do not provide conclusive data about the drug's efficacy in humans. (Ex. 2086, 36:14-37:11, 282:4-7.) To know whether netupitant will have an "effect in humans," a POSA would need "to do human studies" (*id.*, 36:14-21), which Azurity has not shown existed in the prior art.

Azurity cannot sidestep its failure of proof by pointing to Dr. Peroutka's "non-research-based" opinion that there is an "***80 per cent***" probability that ***any*** NK-1 receptor antagonist that had "some preclinical data" showing bioavailability, CNS penetration, and a "half-life that's consistent with human intake" would have been equally (if not more) effective as aprepitant at treating CINV in humans. (Ex.

2086, 86:23-90:12.) Dr. Peroutka's "non-research-based" opinion is not supported by any evidence offered by Azurity in this proceeding, and is also inconsistent with a POSA's understanding regarding the high failure rate between preclinical and clinical studies. (Ex. 2089, ¶¶149-151, 234-236.)

The lack of comparative data between aprepitant and netupitant also undercuts Azurity's unsupported allegation that a POSA would have considered netupitant an appropriate alternative to aprepitant in view of netupitant's allegedly "valuable therapeutic properties" (*e.g.*, selectivity, CNS penetration). (*See, e.g.*, Petition at 16-18; *see also id.* (alleging that netupitant was an "improved" NK-1 receptor antagonist), *id*. at 21 ("Bös discloses netupitant as a favorable alternative NK_1 antagonist to aprepitant."), *id*. at 26 (alleging that netupitant is "a potent and selective NK_1 antagonist").) In its Decision, the Board preliminarily agreed with Azurity and found that such properties were "more than sufficient for the POSA to pursue [netupitant] as an alternative to aprepitant for the treatment of CINV." (Decision, 30.) Helsinn respectfully disagrees with the Board's preliminary finding.

Azurity's assertions here misleadingly conflate the alleged pharmacological properties of netupitant with its ***later***-discovered clinical effects in patients. Importantly, Azurity provides no analysis comparing netupitant's affinity, selectivity, CNS penetration, half-life, and oral antagonism properties to those of

aprepitant. (*Supra* Section V.A.2.) Without such a comparison, a POSA could not have drawn any conclusions whatsoever about whether netupitant was an appropriate alternative to aprepitant for inclusion in the three-drug regimen disclosed in Herrstedt. (Ex. 2089, ¶¶205-216.)

The cited properties, such as the alleged "excellent" CNS penetration, and "high" selectivity for NK-1 receptors would not inform a POSA about netupitant's efficacy in treating emesis and/or nausea ***compared to aprepitant***. Ex. 2089, ¶¶211, 217.)[25] As a result, a POSA would have no reason to change a clinically tested regimen (Herrstedt's triple therapy) that had proven effective against a major side effect of chemotherapy (vomiting) by replacing aprepitant with netupitant. (*Id*., ¶¶195-196.) Dr. Peroutka's testimony confirms this understanding. (Ex. 2086, 293:19-294:10, 295:4-296:14.) For context, "CNS penetration" is a trait common to many NK-1 receptor antagonists, including aprepitant, and describes whether a drug can cross into the central nervous system, which encompasses both

[25] If a POSA were focused on these pharmacological properties, there were many other NK-1 receptor antagonists at the relevant time that shared them. (Ex. 2089, ¶218 (discussing other NK-1 receptor antagonists with preclinical data as of 2009); *supra* Section V.A.4.) Azurity has not explained why a POSA would have picked netupitant from among all of those other NK-1 receptor antagonists.

the brain and the spine.[26] (Ex. 2089, ¶211.) But CNS penetration "doesn't tell you anything about efficacy." (Ex. 2086, 282:4-7.) "Oral antagonistic activity" refers to a drug's ability to have a desired antagonistic effect when ingested orally. (Ex. 2089, ¶212.) "Binding affinity" is simply a measure of how long a given antagonist binds to a given receptor. (Ex. 2086, 254:2-10; Ex. 2089, ¶213.) Azurity has failed to provide any comparison of the pharmacological data for netupitant and aprepitant and thus cannot show that netupitant's alleged "excellent" properties would have motivated a POSA to swap aprepitant for netupitant in the aprepitant three-drug regimen disclosed by Herrstedt.

Azurity and Dr. Peroutka also fail to consider safety data, which is critical to motivation to combine here.[27] A doctor would not treat a patient with a drug that was not considered safe (Ex. 2086, 119:15-22) but Dr. Peroutka completely neglected to consider safety data. (*Id.*, 126:17-24.) Dr. Peroutka claimed he was not aware of any NK-1 receptor antagonists that showed promise in preclinical

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[26] Notably, NK-1 receptors are located throughout the body, including the gastrointestinal tract, skin, and lungs, and are not limited to the CNS. (Ex. 2089, ¶211 n.28.)

[27] Herrstedt discloses administration of aprepitant triple therapy to patients. Thus, any change to triple therapy would (of course) need to consider safety.

data but then failed to show safety and efficacy in humans. (*Id.*, 118:6-14.) But in September 2009, months before the critical date, GlaxoSmithKline stopped development of the NK-1 receptor antagonist casopitant because "significant further safety data would be required to support the registration of casopitant." (Ex. 2077.) All ongoing regulatory files for casopitant were subsequently withdrawn. (*Id.*) As Dr. Peroutka's opinion was based on his view that "there had been no examples of such drugs that failed" (Ex. 2086, 89:17-90:12), he plainly did not consider casopitant's failure when he made his pie-in-the-sky claim that there was a "high likelihood" (*i.e.*, 80%) that NK-1 receptor antagonists could be effective for treating patients for nausea and would be FDA approved. (*Id.*, 269:14-270:3.)

C. Azurity Fails to Demonstrate a POSA Would Have Had a Reasonable Expectation of Success in Combining Prior Art Teachings to Achieve an Improved Method of Treating Nausea

"The reasonable expectation of success requirement refers to the likelihood of success in combining references ***to meet the limitations of the claimed invention***." *Janssen Pharmaceuticals, Inc. v. Teva Pharmaceuticals USA, Inc.*, 141 F.4th 1367, 1383 (Fed. Cir. 2025) (quoting *Intelligent Bio-Systems, Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367 (Fed. Cir. 2016)). The Board preliminarily determined that a POSA would have a reasonable expectation of success "given the favorable pharmacokinetic properties reported in Bös for

netupitant, and its similar mechanism of action to aprepitant (NK_1 receptor antagonism)." (Decision, 30.) But here, the legal question is not whether a POSA could simply swap out aprepitant for netupitant in the triple therapy disclosed in Herrstedt. Instead, the question is whether a POSA would have reasonably expected that the three-drug regimen resulting from replacing aprepitant in triple therapy with netupitant would have been successful in achieving the clinical effects, as claimed.

Here, independent claim 2 and 4 require that the administered drug regimen treat CINV to a statistically significant degree, compared to a baseline. (*Supra* Sections IV.A.) Dependent claims 58 and 59 further require that the claimed regimen prevent and/or reduce the severity of nausea to a statistically significant degree (including delayed nausea), compared to a baseline. (*Id*.; Ex. 1002, claims 58, 59.) Azurity has not explained why a POSA would have reasonably expected that the three-drug regimen resulting from replacing aprepitant with netupitant would have been successful in achieving these effects, as claimed.

The *OSI Pharmaceuticals* case is instructive here. *OSI Pharmaceuticals, LLC v. Apotex Inc.*, 939 F.3d 1375 (Fed. Cir. 2019). In *OSI Pharmaceuticals*, the Federal Circuit reversed the Board's determination that certain claims to methods for treating non-small cell lung cancer ("NSCLC") with the drug erlotinib were unpatentable as having been obvious, concluding that substantial evidence did not

support the Board's finding of reasonable expectation of success. 939 F.3d at 1377-78. Specifically, the Federal Circuit found that "the asserted references do not disclose *any* data or other information about erlotinib's efficacy in treating NSCLC." *Id.* at 1383 (emphasis in original). Notably, the Board had found that the prior art reference Gibbs provided "a clear inference" that "erlotinib has anti-cancer activity against non-small cell lung cancer." *Id.* at 1383. But on review, the Federal Circuit characterized Gibbs as "is a review article that collects, reviews, and analyzes other research studies." *Id.* And looking to the underlying references cited in Gibbs, the Federal Circuit found that none of those references discussed erlotinib's effect on NSCLC. *Id.* at 1383-84.

Like in *OSI*, the cited references here do not demonstrate any efficacy of netupitant for preventing or reducing the severity of nausea, or treating CINV. (Ex. 2086 at 274:12-23 (no data in Hoffmann on netupitant's effect emesis or nausea), 275:16-20; Ex. 2089, ¶¶158-163.) For example, the Board even acknowledged that Bös does not "include data assessing netupitant's potential efficacy in controlling nausea." (Decision, 29-30.) Accordingly, the record lacks any documentary evidence demonstrating that a POSA would have reasonably expected using ***netupitant*** to achieve the claimed effects, including to a statistically significant degree, as compared to a baseline. (Ex. 2089, ¶¶221-225; *see also id.*, ¶¶205-220; *supra* Section IV.A.) Given this lack of evidence, Azurity pivots to the

clinical results from triple therapy, and suggests that those results apply equally to the claimed netupitant three-drug regimen because "both compounds are NK_1 antagonists achieving the same purpose (decreasing nausea and vomiting) through the same mechanism (NK_1 receptor antagonism, induced by therapeutically effective blood levels)." (*See, e.g.,* Petition at 28.)At deposition, Dr. Peroutka touted a similarly faulty, and admittedly "non-research-based," logic. (Ex. 2086, 89:11-90:6 (opining that there is an "80 percent likelihood" that another NK-1 receptor antagonist would be as effective for treating CINV in humans as aprepitant based on some preclinical data on bioavailability, CNS penetration, and half-life), 279:5-280:20; *see also id.*, 243:18-245:15 (relying on aprepitant and casopitant data).) Dr. Peroutka went as far as saying that "any NK-1 receptor antagonist that can penetrate into the CNS or the brain . . . would have a high chance [to treat nausea] if properly powered." (Ex. 2086, 261:2-13.) This argument fails for multiple reasons.

First, as discussed above in Sections V.A.2 and V.B, there is no evidence supporting the proposition that a POSA would have viewed netupitant and aprepitant as "equivalent" in the clinical sense. Neither Azurity nor its expert have offered any evidence comparing aprepitant and netupitant's efficacy against nausea and emesis. (*Supra* Sections V.A.2 and V.B; Ex. 2086, 280:21-281:17 (testifying that providing such a comparison "was not in [his] purview").) Nor have they

offered any evidence comparing aprepitant and netupitant's physical, chemical, or pharmacological properties or how those may impact the affinity with the NK-1 receptor. (Ex. 2086, 240:25-241:3, 242:25-243:5, 253:7-255:15.) All they have offered is that netupitant is an NK-1 receptor antagonist and had preclinical data on bioavailability, CNS penetration, affinity, and half-life. But that data says nothing about netupitant's expected efficacy against nausea or emesis when administered to a ***human*** patient, or how such efficacy compares to aprepitant's efficacy for nausea or emesis. (Ex. 2089, ¶¶223-225; *see also id.*, ¶¶226-233; Ex. 2086, 36:14-21; *supra* Sections V.A.2 and V.B.) Just because aprepitant and netupitant are both NK-1 receptor antagonists does not mean that they would achieve the same or similar clinical results. (Ex. 2089, ¶¶221-226; *see also id.*, ¶¶205-216.)

Second, as admitted by Dr. Peroutka, an NK-1 receptor antagonist not only could fail to treat nausea, but it could potentially ***cause*** it. (Ex. 2086, 275:9-12 ("Q: And you'll agree with me that NK-1 receptor antagonists can have an adverse event of nausea, correct? A. Possibly.").) Given this potential side effect, a POSA would have wanted data regarding netupitant's efficacy on nausea to determine whether netupitant would have a desirable effect on nausea, rather than make a patient who was already suffering from nausea even more nauseous. (*See* Ex. 2089, ¶224.) Azurity has provided no such data.

Third, as explained in detail below, a POSA in November 2009 would have understood that triple therapy failed to treat nausea to ***a degree of statistical significance***. (Ex. 2089, ¶¶62-63; *see, e.g.*, Ex. 1010, 148; Ex. 1048, 534; Ex. 2036, 522; Ex. 2001, 1874; *see also* Ex. 2089, ¶¶87-148.) Thus, under Azurity's reasoning, a POSA also would not have reasonably expected a three-drug regimen of netupitant, a 5-HT_3 antagonist, and dexamethasone to treat nausea. Indeed, the contemporaneous scientific literature lamenting aprepitant's failure to treat nausea shows the fallacy in Dr. Peroutka's uncorroborated assertion that "***any***" NK-1 receptor antagonist that penetrates the CNS or the brain will treat nausea if properly powered. (Ex. 2089, ¶193; *see also id.*, ¶¶87-148.)

1. Emend® Label from 2008

Based on the disclosures in the FDA-approved package insert for Emend® (aprepitant), a POSA knew that triple therapy did not successfully treat nausea. Tables copied directly from the FDA-approved labeling for Emend®[28] are reproduced below and show the results of a clinical study in patients receiving two cycles of 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);

[28] Merck markets and sells aprepitant in the U.S. under the trade name Emend®. (Ex. 2086, 191:19-22.)

see also Ex. 2016; Ex. 1030.) These tables plainly demonstrate that the effect of aprepitant (as part of triple therapy) on nausea or significant nausea were found ***not*** to be statistically significant when compared to standard therapy, as indicated by the "NS**" that appears in the "p-Value" column on the right-hand side of the table:

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.

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.

(Ex. 1030 at 4-5 (Tables 1 and 2) (annotations added)[29].)

While these tables show a ***numerical*** improvement in nausea parameters, they do not show an improvement in nausea to a degree of ***statistical significance*** as compared to standard therapy. Rather than address head-on the lack of statistical significance for aprepitant's treatment of "nausea" and "significant nausea" in the Emend® label, Azurity shifts to focus on the data for the "complete protection" parameter provided elsewhere in that label. (Petition, 48.) But as Dr. Roeland explains, "complete protection" is a composite endpoint and not the correct metric to measure a drug's effect on nausea, nor the metric that a POSA reading the Emend® label would use. (Ex. 2089, ¶¶52-55, 97, 111-117.) 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, and that is the information that would be most relevant to a POSA. (*See* Ex. 2089, ¶¶102-110; Ex. 1030, 4-5.)

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[29] Table 2 provides that improvement in "nausea" was not statistically significant when adjusted for multiple comparisons. Both experts agree that adjusting for multiplicity is a standard correction and should be done to properly measure statistical significance. (Ex. 2089, ¶¶98-101, 118; Ex. 2086, 170:24-172:1.)

2. Other Clinical Studies

Other clinical studies also confirm that the aprepitant in triple therapy did not have a statistically significant nor clinically meaningful effect on nausea or significant nausea when compared to standard therapy. (Ex. 2089, ¶¶128-148.) Herrstedt (Ex. 1010), Azurity's lead reference, summarizes that "[f]our phase III trials have investigated the use of aprepitant in patients receiving cisplatin-based, highly emetogenic chemotherapy [37-39] or a combination of cyclophosphamide plus an anthracycline [40]," and these four references are Poli-Bigelli, Hesketh, Warr, and Schmoll. (Ex. 1010, 146.)[30] At his deposition, Dr. Peroutka admitted that Poli-Bigelli (Ex. 1039) discusses the same data that is reported in Table 2 of the Emend® label (Ex. 2086, 167:22-168:2). As Dr. Peroutka also acknowledged, both "Merck and the FDA" confirmed in 2008 that this data from Poli-Bigelli did not show statistically significant improvement in either "no nausea" or "no significant nausea" aprepitant based triple therapy as compared to standard therapy. (Ex. 2086, 170:18-177:13; *see also* Ex. 1030 at Table 2.) Hesketh (Ex. 1037) and Warr (Ex. 1034) likewise did not show a statistically significant improvement in "no nausea" for aprepitant triple therapy as compared to standard

[30] References 37-40 in Herrstedt are Hesketh (Ex. 1037), Poli-Bigelli (Ex. 1039), Schmoll (Ex. 2073), and Warr (Ex. 1034).

therapy, and this fact was confirmed by Schmoll (Ex. 2073). (Ex. 1037, 4115-16 (Table 2); Ex. 1034, 2827-29; Ex. 2073, 1005 (citing Ex. 1037, Ex. 1034); Ex. 2086, 192:16-195:7, 206:8-210:6.)

The Campos study cited by Azurity and Dr. Peroutka does not warrant a different conclusion.[31] (Ex. 1009, ¶¶ 1352-54.) As a threshold matter, Campos was published in 2001 and is superseded by the data provided in the FDAapproved- Emend® label. (Ex. 2089, ¶¶119-127 (citing Ex. 1023); Ex. 2086, 145:15-20 (Peroutka Tr.).) And like the Emend® label, Campos was based on work by Merck scientists who were studying aprepitant. (Ex. 2089, ¶120) (citing Ex. 1023).) Campos, however, administered aprepitant at significantly higher doses as compared to the lower FDA-approved doses in the Emend® label. Specifically, Campos administered 400 mg of aprepitant as pre-treatment on day 1, and 300 mg on days 2 through 5. (Ex. 1023, 1759-60; Ex. 2089, ¶¶126-127.) In the Emend®

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31 Dr. Peroutka, during deposition, also pointed to Herrington (Ex. 1016) for the first time as an example of aprepitant having control over nausea. (Ex. 2086, 59.24-60:8 (Peroutka Tr.).) But, Herrington, concludes "[t]he **incidence of overall nausea**, **significant nausea** (>25 mm on the 100-mm visual analog scale), and the **severity of nausea was not different among the 3 arms** (Table 4 and **Fig. 2**)." (Ex. 1016, 2084; Ex. 2089, ¶130 (citing Ex. 1016).)

label, 125 mg of aprepitant (less than one-third the dose in Campos) was administered as pretreatment on day 1, and 80 mg was administered on days 2 and 3. (*Compare* Ex. 1023 *with* Ex. 2016, 11-12; Ex. 2089, ¶126; Ex. 2086, 153:16-154:21.) Importantly, the higher doses of aprepitant in Campos could potentially have a negative impact on cancer patients, for as Dr. Peroutka admitted, higher doses of NK-1 receptor antagonists can potentially ***cause*** nausea in the very same patients who are seeking better nausea control. (Ex. 2086, 155:9-13; 156:10-17, 157:22-158:24, 159:21-160:5, *cf.* Ex. 1009, ¶1376 (Dr. Peroutka stating that a 285 mg dose of aprepitant is "such a large single dose of aprepitant [that] might affect nausea and vomiting . . . [and] adverse events (including nausea and vomiting) could arise" when Campos has an even larger dose at 400 mg).)

Notwithstanding that Campos reported an alleged effect on nausea, the Merck scientists chose a significantly lower dose for use in their FDA-approved product for cancer patients and reported that product did not have a statistically significant effect on nausea. (Ex. 2089, ¶123.) Likewise, the guidelines for clinicians instruct them to follow the FDA-approved dosage in the Emend® label and makes no mention of administering the higher doses described in Campos. (Ex. 2089, ¶126 n.16.)

Thus, when considered as a whole, the prior art taught a POSA that administration of aprepitant to cancer patients receiving chemotherapy did not

control nausea in a clinically meaningful way or show a statistically significant improvement over standard therapy. (Ex. 2089, ¶193; *see also id.*, ¶¶87-148.)

VI. Azurity Fails to Demonstrate that All of the Limitations Are Disclosed by the Cited References

Even setting aside Azurity's legally and factually incorrect obviousness analysis (*see supra* Section V) and assuming *arguendo* a POSA would have found it obvious to combine Azurity's prior art references, Azurity cannot prevail. For even when the prior art is combined, it fails to disclose or suggest all of the limitations of claim 55.

Claim 55 recites "wherein said netupitant occupies at least 70% of said patient's striatum NK1 receptors ***ninety-six hours*** after said administration." (Ex. 1002, claim 55.) As explained below, none of the cited references (Herrstedt, Bös, and Hargreaves) disclose the claimed receptor occupancy in the human striatum for ***ninety-six hours***.

Herrstedt does not even mention netupitant, let alone administration of a particular amount of netupitant. The portion of Hoffman cited by Azurity is limited to disclosing that netupitant can penetrate the central nervous system ("CNS") in gerbils. (*See* Petition, 44 (citing Ex. 1011, Abstract, 1364).) Azurity also does not contend that any of these references discuss the claimed level of NK-1 receptor occupancy (at least 70%) in the striatum of a human by any NK-1

receptor antagonist (let alone netupitant) for the claimed time period (96 hours). (*See* Petition, 44-48; Ex. 2089, ¶¶179-180; *see also id.*, ¶¶181-189.)

That leaves Hargreaves, which is a publication describing the use of positron emission tomography ("PET") for studying NK-1 receptor occupancy. (Ex. 1012, 18.) Hargreaves does not disclose that a therapeutically effective dose of netupitant (or any other NK-1 receptor antagonist) would occupy at least 70% of NK-1 receptors in the human striatum for at least ***96 hours***. (Ex. 2089, ¶¶182-189.) Hargreaves reported only aprepitant's NK-1 receptor occupancy for a six-hour period that began 24 hours after the administration of aprepitant and ended six hours later (*i.e.*, 30-hours after the administration of aprepitant). (Ex. 1012, 21-22; Ex. 2089, ¶184.) This data simply would not have disclosed to a POSA what aprepitant's NK-1 receptor occupancy was ***96 hours*** after administration, much less what ***netupitant***'s NK-1 receptor occupancy was ***96 hours*** after administration as required by the claim. (Ex. 2089, ¶¶157, 182-189.)

Furthermore, neither Azurity nor Dr. Peroutka have provided any explanation for why the NK-1 receptor occupancy of ***aprepitant*** should or would translate to the NK-1 receptor occupancy of ***netupitant***. In fact, Dr. Peroutka did not believe that such a comparison was "in the scope" of his declaration. (Ex. 2086 at 253:7-254:17; *see also id.*, 240:3-241:3, 242:25-243:5.) Azurity's assertion that "administering a therapeutically-effective dose of netupitant would

also occupy at least 75% or at least 90% (i.e., at least 70%) of neurokinin-1 (NK_1) receptors in the striatum ninety-six hours after administration" thus has no factual support (Petition, 46), and Dr. Peroutka's analysis fails for the same reasons. (*See* Ex. 1009, ¶1116.)

Perhaps in view of these clear deficiencies, Azurity and Dr. Peroutka resort to arguing inherency. (Petition, 46 (alleging that the "effects recited in claim 55 simply reflexively define what is required of a therapeutically-effective netupitant (or any NK_1 antagonist) dose"); Ex. 1009, ¶1116.) But Azurity has not shown that this limitation is an inherent property of a therapeutically effective dose of an NK-1 receptor antagonist. *See, e.g.*, *Cytiva BioProcess R&D AB v. JSR Corp.*, 122 F.4th 876, 889 n.15 (Fed. Cir. 2024) ("[A] petitioner must still meet its burden to demonstrate that the claimed limitation is indeed inherent. Simply saying it is so without sufficient evidence will not demonstrate unpatentability."). Here, Azurity wholly fails to establish that ***all*** "therapeutically effective amount[s]" of an NK-1 receptor antagonist will occupy at least 70% of NK-1 receptors in the striatum ninety-six hours after administration.

Azurity's reliance on the '357 patent specification for the proposition that the limitation is a characteristic of netupitant itself (*see* Petition, 47 (citing Ex. 1002, 4:37-51) is unavailing. The cited portion of the patent specification merely states that less than 20 or 30% of the bound netupitant is released from the striatum

NK-1 receptors even 96 hours after administration, but provides no explanation for what percentage of receptors are originally occupied by netupitant in the first place. (Ex. 2089, ¶189.) The claimed 70% receptor occupancy is a function of the concentration of netupitant in the body at a given time, which in turn is dependent on dose and other complex pharmacological and pharmacokinetic factors, and not a mere function of netupitant. (*Id.*)

Azurity also cannot rely on the Examiner's alleged contention that the 70% occupancy limitation at issue here is "an inherent property." (Petition, 46.) Helsinn's decision to not challenge ***some*** of the Examiner's findings is not an admission as to their correctness. *See Salazar v. Procter & Gamble Co.*, 414 F.3d 1342, 1347 (Fed. Cir. 2005) ("an applicant's silence regarding [an Examiner's] statements does not preclude the applicant from taking a position contrary to the examiner's statements when the claim terms are construed during litigation.").

Azurity's further contention that "ninety-six hours is squarely within the therapeutic period and reflects the known prolonged half-life of netupitant" likewise fails. (Petition, 47 (citing Ex. 1014, 19:7-38).) Azurity has provided no analysis regarding why a POSA would have been motivated to choose to focus on receptor occupancy at ninety-six hours rather than other time points, nor has Azurity explained whether a POSA would have a reasonable expectation of success in focusing on that particular time point. Bös does not state that netupitant

has a 96-hour half-life. Moreover, as explained by Dr. Roeland, netupitant's half-life does not directly translate to receptor occupancy, which is a function of numerous different factors, including but not limited to netupitant's receptor affinity and its concentration in a given location in the human body. (Ex. 2089, ¶233; *see also id.*, ¶¶152-155.) Importantly, Azurity and Dr. Peroutka do not (and cannot) point to any prior art that discloses how much netupitant will need to be administered to result in the claimed amount of receptor occupancy over the claimed time period.

For at least these reasons, Azurity has not shown that all limitations of claim 55 are disclosed by the cited references.

VII. Objective Indicia of Nonobviousness Confirm that the Claimed Invention Is Not Obvious

"Objective indicia must always when present be considered in the overall obviousness analysis." *Adapt Pharma Operations Ltd. v. Teva Pharms. USA, Inc.*, 25 F.4th 1354, 1372 (Fed. Cir. 2022). But they are especially notable in this case because they confirm the use of impermissible hindsight in Azurity's analysis. As explained below, the method of treatment embodied in the '357 patent claims constituted a breakthrough when first unveiled, which unexpectedly showed a statistically significant effect on nausea compared to the standard-of-care treatment as of November 2009 despite skepticism in the prior art.

A. Nexus

Nexus exists where objective indicia are reasonably commensurate with the claims. *In re Huai-Hung Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011). Nexus is found where the evidence of objective indicia results from unique features of a claimed combination even if the combined elements were known. *Chemours Co. FC, LLC v. Daikin Indus., Ltd.*, 4 F.4th 1370, 1378 (Fed. Cir. 2021); *WBIP,* 829 F.3d at 1330-32. Here, the objective indicia evidence is commensurate with the claims. The evidence relates to the administration of a drug regimen, including netupitant and palonosetron, to treat nausea and vomiting in patients undergoing chemotherapy, as claimed in the various challenged claims. The administration of a drug regimen including netupitant and palonosetron to treat nausea, and especially delayed nausea, is a unique feature of the claimed invention. (*See supra* Section V.)

The meaningful clinical benefits provided to cancer patients by this inventive combination of netupitant and palonosetron are illustrated in Example 5 of the ’357 patent, which is a clinical study describing a Phase 2 multicenter, randomized, double-blind clinical trial, where patients were randomized into one of five treatment groups. (Ex. 1002, 17:12-64.) The 200 mg (Group 3) and 300 mg (Group 4) doses of netupitant, administered along with palonosetron and dexamethasone to the patients in that study, had a ***statistically significant*** effect on

both emesis and nausea compared to palonosetron and dexamethasone alone. (Ex. 2089, ¶¶239-245; *supra* Section II.C.) Both doses showed this effect in the "delayed" nausea phase, which was particularly important for clinicians and patients. (*Id.*; *supra* Sections II.A, II.C.) The objective indicia of unexpectedly improving nausea in the delayed phase thus has a nexus to the claim, because it arises from the use of netupitant and palonosetron in the administered three-drug regimen.

B. Unexpected Results and Skepticism

Unexpected results can be demonstrated when "the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected." *Procter & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009). "If industry participants or skilled artisans are skeptical about whether or how a problem could be solved or the workability of the claimed solution, it favors non-obviousness." *WBIP,* 829 F.3d at 1335.

As explained above in Section VII.A, both the 200 mg and 300 mg doses of netupitant, demonstrated a statistically significant effect in improving "no significant nausea" in the ***delayed*** phases, compared to standard therapy. (Ex. 1002, 16:59-18:24, 18:60-19:40.) This improvement in the delayed phase of nausea would have been particularly meaningful to a POSA, because this is the

phase of nausea that patients found to be most debilitating and is often the hardest to treat. (Ex. 2089, ¶¶246-247; *supra* Section II.) This improvement was likewise unexpected, as underscored by the skepticism in contemporaneous literature regarding the ability of NK-1 receptor antagonists to treat chemotherapy-induced nausea. (Ex. 2089, ¶¶248-251.)

Moreover, the data in Table 6 above shows unexpected results compared to the closest prior art teaching. Table 6 shows that the FDA-approved aprepitant triple therapy (aprepitant, a 5-HT_3 antagonist, and dexamethasone) did not show a statistically significant improvement for "no nausea" and "no significant nausea" over standard therapy, while the netupitant three-drug regimen (netupitant, palonosetron, and dexamethasone) did. Triple therapy with aprepitant is the closest prior art as evidenced by Azurity's lead reference, Herrstedt.

VIII. Conclusion

The patentability of the challenged claims should be confirmed.

Respectfully submitted,

Dated: February 25, 2026

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CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(d), the undersigned certifies that the foregoing Patent Owner's Response contains, as measured by the word-processing system used to prepare this paper, 11,516 words. This word count does not include the items excluded by 37 C.F.R. § 42.24.

Respectfully submitted,

Dated: February 25, 2026

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I certify that I served on the counsel identified below a true and correct copy of the foregoing Patent Owner's Response and supporting evidence by electronic means on February 25, 2026:

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