

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AZURITY PHARMACEUTICALS, INC.,
Petitioner,

v.

HELSINN HEALTHCARE S.A.,
Patent Owner.

Case IPR2025-00948
Patent No. 9,943,515 B2

PATENT OWNER'S PRELIMINARY RESPONSE

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2001	Curran, P. et al., <i>Aprepitant A Review of its Use in the Prevention of Nausea and Vomiting</i> , <i>Drugs</i> 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, <i>Casopitant: a novel NK1-receptor antagonist in the prevention of chemotherapy-induced nausea and vomiting</i> , <i>Therapeutics and Clinical Risk Management</i> 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, <i>ihealthcareanalyst</i> , Feb. 3, 2025, available at https://www.ihealthcareanalyst.com/global-chemotherapy-induced-nausea-vomiting-drugs-market/	X
2007	Heron Form 10-K, Feb. 27, 2025	X
2008	Azurity (Aprepitant Injectable Emulsion) FDA Tentative Approval Letter, NDA 218754, dated July 25, 2024, available at https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2024/218754Orig1s000TAltr.pdf	X
2009	U.S. Patent No. 12,097,197 to Dubewar et al.	X

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2010	IDS Statement, Application No. 18/069,204, dated June 29, 2023	X
2011	Press Release – CutisPharma Announces Acquisition of Silvergate Pharmaceuticals, Name Change to Azurity Pharmaceuticals, June 12, 2019	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
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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
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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

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2036	Navari, R.M. Pharmacological Management of Chemotherapy-Induced Nausea and Vomiting. <i>Drugs</i> 69, 515–533 (2009). https://doi.org/10.2165/00003495-200969050-00002 (Published March 2009)	
2037	Ettinger et al., Antiemesis Clinical Practice Guidelines in Oncology, <i>Journal of the National Comprehensive Cancer Network</i> , 7(5): 572-595 (May 2009)	
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2045	Albert, J.S. et al., "Structural analysis and optimization of NK1 receptor antagonists through modulation of atropisomer interconversion properties." <i>J. Med. Chem.</i> 2004, 47, 519-529.	
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2047	Goldstein D.J. et al., "Lanepitant, an NK-1 antagonist, in migraine prevention," <i>Cephalalgia</i> , 2001 Mar; 21(2):102-6	
2048	George D.T. et al. "Neurokinin 1 Receptor Antagonism as a possible therapy for alcoholism," <i>Science</i> 319: 1536-1539 (2008)	

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

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2058	Shishido, Y. et al. "Discovery and stereoselective synthesis of the novel isochroman neurokinin-1 receptor antagonist 'CJ-17,493'." <i>Bioorganic & Medicinal Chemistry</i> 16(15): 7193-7205 (2008)	
2059	De la Puente-Redondo, V. et al. "The neurokinin-1 antagonist activity of maropitant, an antiemetic drug for dogs, in a gerbil model." <i>Journal of Veterinary Pharmacology and Therapeutics</i> 30(4): 281-287 (2007)	
2060	Rudd, J et al., "Inhibition of emesis by tachykinin NK1 receptor antagonists in <i>Suncus murinus</i> (house musk shrew)." <i>European Journal of Pharmacology</i> 366(2-3): 243-252 (1999)	
2061	Quartara, Laura and Altamura, Maria, "Tachykinin receptors antagonists: from research to clinic." <i>Current Drug Targets</i> 7(8): 975-992 (2006)	
2062	Emonds-Alt, Xavier et al. "SSR240600 [(R)-2-(1-{2-[4-{2-[3, 5-Bis (trifluoromethyl) phenyl] acetyl}-2-(3, 4-dichlorophenyl)-2-morpholinyl] ethyl}-4-piperidiny)-2-methylpropanamide], a Centrally Active Nonpeptide Antagonist of the Tachykinin Neurokinin-1 Receptor: I. Biochemical and Pharmacological Characterization." <i>The Journal of Pharmacology and Experimental Therapeutics</i> 303(3): 1171-1179 (2002)	
2063	Shue, H. et al. "Cyclic urea derivatives as potent NK1 selective antagonists." <i>Bioorganic & Medicinal Chemistry Letters</i> 15(17): 3896-3899 (2005)	
2064	Araya, I. et al. "Process development and large-scale synthesis of NK1 antagonist." <i>Chemical and Pharmaceutical Bulletin</i> 56(2): 176-180 (2008)	
2065	Hesse, C. et al. "Kinetics and dynamics of the peripheral neurokinin-1 receptor antagonist SLV317 in healthy individuals." <i>British Journal of Clinical Pharmacology</i> 61(4): 414-419 (2006)	

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2066	Megens AA, Ashton D, Vermeire JC, Vermote PC, Hens KA, Hillen LC, Fransen JF, Mahieu M, Heylen L, Leysen JE, Jurzak MR, Janssens F. Pharmacological profile of (2R-trans)-4-[1-[3,5-bis(trifluoromethyl)benzoyl]-2-(phenylmethyl)-4-piperidinyl]-N-(2,6-dimethylphenyl)-1-acetamide (S)-Hydroxybutanedioate (R116301), an orally and centrally active neurokinin-1 receptor antagonist. J Pharmacol Exp Ther. 302(2):696-709 (2002 Aug)	
2067	Reserved	
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2069	IPR2025-00948: Declaration of Rudolph Modesto Navari, M.D., Ph.D, F.A.C.P.	
2070	Reserved	

I. INTRODUCTION

Patent Owner Helsinn Healthcare S.A. (“Helsinn” or “PO”) respectfully submits this Preliminary Response to the Petition for *inter partes* review (Paper 1) (“Petition” or “Pet.”) filed by Azurity Pharmaceuticals, Inc. (“Azurity” or “Petitioner”) against claims 1-23 of U.S. Patent No. 9,943,515 (“the ’515 patent”). For the reasons explained below, the Petition should be denied under 35 U.S.C. § 314(a) because Azurity has not met its burden of demonstrating a reasonable likelihood of prevailing on any of the challenged claims.

Chemotherapy-induced nausea and vomiting (“CINV”) is and has been a major concern for patients undergoing chemotherapy. As of November 2009, the available CINV treatments that had been FDA-approved were known to be effective against vomiting, but did not also allow for the control of nausea. The ’515 patent invention offered a CINV treatment that was also effective against nausea and represented a significant, and much-needed, advance in supportive care for cancer patients undergoing chemotherapy. For example, the inventors discovered that a compound called “netupitant is active against nausea” and “that a single dose of netupitant is able to treat nausea and vomiting in response to highly and moderately emetogenic chemotherapy for five consecutive days.” (Ex. 1003 at

4:55-60.)¹ The inventors claimed a method of treating CINV using netupitant in each challenged independent claim of the '515 patent.

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

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

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

The legal error arising from Azurity's misframing of the obviousness analysis is compounded by its narrow view of the many potential options that were available to a POSA in November 2009. Azurity contends that it would have been obvious for a POSA at the time of the invention to start with a three-drug regimen that included a drug called "aprepitant," and then replace aprepitant with netupitant to arrive at the claimed invention. (*See, e.g.*, Petition at 31 ("A POSA had good reason to substitute Bös' newer NK₁ antagonist (netupitant) for the existing NK₁ antagonist aprepitant in Herrstedt's combination and reasonably expect the combination to work as well or better.")) Azurity's proposed motivation for a POSA to make this specific change directly hinges on its allegation that the prior art recognized netupitant as somehow "improved" over aprepitant. (*See, e.g.*, Petition at 15.) But Azurity ignores that netupitant was just *one of many* drugs in the same class as aprepitant that were available in November 2009. Moreover, Azurity's contention that netupitant was somehow "improved" compared to aprepitant finds no support in Azurity's cited art, nor does Azurity connect this alleged "improved" profile to any clinically meaningful results that would have

motivated a POSA. (*See infra* Section V.B.) Azurity’s Petition also fails because the cited references do not disclose or render obvious the claim limitation relating to a single, one-time dose of netupitant, as recited in each independent claim. (*See infra* Section V.C.) Moreover, Azurity fails to demonstrate that a POSA would have had a reasonable expectation as the Petition provides no evidence that a POSA would have reasonably expected the claimed netupitant-based treatment to be effective against both *nausea* and vomiting. (*See infra* Section V.D.)

Finally, Azurity’s allegation that Helsinn “misrepresented” certain data during prosecution is demonstrably false, as confirmed by Azurity’s failure to cite a single statement from the prosecution history of the ’515 patent. (*See* Petition at 60-63.) The Petition mostly cites the declaration of Azurity’s expert (*see id.*) but the cited portions of his declaration also fail to discuss the ’515 patent’s prosecution history. The declaration instead discusses statements from the file history of the grandparent patent without explaining how those statements are relevant to the ’515 patent or its claims. Even if they were to be considered, Azurity’s allegations are meritless. (*See infra* Section V.E.)

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

II. BACKGROUND

A. Chemotherapy-Induced Nausea and Vomiting

Chemotherapy-induced nausea and vomiting is a major concern for patients undergoing chemotherapy. (Ex. 2001 at 1856; Ex. 2069 at ¶¶ 23-27.) Poorly controlled CINV can greatly impact the quality of life of patients with cancer and, in some cases, can be so severe that patients make the difficult decision to discontinue chemotherapy altogether. (Ex. 2001 at 1856; Ex. 2069 at ¶ 24.)

Vomiting (also commonly referred to as emesis)² and nausea are two separate adverse events associated with chemotherapy and often need to be treated individually. (Ex. 2069 at ¶23.) This distinction between the nausea and vomiting components of CINV is significant, as the nausea arising from chemotherapy has historically been much more difficult to control than vomiting. (*See, e.g.*, Ex. 1010 at 143, 148; Ex. 2069 at ¶¶ 24, 74-80.) As of November 2009, treatments indicated for “CINV” were known to be effective against vomiting, but did not allow for the control of nausea. (Ex. 2069 at ¶¶ 31-42.) A POSA would have thus understood the phrase “CINV” to be somewhat of a misnomer, as treatments for CINV actually did “*not* need to demonstrate an effect on *nausea* to secure approval for

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

this indication.” (Ex. 1005 at 347, ¶ 38; Ex. 2069 at ¶¶ 28-30.) Instead, to receive FDA-approval for the indication of treating CINV, “drug sponsors . . . [were] only required to demonstrate an effect on ‘complete response,’ defined as no emetic episodes (i.e., vomiting or retching) and no use of rescue therapy during the relevant time period.”³ (Ex. 1005 at 347, ¶ 38; Ex. 2069 at ¶¶ 28-30.)

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

As of November 2009, the available CINV treatments that had been FDA-approved were known to be effective against vomiting, but did not also allow for the control of nausea. (Ex. 2069 at ¶¶ 31-42.) And while various drug options had shown promise for controlling nausea, none of the options pointed to the netupitant-based CINV treatment described and claimed in the ’515 patent.

Clinicians in 2009 had several options for controlling chemotherapy-induced emesis component of CINV, including through various drug products. (Ex. 2069 at ¶¶ 31-42.) For example, at that time, the drug aprepitant had been shown to be effective in clinical trials for controlling emesis, but did not show any statistically

³ Rescue therapy is when additional treatment beyond the administered prophylactic drugs is required because vomiting and/or nausea occurred within five days of chemotherapy administration. (Ex. 2069 at ¶ 27, 27 n.4.)

significant effect on nausea. (Ex. 1005 at 345-46, ¶¶ 32-34; Ex. 1016 at 2086 (“According to its package insert, aprepitant fails to demonstrate improved efficacy over placebo for the prevention of nausea”); Ex. 2069 at ¶¶ 107-17.) Aprepitant, which is a member of a family of chemical compounds known as NK-1 receptor antagonists,⁴ was typically administered to treat CINV in combination with other drugs, such as 5-HT₃ receptor antagonists and dexamethasone. This three-drug regimen (also referred to as “triple therapy”) was found to be effective in treating emesis but did not allow for control of nausea. (Ex. 2069 at ¶¶ 31-40, 42.) As a result, as of November 2009, control of nausea was considered a problem for treating patients for CINV, especially because patients often experience more nausea than vomiting. (Ex. 2069 at ¶¶ 31-40, 73-80.)

While no FDA-approved treatment for CINV that also allowed for the control of nausea was available in 2009, a POSA would have known from the pertinent art that numerous different drugs from various classes showed promise for potentially controlling nausea. (Ex. 2069 at ¶¶ 81-87.) Some exemplary

⁴ An “antagonist” is a chemical compound administered to block certain neurotransmitters from binding to receptors. (Ex. 1010 at 144.) For example, a chemical compound that blocks or inhibits activity of an NK-1 receptor is referred to as an “NK-1 receptor antagonist.” (Ex. 2069 at ¶ 25.)

categories of drugs that a POSA could have considered included antipsychotics (*e.g.*, olanzapine), antiepileptics (*e.g.*, gabapentin), and cannabinoids (*e.g.*, dronabinol and nabilone), which had demonstrated encouraging anti-nausea efficacy as candidates for potential further investigation. (Ex. 2069 at ¶¶ 42-50, 81-87.) None of these options, however, pointed to the claimed inventions of the '515 patent.

Among the numerous drug candidates that were promising at this time, olanzapine was described by one prior art publication as the “most promising” new anti-emetic “with very high complete response rates of both *nausea* and vomiting when combined with a 5-HT₃-receptor antagonist and a corticosteroid.” (Ex. 2069 at ¶¶ 43-45 (quoting Ex. 1010 at 149), 81-83). The antiepileptic gabapentin was another available option, and further studies had been suggested to determine its potential effects on reducing nausea. (Ex. 2069 at ¶¶ 43, 47-48, 85.) Additionally, cannabinoids had also been suggested for further trials to evaluate their use in the control of nausea. (Ex. 2069 at ¶¶ 49-50, 86-87.) By November 2009, two oral cannabinoid formulations were already FDA-approved for refractory CINV treatments, and cannabinoids were listed in the NCCN guidelines as a potential “breakthrough” CINV treatment. (Ex. 2069 at ¶¶ 50, 87.)

C. The '515 Patent Offered a Much-Needed CINV Treatment That Surprisingly Allowed for Control of Nausea

The invention of the '515 patent offered an improved CINV treatment that was also effective against nausea and represented a significant and much-needed advance in supportive care for cancer patients undergoing chemotherapy. For example, the '515 patent inventors discovered that (1) “netupitant is active against nausea” and (2) “that a single dose of netupitant is able to treat nausea and vomiting in response to highly and moderately emetogenic chemotherapy for five consecutive days.” (Ex. 1003 at 4:55-60.) This unexpected discovery follows from netupitant’s “unexpectedly . . . unique binding habits to the NK₁ receptors in the brain.” (*Id.* at 4:60-62.)

In particular, [the inventors] discovered that netupitant binds to NK₁ receptors in the striatum in a long-lasting manner, and that less than 20 or 30% of netupitant is released from striatum receptors even ninety-six hours after administration. This is in stark contrast to aprepitant, in which receptor binding drops swiftly over time . . .

(*Id.* at 4:62-67.)

The inventors’ discovery that a single dose of netupitant is able to treat nausea and vomiting stands in stark contrast with the FDA-approved drug aprepitant. Specifically, as directed by the Emend[®] (aprepitant) label, aprepitant

must be administered for CINV over three days. (Ex. 2016 at 11 (“EMEND is given for 3 days as part of a regimen that includes ... 125 mg orally 1 hour prior to chemotherapy treatment (Day 1) and 80 mg once daily in the morning on Days 2 and 3.”); Ex. 1016 at 2081 (“FDA-approved 3-day regimen of aprepitant 125 mg orally on Day 1 followed by 80 mg orally per day on Days 2 and 3”).) And even when this FDA-approved dosing schedule is followed, “aprepitant fails to demonstrate improved efficacy over placebo for the prevention of nausea” (Ex. 1016 at 2086.)

The inventors claimed their regimen of a single, one-time dose of netupitant for treating CINV over a five-day period in, *inter alia*, the '515 patent. Claim 1 of the '515 patent, for example, recites:

A method of treating nausea and vomiting from an emesis-inducing event for a period of five consecutive days in a patient in need thereof, comprising
administering to said patient netupitant or a pharmaceutically acceptable salt thereof, in a therapeutically effective amount which is effective to treat nausea and vomiting during the acute and delayed phases of emesis, and which enters the systemic circulation, crosses the blood brain barrier and occupies 70% or more of NK1 receptors in the striatum seventy-two hours after said administration,

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

(Ex. 1003 at Claim 1.)

The Office allowed the claims after Helsinn added the bolded, italicized limitation to the claims to clarify that “one single dose of netupitant is administered over a five-day period of time, and the single dose is effective to prevent nausea and vomiting during the entire five-day period.” (Ex. 1007 at 324, 328, 342.) As discussed below, none of Azurity’s prior art discloses or suggests this limitation.

III. LEVEL OF ORDINARY SKILL

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

A POSA was skilled in one of “clinical medicine, medical oncology, radiation oncology, oncology nursing, statistics, pharmacy, medical policy and decision making, and pharmacology.” . . . In 2009, such professionals had advanced degrees in pharmacology, medicine, or allied fields, and would have worked in consultation with other specialists in these fields, and would have practical

knowledge and experience about metabolism studies, in-vitro and in-vivo testing, formulation, and combination therapy.

(Petition at 8-9 (citing Ex. 1009 at ¶¶ 1-7, 57-60).) Patent Owner disagrees with Azurity's definition of a POSA to the extent Azurity's POSA definition does not require experience in the field of oncology, including work experience with cancer supportive care medications.

Patent Owner proposes the following definition for a POSA:

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

(Ex. 2069 at ¶ 19.)

Based on the information disclosed in his declaration (Ex. 1009) and *curriculum vitae* (Ex. 1020), Dr. Peroutka appears to lack any substantial

experience practicing in the field of oncology during the relevant time period of November 2009.⁵ (See Ex. 1009 at 1-3, ¶¶ 1-7; Ex. 1020 at 4.) Dr. Peroutka also appears not to have any experience with treating cancer patients or patients suffering from CINV. And while Dr. Peroutka states that his “research includes publications involving chemotherapeutic agents and antiemetic agents, such as 5-hydroxytryptamine-3 (‘5-HT₃’) receptor inhibitors” (Ex. 1009 at ¶ 5), the most recent of those publications is dated 1989—two decades before the time of invention. (Ex. 1020 at 16.) Accordingly, Dr. Peroutka does not appear to have sufficient experience in the field of oncology to accurately opine from the perspective of a POSA in November 2009.

IV. CLAIM CONSTRUCTION

The Board need not construe Azurity’s proposed claim terms because construction of those terms is unnecessary to resolve the parties’ disputes here.

⁵ During the time that Dr. Peroutka practiced medicine, his practice was limited to the field of neurology. He has not practiced as a clinician in any capacity since about 1990. (Ex. 1020 at 4.) Accordingly, he would have not had an opportunity to prescribe any NK-1 receptor antagonist or palonosetron, as those drugs were not FDA-approved at the time he practiced medicine or for over a decade after that time.

Under any reasonable construction of the claim terms, the prior art fails to disclose or suggest the claimed features. Thus, no claims need be construed here because the Board only construes the claims when necessary to resolve the underlying controversy. *Toyota Motor Corp. v. Cellport Systems, Inc.*, IPR2015-00633, Paper 11 at 16 (Aug. 14, 2015) (citing *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999)).

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

**A. Azurity's Obviousness Analysis
Applies the Wrong Legal Framework⁶**

In its Petition, Azurity ignores that the obviousness analysis does not begin with the invention, but rather with the problem facing the POSA at the relevant time. Here, Azurity begins with Helsinn's invention, and then works backwards by cobbling together the prior art so as to arrive at the claimed inventions. (*See, e.g.*, Petition at 30 (“[A POSA would have reasonably expected success modifying Herrstedt's antiemetic combination with netupitant because the substituted newer

⁶ Helsinn's Preliminary Response focuses on the challenged independent claims. Azurity's challenges to the dependent claims in each of its grounds, however, fail equally for the same reasons as the independent claims.

NK₁ antagonist (netupitant for the older aprepitant) would have been expected act in the same manner to achieve a similar (or better) outcome.”.) The Federal Circuit has criticized this kind of approach to the obviousness analysis:

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

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

Under the proper legal framework, Azurity must show that a POSA at the time of the invention ““would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and . . . would have had a reasonable expectation of success in doing so.”” *Insite*, 783 F.3d at 859; *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Pat. Litig.*, 676 F.3d 1063, 1068-69 (Fed. Cir. 2012). Importantly, the problem facing the POSA

provides the foundation for this framework, as “[w]hat matters is the path that the [POSA] would have followed, as evidenced by the pertinent prior art.” *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1296 (Fed. Cir. 2012); *WBIP*, 829 F.3d at 1337 (“The real question is whether that skilled artisan would have plucked one reference out of the sea of prior art . . . and combined it . . . to address some need present in the field . . .”). After the problem facing a POSA is defined, the next step is determining whether a POSA would have “narrow[ed] [their] research focus” in a manner that arrived at the invention. *See Insite*, 783 F.3d at 860.

The Federal Circuit’s *Insite* decision is particularly instructive for determining the proper starting point for an obviousness analysis. In *Insite*, the disputed claim recited “a method of treating an ocular infection, comprising topically administering . . . an ocular infection-treating amount of azithromycin.” 783 F.3d at 856. There, the district court had defined “the problem facing a [POSA] at the time of the invention as the development of ‘improved topical treatments for ocular infections.’” *Id.* at 857. While affirming the district court’s finding on appeal, the Federal Circuit rejected the patent challenger’s attempt to narrowly construe the problem facing a POSA and held that the problem “was broader than merely seeking to use azithromycin to treat conjunctivitis.” *Id.* at 860.

As explained below, the problem facing a POSA in 2009 was the need for an improved treatment for CINV that allowed for controlling chemotherapy-induced nausea. (Ex. 2069 at ¶¶ 69-80.) Rather than analyze the prior art options a POSA would have considered for solving this problem, Azurity impermissibly cherry-picks prior art using the claims as a roadmap. For example, Azurity incorrectly assumed that a POSA would first look to the aprepitant-based triple therapy used to treat CINV, which did not even allow for the treatment of nausea, and then consider swapping the then-gold-standard aprepitant for netupitant to arrive at the claimed invention. (*See, e.g.*, Petition at 31 (“A POSA had good reason to substitute Bös’ newer NK₁ antagonist (netupitant) for the existing NK₁ antagonist aprepitant in Herrstedt’s combination and reasonably expect the combination to work as well or better.”).)

Contrary to Azurity’s assertions, the obviousness question here cannot be narrowly framed to focus only on whether it would have been obvious to a POSA substitute netupitant for aprepitant in the three-drug regimen. The obviousness analysis must take into account the many different potential paths that a POSA would have considered to possibly address the problem facing the POSA, and whether any of these paths would have actually led a POSA to the claimed netupitant-based regimen for treating CINV. *See generally Insite*, 783 F.3d at 858-61. Azurity’s failure to engage in the requisite analysis is dispositive here.

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

In November 2009, the problem facing a POSA was improving the treatment of CINV to allow for controlling nausea. (Ex. 2069 at ¶¶ 42 (citing Ex. 2036 at 528), 73-80.) The problem facing a POSA in November 2009 is exemplified by the 2009 National Comprehensive Cancer Network (“NCCN”) Guidelines (Ex. 2037). These guidelines informed clinicians in 2009 who treated patients suffering from CINV by providing a consensus of expert views on currently accepted approaches to treatment. While NCCN Guidelines recommended administration of the “triple therapy” to reliably control emesis in patients suffering from CINV, the NCCN Guidelines also reported its lack of control of nausea remained a significant problem for patients. (Ex. 2069 at ¶¶ 24, 31-32; Ex. 2037 at 573, 587; Ex. 1010 at 143 (“Today, the majority of patients consider nausea as the main problem.”).) As discussed above, untreated chemotherapy-induced nausea was a significant patient concern that affected quality of life for cancer patients, potentially leading to poor compliance with future chemotherapy treatment. (Ex. 2069 at ¶ 24; Ex. 2037 at 572.) Accordingly, framing the problem facing a POSA as improving treatments for CINV to allow for the control of nausea properly reflects the path that a POSA in November 2009 “would have followed, as evidenced by the pertinent prior art.” *Otsuka*, 678 F.3d at 1296.

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

The prior art that Azurity focuses upon in its Petition, as well as its analysis of what that art would have taught a POSA in November 2009, underscores the hindsight-based nature of Azurity's obviousness analysis. Azurity's Petition relies on Herrstedt as disclosing a "triple-drug combination including an NK₁ antagonist (aprepitant)" for treating CINV. (*See, e.g.*, Petition at 16-17, 32-33.) By November 2009, this three-drug regimen ("triple therapy") had been proven effective against vomiting, but did *not* successfully control nausea. (Ex. 2069 at ¶¶ 31-40.) Herrstedt even acknowledges this shortcoming, stating that nausea remained "the main problem[] for the majority of patients," despite the availability of aprepitant and this three-drug dosing regimen. (Ex. 1010 at 148; *see also id.* at 143.) Azurity fails to explain in its obviousness analysis why a POSA would have started with the three-drug regimen when it was not effective in controlling nausea.

But even if the three-drug regimen in Herrstedt were to be used as a starting point, Azurity's analysis fails to consider the many paths that a POSA in November 2009 would have considered to allow for the treatment of nausea. *See Insite*, 783 F.3d at 859-60 (after the problem facing a POSA is defined, the next step is determining whether a POSA would have "narrow[ed] [their] research focus to lead to the invention"). For example, one possible pathway for a POSA to

consider would have been adding a *fourth* drug to the three-drug regimen to control nausea instead of substituting for individual drugs (*e.g.*, aprepitant) in that regimen. (Ex. 2069 at ¶¶ 81-87.)

As one possibility, a POSA in 2009 could have explored the addition of olanzapine, a different drug that had already shown potential for controlling nausea, as a fourth drug in the three-drug regimen.⁷ (Ex. 2069 at ¶¶ 82-83.) In fact, Herrstedt touts the potential of olanzapine in controlling the nausea component, describing olanzapine as the “most promising” new anti-emetic “with very high complete response rates of both *nausea* and vomiting when combined with a 5-HT₃-receptor antagonist and a corticosteroid.” (Ex. 2069 at ¶ 83 (quoting Ex. 1010 at 149).)⁸ Azurity provides no reason why a POSA would have not considered adding a fourth drug, like olanzapine, to the three-drug regimen of Herrstedt, especially given Herrstedt’s own statements about the potential benefit

⁷ In fact, in subsequent clinical studies carried out in 2016, olanzapine was found to have “significantly improved nausea prevention, as well as the complete-response rate” when added to triple therapy patients receiving highly emetogenic chemotherapy. (Ex. 2069 at ¶ 83 (quoting Ex. 2039 at 134).)

⁸ This discussion of the olanzapine regimen in Herrstedt does not even include any mention of an NK-1 receptor antagonist in the regimen.

of olanzapine. Indeed, “it is impermissible to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art.” *In re Wesslau*, 353 F.2d 238, 241 (C.C.P.A. 1965); *see, e.g., Henny Penny Corp. v. Frymaster LLC*, 938 F.3d 1324, 1332 (Fed. Cir. 2019) (“The benefits, *both lost and gained*, should be weighed against one another. That is consistent with the longstanding principle that the prior art must be considered for all its teachings, not selectively.”) (citation modified); *Polaris Indus., Inc. v. Arctic Cat, Inc.*, 882 F.3d 1056, 1069 (Fed. Cir. 2018) (“[A] reference must be considered for all it taught, disclosures that diverged and taught away from the invention at hand as well as disclosures that pointed towards and taught the invention at hand.”).

Azurity also ignores other potential paths that were available to a POSA in November 2009—none of which would have led to the claimed inventions. For example, a POSA could have considered adding other drugs, like gabapentin and cannabinoids, from other, different drug classes to the three-drug regimen for controlling nausea. As Dr. Navari explains, the anti-epileptic gabapentin was one possible option, and further studies had been suggested to determine its potential effects on reducing nausea. (Ex. 2069 at ¶ 85.) Additionally, cannabinoids had also been suggested for further trials to evaluate their use in the control of nausea.

(Ex. 2069 at ¶¶ 86-87.) By 2009, two oral cannabinoid formulations were already FDA-approved for refractory CINV treatments, and cannabinoids were listed in the NCCN guidelines as a potential “breakthrough” CINV treatment. (Ex. 2069 at ¶¶ 86-87.)

The prior art, including Herrstedt itself, makes clear that a POSA could have pursued numerous paths to solve the underlying problem of nausea. Again, none of these pathways involve netupitant or point to the claimed netupitant-based CINV treatment. Azurity’s lack of consideration of these alternate paths, coupled with its singular focus on netupitant, underscores that its obviousness analysis is infected by impermissible hindsight. (Ex. 1010 at 149.) Accordingly, for this reason alone, Azurity cannot establish a reasonable likelihood of showing the challenged claims would have been obvious.

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

Azurity’s analysis also fails to show a POSA would have focused on using netupitant for a potential CINV treatment over other NK-1 receptor antagonists. As explained below, Azurity’s hindsight-based analysis that substituting netupitant for aprepitant in Herrstedt’s three-drug CINV treatment regimen would have been obvious (*see, e.g.*, Petition at 29-30) suffers from a lack of factual support. Indeed, Azurity fails to explain why a POSA would have immediately wanted to “swap

out” part of the three-drug regimen for CINV (aprepitant) that was known to be extremely effective against vomiting. (Ex. 2069 at ¶¶ 88-95.) Moreover, Azurity’s bald assertion that netupitant was “newer” and “improved” compared to aprepitant (*see, e.g.*, Petition at 31, 34-35) is not only unsupported, but fails to consider the prior art as a whole.

In November 2009, a POSA would have been aware of numerous NK-1 receptor antagonists. At that time, a long list of NK-1 receptor antagonists were either under investigation or had been investigated, and thus, were at various stages of development. (Ex. 2069 at ¶¶ 41, 89.) Azurity, however, fails to consider any of these alternative NK-1 receptor antagonists that were known by November 2009—let alone their advantages or shortcomings—and instead contends that a POSA would have zeroed in on netupitant.⁹ But a POSA at this time would have considered all of these NK-1 receptor antagonists if they were looking at a potential replacement for aprepitant in the triple-drug regimen. (Ex. 2069 at ¶ 89.)

Moreover, when the reference (Bös) that Azurity cites for teaching the NK-1 receptor antagonist netupitant is examined, netupitant is one of millions of

⁹ Azurity’s focus on NK-1 receptor antagonists for its obviousness analysis is at odds with its broad definition of a POSA who is not focused on such antagonists.

disclosed compounds.¹⁰ Bös is a U.S. patent directed to 4-phenyl-pyridine derivatives generally, and netupitant is just one specific derivative that is claimed among millions of compounds. (Ex. 1014 at Cover; Ex. 2069 at ¶¶ 59-63.) Bös also does not include any express language suggesting that netupitant had greater antagonist activity at the NK-1 receptor than any of the other millions of other compounds it disclosed. (Ex. 2069 at ¶¶ 90-95.) Again, Azurity provides no analysis as to why a POSA would have homed in on netupitant to the exclusion of other compounds disclosed in Bös.

Azurity's proposed motivation for a POSA to choose netupitant as the NK-1 receptor antagonist to replace aprepitant in Herrstedt's triple-drug regimen is likewise wholly unsupported. Azurity contends that Bös recognizes netupitant as an "*improved* NK₁ antagonist." (Petition at 31; *see also id.* at 18 (alleging that Bös recognizes netupitant as a "potent and selective NK₁ antagonist").) Dr. Peroutka, Azurity's expert, further contends that Bös "identified netupitant had a long half-

¹⁰ Azurity injects the "Herrington" reference (Ex. 1016) and the "Hargreaves" reference (Ex. 1012) as tertiary references into one or more grounds of its Petition to address the admitted deficiencies of Herrstedt and Bös. The addition of these references does not resolve the deficiencies with the combination of Azurity's proposed primary and secondary references.

life and high bioavailability.” (Ex. 1009 at ¶ 590.) But neither Azurity’s Petition nor Dr. Peroutka provide any evidence that netupitant was recognized as an “improved” NK-1 receptor antagonist compared to aprepitant.

Bös lacks any human clinical data and only provides data from *in vivo* animal studies and *in vitro* CHO cells (cells derived from hamsters) where human NK-1 receptors were expressed. (Ex. 1014 at 18:42-19:38.) The *in vivo* animal studies were early exploratory studies on, *inter alia*, potential uses for NK-1 receptor antagonists that used animal models for anxiety (gerbil foot tapping), motion sickness (*suncus murinus*), and emesis (ferrets). (*Id.* at 18:42-19:38.) None of these animal models were used to assess any potential efficacy of netupitant in controlling nausea in humans. (*Id.* at 14:09-30, 18:42-19:38.)

Moreover, as a threshold matter, Bös does not include any comparative analysis between aprepitant and netupitant from which a POSA could draw conclusions regarding their comparative clinical efficacy. (Ex. 2069 at ¶ 94.) Bös therefore does not show netupitant’s profile was in any way “improved” over aprepitant.

Furthermore, Dr. Peroutka’s contention that Bös “identified netupitant” as having “a long half-life and high bioavailability” is plainly insufficient to constitute an adequate motivation. (Ex. 1009 at ¶ 590.) He does not explain why the half-life values identified in Bös would be considered “large” and how they

compare with aprepitant. Nor does he explain what he means by “high bioavailability” and how netupitant’s alleged “high bioavailability” compares with aprepitant. Dr. Peroutka’s conclusory analysis is not entitled to any weight. *See* 37 C.F.R. § 42.65(a) (“Expert testimony that does not disclose the underlying facts or data on which the opinion is based is entitled to little or no weight.”).

Azurity’s failure to offer a legally acceptable motivation to combine the prior art is an independently sufficient reason for finding that Azurity failed to establish a reasonable likelihood that the challenged claims would have been obvious.

C. Azurity Has Not Shown that the Prior Art Disclosed or Suggested the Claimed Single, One-Time Dose of Netupitant

The Office allowed the ’515 patent after Helsinn amended the claims to specify that “one single dose of netupitant is administered over a five-day period of time, and the single dose is effective to prevent nausea and vomiting during the entire five-day period.” (Ex. 1007 at 324, 328, 342.) For example, independent claim 1 recites “a single dose of netupitant or pharmaceutically acceptable salt thereof is administered on day one of said five consecutive days, no further netupitant or pharmaceutically acceptable salt thereof is administered during said five consecutive days, and said single dose of netupitant or pharmaceutically acceptable salt thereof if [sic] effective to treat said nausea and vomiting for said

five consecutive days.” (Ex. 1003 at Claim 1.) Claim 11 similarly recites “said therapeutically effective amount of netupitant or pharmaceutically acceptable salt thereof is administered on day one of said five consecutive days, no further netupitant or pharmaceutically acceptable salt thereof is administered during said five consecutive days, and said single dose of netupitant or pharmaceutically acceptable salt thereof is effective to treat said nausea and vomiting for said five consecutive days.” (*Id.* at Claim 11.) Azurity has not present evidence from which the Board can find that Azurity’s cited art discloses or renders this limitation obvious.

Azurity relies on Bös and Herrington as teaching or suggesting this limitation. (*See, e.g.*, Petition at 20 (relying on Bös’s teaching of a 30 hour “half-life”), 20-21 (relying on Herrington for teaching “a single dose of aprepitant” has “similar effectiveness” as “dosing aprepitant three times”).) But neither reference discloses any dosing regimen for netupitant, much less that administering a *single dose* of netupitant is effective in treating *nausea* and vomiting for five consecutive days after an emesis-inducing event, as claimed. (Ex. 2069 at ¶¶ 96-103.) Bös’s studies were limited to emesis, not nausea, a completely separate effect to chemotherapy. (*See* Ex. 2069 at ¶¶ 62-63, 99; Ex. 1014 at 19:10-30.) Moreover, Bös is silent on how many times netupitant should be administered. (Ex. 2069 at

¶ 99.) Herrington does not even mention netupitant, let alone disclose any dosing for netupitant. (Ex. 2069 at ¶ 65.)

Azurity's prior art references also do not render the limitation obvious. Azurity argues a POSA would have a "good reason to use a single, day-one dose of Bös' NK₁ antagonist (netupitant) for the 5-day treatment period because Herrington had shown no added benefit to dosing with an NK₁ antagonist on subsequent days of the 5-day period." (Petition at 29.) But this argument is wrong for at least three reasons, and these deficiencies pertaining to the independent claims infect every ground in Azurity's the Petition.

First, Azurity assumes that Herrington's *aprepitant* results are equally applicable to a drug regimen involving netupitant but provides no basis for why a POSA would have made such an assumption. In fact, Herrington teaches that "*aprepitant fails to demonstrate* improved efficacy over placebo for the prevention of *nausea*" (Ex. 2069 at ¶ 68; Ex. 1016 at 2086 (citing the Emend[®] label).) Herrington found that "[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*"—meaning there was no difference in nausea whether *aprepitant* was administered or not. (Ex. 2069 at ¶ 67; Ex. 1016 at 2084.) Thus, if a POSA were (like Azurity is doing here) to attempt to extrapolate *aprepitant*'s

results to netupitant, the POSA would not have expected netupitant to be effective against nausea, as required by the claims.

Second, a POSA would not have drawn any conclusions about using a single dose of an NK-1 receptor antagonist based on Herrington because using a single dose was contrary to what the art taught a POSA at the relevant time. While Herrington evaluated oral aprepitant as a single dose, the Emend® (aprepitant) labelling, the relevant clinical guidelines, and Herrstedt itself taught that aprepitant is dosed over three days. (Ex. 2069 at ¶¶ 100-02; Ex. 1010 at 146 (“Two of the HEC studies used . . . aprepitant day 1 . . . plus aprepitant days 2-3.”).) A POSA would have followed the FDA-approved recommended dosing, as determined by aprepitant’s manufacturer, as well as the relevant clinical guidelines. (Ex. 2069 at ¶ 102.)

Third, Bös also does not provide any reason to use a single dose of netupitant for treating nausea and vomiting for five days following an emesis-inducing event. Bös’s brief description of various *in vivo* animal studies that included netupitant, stated that netupitant’s “antagonism . . . had a functional half life of 30 hours” in one study, while in other studies “the compound has a terminal half life of 24 hours” and “18 hours.” (Ex. 1014 at 18:64-19:38.) Based solely on these statements, Azurity concludes without any support that a half-life of 30 hours is a “*large* half-life value” that provides “reason to omit subsequent

NK₁-antagonist dosing.” (Petition at 20.) Azurity’s expert Dr. Peroutka then parrots this conclusory attorney argument without further explanation. (*Compare id.*, with Ex. 1009 at ¶ 522.) Azurity, however, provides no explanation regarding why or how a 30-hour half-life suggests that administering netupitant would be effective against nausea and vomiting for five consecutive days (120 hours). (Ex. 2069 at ¶¶ 98-99.) This lack of explanation is particularly conspicuous given that netupitant was found to have a shorter half-life (24 hours and 18 hours) in other animal studies. (Ex. 2069 at ¶¶ 98-99.)

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

Azurity also fails to provide sufficient evidence from which the Board can find that a POSA would have had a reasonable expectation of success in arriving at the claimed invention. Specifically, each independent claim of the ’515 patent requires that the claimed method be effective at treating *both nausea* and vomiting. (Ex. 1003 at Claim 1 (“said single dose of netupitant or pharmaceutically acceptable salt thereof if effective to treat said nausea and vomiting for said five consecutive days”), Claim 11 (“said single dose of netupitant or pharmaceutically acceptable salt thereof if [*sic*] effective to treat said nausea and vomiting for said five consecutive days”).) But Azurity provides no evidence that a POSA would have reasonably expected a single dose of netupitant to be effective at treating

nausea and vomiting for five consecutive days. This deficiency infects all grounds of Azurity's Petition, so its Petition fails this reason alone.

For example, Azurity argues that “[a] POSA would have reasonably expected success modifying Herrstedt’s antiemetic combination with netupitant because the substituted newer NK1 antagonist (netupitant for the older aprepitant) would have been expected act in the same manner to achieve a similar (or better) outcome.” (Petition at 30; *see also id.* (“a POSA would have reasonably expected a single therapeutically-effective dose of netupitant (having an even longer half-life) to work for 5-days, just as the older aprepitant that it replaced did.”).) But Azurity fails to allege, let alone demonstrate, that a POSA would have had a reasonable expectation of success *in treating nausea* with this regimen, as required by the claims. (Ex. 2069 at ¶¶ 104-06.) In fact, the triple therapy with aprepitant in Herrstedt failed to treat nausea (*supra* Section V.A) and Azurity offers no evidence that a POSA would have expected incorporating netupitant to provide a different result. Further, Herrington shows that a single dose of aprepitant failed to treat nausea, (Ex. 2069 at ¶¶ 67-68; Ex. 1016 at 2084), and Azurity offers no evidence that a POSA would have expected a single dose of netupitant to provide a different result. Azurity’s conclusory allegations regarding a reasonable expectation of success are insufficient as a matter of law, and based on this deficiency alone, a reasonable likelihood of success cannot be found.

All of Azurity's grounds fail for this reason alone because the above-identified deficiency infects all grounds.

E. Helsinn Did Not Misrepresent Any Data During Prosecution

In an apparent attempt to distract from the deficiencies in its analysis, Azurity contends that Helsinn allegedly misrepresented certain data during prosecution to “exaggerate[] the differences between its triple therapy of netupitant, palonosetron, and dexamethasone versus the prior art combination.” (Petition at 60-63.) As an initial matter, Azurity's allegations do not even correspond to the prosecution history of the '515 patent, as confirmed by Azurity's failure to cite a single statement from the prosecution history of the '515 patent. (*Id.*) Instead, Azurity's allegations appear directed to the prosecution history of the grandparent of the '515 patent, *i.e.*, U.S. Patent No. 8,626,826 (“the '826 patent”). Regardless, Azurity's allegations with respect to the '826 patent's prosecution are unfounded.

As explained below, Helsinn's submissions during prosecution of the '826 patent accurately characterized the cited data. Importantly, the majority of the data cited by Helsinn was *readily available for the Office to review through the same public documents* that were cited in the Rule 132 declaration of Dr. Giorgia Rossi and Mr. Claudio Pietra submitted by Helsinn. (Ex. 1005 at 341-350.) “[T]he Examiner was free to reach his own conclusions and accept or reject [the Rule 132

declaration's] arguments.” *Young v. Lumenis, Inc.*, 492 F.3d 1336, 1349 (Fed. Cir. 2007) (holding that a patentee's “interpretation” of prior art before the Examiner fails to “constitute affirmative misrepresentations of material fact”).

Azurity contends that, contrary to Helsinn's statements, “aprepitant has a substantial effect on nausea.” (Petition at 61.) But as explained by Dr. Navari, Azurity is wrong. (Ex. 2069 at ¶¶ 107-27.) The Rule 132 declaration stated that “we generated unexpectedly superior results when using netupitant against CINV instead of aprepitant” and “observed an unanticipated statistically significant effect against nausea from the combination of netupitant and palonosetron that has not previously been observed in clinical studies involving the combination of aprepitant with ondansetron or aprepitant with palonosetron.” (Ex. 1005 at 345, ¶ 28.) In support of this statement, the Rule 132 declaration cited two tables copied directly from the FDA-approved labeling for Emend[®] (aprepitant), which are reproduced below and show the results of a clinical study in patients receiving highly emetogenic chemotherapy. (*Id.* at 345-46, ¶ 32 (TABLE 2 referring to Ref. E), 350 (describing Ref. E as the March 27, 2003 Emend[®] label); *see also* Ex.

2016; Ex. 1030.)¹¹ These tables plainly demonstrate that the effect of an aprepitant regimen on nausea or significant nausea were found *not* to be statistically significant in this clinical study, as compared to standard therapy and indicated by the “NS**” that appears in the p-Value column on the right-hand side:

¹¹ Azurity and Dr. Peroutka cite to the Emend[®] label from 2008. (*See, e.g.*, Ex. 1009 at ¶ 1334 (citing Ex. 1030).) But during examination, Helsinn referenced the Emend[®] label from 2003 (*see, e.g.*, Ex. 1005 at 346, ¶ 32 (TABLE 2 referring to Ref. E), 350 (describing Ref. E as the March 27, 2003 Emend[®] label)), which is Exhibit 2016 in this proceeding. For the purposes of this proceeding, Patent Owner references Exhibit 1030 cited by Dr. Peroutka and Azurity because the underlying data is the same.

Table 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.

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

Industry publications, including Azurity's own cited Herrington reference (Ex. 1016), support the Rule 132 declaration's interpretation of this data. Herrington expressly cites the Emend[®] (aprepitant) label in stating that, "[a]ccording to its package insert, *aprepitant fails to demonstrate* improved efficacy over placebo for the prevention of nausea" (Ex. 1016 at 2086.) Yeo 2009 (Ex. 1048), another publication cited by Azurity, states that aprepitant makes "no difference in the nausea domain." (Ex. 2069 at ¶ 112; Ex. 1048 at 534.)

Rather than address lack of statistical significance for aprepitant's treatment of "nausea" and "significant nausea" that is shown in the Emend[®] label, Azurity focuses on the "complete protection" data that is provided elsewhere in that label. (Petition at 62.) Azurity asserts that "'complete protection' includes a lack of significant nausea" and "a POSA would have recognized improved treatment of nausea, particularly significant nausea" in view of the complete protection data that is provided. (*Id.*) As Dr. Navari explains, however, "complete protection" is not the correct metric by which to measure a drug's effect on nausea, as complete protection is a composite that represents a combination of data from three separately measured endpoints (*i.e.*, no emesis, no use of rescue antiemetics, and no significant nausea). (Ex. 2069 at ¶¶ 114-17; *see also id.* at ¶¶ 28-29.) The only information in the Emend[®] label that specifically provides information on

aprepitant's impact on nausea unequivocally stated that aprepitant had no statistically significant impact. (*See* Ex. 2069 at ¶ 117; Ex. 1030 at 4-5.)

Turning back to the Rule 132 declaration, Azurity further asserts that the data presented in Table 2 of that declaration was "lacking." (Petition at 61-63.) For example, Azurity alleges that the declaration never provided the Office with the "underlying data for any palonosetron-netupitant combination." (*Id.* at 61.) But as can be seen in Columns 1 and 3 of Table 2 (reproduced below), the Rule 132 declaration did provide Helsinn's internal data for the netupitant/palonosetron combination. Moreover, the Rule 132 declaration cited specific internal studies (NETU-07-07 and NETU-08-18) as the source of the data in Table 2. (*See* Ex. 1005 at 345-46, ¶ 32.) If the Office had wanted to further evaluate the underlying data, they could have simply asked Helsinn to provide it, and Helsinn would have obliged without issue.

TABLE 2

	1	2	3	4	4a	5	6	7	8
Efficacy Endpoint	Palo + Netu (HEC) ^a	Ondan + Aprep (HEC) ^a	Palo + Netu (MEC) ^b	Ondan + Aprep (MEC) ^c	Ondan + Aprep (HEC) ^{c1}	Palo + Aprep (HEC) ^d	Palo + Aprep (MEC) ^e	Ondan + Aprep (MEC) ^f	Palo + Aprep (HEC) ^g
Percentage of Patients with No Nausea									
Overall (0-120h)	61.5	58.2	50.3	33	48,49	nr	32 ^{nc1}	30.6	59.9 ^{nc1}
Acute (0-24h)	80.0	77.6	70.4	nr	nr,nr	nr	nr	nr	nr
Delayed (25-120h)	68.1*	60.4	53.3	nr	51,53	nr	nr	nr	nr
Percentage of Patients with No Significant Nausea									
Overall (0-120h)	89.6*	85.8	74.6*	61	73,71	88.5	56 ^{nc1}	66.1	91 ^{nc1}
Acute (0-24h)	98.5*	94.0	87.3	nr	nr,nr	nr	nr	nr	nr
Delayed (25-120h)	90.4*	88.1	76.9	nr	75,73	nr	nr	nr	nr

*Statistically Significant (p < 0.05)

nr Data Not Reported

nc1 Non-Comparative Study; statistical significance not evaluated

^a Helsinn Study NETU-07-07

^b Helsinn Study NETU-08-18

^c Warr *et al.* (2005) (Ref. D)

^{c1} FDA-Approved Prescribing Information for Emend[®] (aprepitant) (results of two studies reported) (Ref. E)

^d Herrington *et al.* (2008) (Ref. F)

^e Grunberg *et al.* (2008) (Ref. G)

^f Yeo *et al.* (2009) (Ref. H)

^g Longo *et al.* (2012) (Ref. I)

(Ex. 1005 at 345-46, ¶ 32.)

Azurity also argues that Columns 4 and 7 in Table 2 “excluded data from the studies it summarized when the data showed a similar effect for ondansetron and aprepitant versus netupitant and palonosetron, and instead indicated the data was ‘not reported.’” (Petition at 62 (citing Ex. 1009 at ¶¶ 1367-68).) Columns 4 and 7 set forth data from two publicly available documents, Warr (Ex. 1034) and Yeo (Ex. 1048), and expressly cite those documents within the table. These

publications were thus before the Office. Moreover, the data provided in these two publications is consistent with statements in the Rule 132 declaration that there was not a statistically significant effect of aprepitant on nausea. (Ex. 2069 at ¶¶ 124-25.)

Azurity further asserts that Column 4a in the Rule 132 declaration “[did] not include Emend’s ‘complete protection’ data, despite this parameter requiring evaluation of significant nausea.” (Petition at 62.) As discussed above, complete protection is a composite metric, and not a specific or appropriate measure of nausea. Moreover, data about complete protection does not inform a POSA about whether aprepitant has a specific effect on nausea. (Ex. 2069 at ¶ 117.)

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

VI. CONCLUSION

For at least these reasons, Helsinn respectfully requests that the Board deny the Petition for *inter partes* review of the ’515 patent.¹²

¹² If trial is instituted, Helsinn reserves the right to raise additional arguments as to why Azurity has failed to carry its burden and why the challenged claims should be confirmed.

Respectfully submitted,

Dated: September 4, 2025

By: /Eric W. Dittmann/
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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 Preliminary Response contains, as measured by the word-processing system used to prepare this paper, 8,202 words. This word count does not include the items excluded by 37 C.F.R. § 42.24.

Respectfully submitted,

Dated: September 4, 2025

By: /Eric W. Dittmann/
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CERTIFICATE OF SERVICE

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

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