

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 IPR2025-00945
Patent 8,623,826

PATENT OWNER'S SUR-REPLY

TABLE OF CONTENTS

I.	AZURITY’S REPLY CONFIRMS NO MOTIVATION TO COMBINE	1
A.	Azurity’s Reply Confirms That the Petition’s Legal Analysis Is Insufficient to Prove Obviousness	1
B.	The Reply’s Belated Attempt to Identify the Problem Facing a POSA Should Be Rejected.....	3
C.	Even Under Its Proposed Problem Facing a POSA, Azurity Has Failed to Show a Motivation to Combine.....	4
D.	Azurity’s References Do Not Support a Motivation to Combine.....	6
E.	Unable to Show a Motivation to Combine, Azurity’s Reply Resorts to Irrelevant Misdirection.....	8
II.	AZURITY’S REPLY CONFIRMS ITS FAILURE TO PROVE A REASONABLE EXPECTATION OF SUCCESS	10
A.	Claim 1 Requires Treating “Both” Nausea and Vomiting.....	10
B.	Claim 1 Requires a Statistically Significant Improvement in Both Nausea and Vomiting	12
C.	Azurity Has Not Shown a POSA Would Have Had a Reasonable Expectation of Success for at Least Claim 1	13
D.	Azurity’s Untimely “Restoration” Argument Fails	14
III.	AZURITY HAS FAILED TO SHOW THAT ITS CHOSEN ART DISCLOSES EVERY CLAIM LIMITATION.....	16
A.	No Disclosure of a “Therapeutically Effective Amount” of Netupitant That Meets the “Striatum-Occupancy” Limitation	16
1.	Azurity’s Interpretation of This Limitation Is Legally Unsupported.....	16
2.	Azurity Has Not Shown the “Striatum-Occupancy” Limitation Is Expressly Taught or Inherently Present.....	18
B.	No Disclosure of the “Improved Treatment” Limitation.....	20
IV.	AZURITY’S ATTORNEY ARGUMENT FAILS TO REBUT THE OBJECTIVE INDICIA CONFIRMING NONOBVIOUSNESS.....	21

A.	Azurity’s Response to Skepticism Relies on Two Misstatements of the Record.....	21
B.	Helsinn Has Proven Unexpected Results, Even Using the Test That Azurity’s Reply Prescribes.....	22
V.	AZURITY FAILS TO REHABILITATE DR. PEROUTKA’S QUALIFICATIONS	25

TABLE OF AUTHORITIES

	Page(s)
Cases	
<i>Allergan Sales, LLC v. Sandoz, Inc.</i> , 935 F.3d 1370 (Fed. Cir. 2019)	17, 18, 24
<i>Ariosa Diagnostics v. Verinata Health, Inc.</i> , 805 F.3d 1359 (Fed. Cir. 2015)	3, 14
<i>Auris Health, Inc. v. Intuitive Surgical Operations, Inc.</i> , 32 F.4th 1154 (Fed. Cir. 2022)	22
<i>Bayer Pharma AG v. Watson Labs., Inc.</i> , 874 F.3d 1316 (Fed. Cir. 2017)	9
<i>Best Med. Int'l, Inc. v. Elekta Inc.</i> , 46 F.4th 1346 (Fed. Cir. 2022)	25
<i>Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.</i> , 752 F.3d 967 (Fed. Cir. 2014)	22
<i>Cat Tech LLC v. TubeMaster, Inc.</i> , 528 F.3d 871 (Fed. Cir. 2008)	12
<i>In re Cyclobenzaprine Hydrochloride</i> , 676 F.3d 1063 (Fed. Cir. 2012)	21, 24
<i>Cytiva BioProcess R&D AB v. JSR Corp.</i> , 122 F.4th 876 (Fed. Cir. 2024)	4, 19
<i>Eli Lilly & Co. v. Teva Parenteral Medicines, Inc.</i> , 2012 WL 2358102 (S.D. Ind. June 20, 2012).....	11
<i>Endo Pharms. Sols., Inc. v. Custopharm Inc.</i> , 894 F.3d 1374 (Fed. Cir. 2018)	1
<i>Hoffer v. Microsoft Corp.</i> , 405 F.3d 1326 (Fed. Cir. 2005)	17, 18

<i>Insite Vision Inc. v. Sandoz, Inc.</i> , 783 F.3d 853 (Fed. Cir. 2015)	4
<i>Intel Corp. v. Qualcomm Inc.</i> , 21 F.4th 801 (Fed. Cir. 2021)	11
<i>InTouch Techs., Inc. v. VGO Commc'ns, Inc.</i> , 751 F.3d 1327 (Fed. Cir. 2014)	9
<i>L'Oreal USA, Inc. v. Olaplex, Inc.</i> , 844 F. App'x 308 (Fed. Cir. 2021).....	17
<i>Leo Pharm. Prods., Ltd. v. Rea</i> , 726 F.3d 1346 (Fed. Cir. 2013)	2, 3
<i>Minton v. Nat'l Ass'n of Sec. Dealers, Inc.</i> , 336 F.3d 1373 (Fed. Cir. 2003) (Reply, 7-8).....	17, 18
<i>Mintz v. Dietz & Watson, Inc.</i> , 679 F.3d 1372 (Fed. Cir. 2012)	4
<i>Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH</i> , 139 F.3d 877 (Fed. Cir. 1998)	7
<i>OSI Pharmaceuticals, LLC v. Apotex Inc.</i> , 939 F.3d 1375 (Fed. Cir. 2019)	14, 15
<i>Osseo Imaging, LLC v. Planmeca USA Inc.</i> , 116 F.4th 1335 (Fed. Cir. 2024)	26
<i>PAR Pharm., Inc. v. TWI Pharms., Inc.</i> , 773 F.3d 1186 (Fed. Cir. 2014)	16
<i>PersonalWeb Techs., LLC v. Apple, Inc.</i> , 917 F.3d 1376 (Fed. Cir. 2019)	19
<i>Phillips v. AWH Corp.</i> , 415 F.3d 1303 (Fed. Cir. 2005)	13
<i>Rambus Inc. v. Rea</i> , 731 F.3d 1248 (Fed. Cir. 2013)	24

<i>Sirona Dental Sys. GmbH v. Institut Straumann AG</i> , 892 F.3d 1349 (Fed. Cir. 2018)	3
<i>Teleflex, Inc. v. Ficosa N. Am. Corp.</i> , 299 F.3d 1313 (Fed. Cir. 2002)	12
<i>Virtek Vision Int'l ULC v. Assembly Guidance Sys., Inc.</i> , 97 F.4th 882 (Fed. Cir. 2024)	7
<i>WBIP, LLC v. Kohler Co.</i> , 829 F.3d 1317 (Fed. Cir. 2016)	7

LIST OF EXHIBITS

Exhibit No.	Description	Previously Submitted
2001	Curran, P. et al., <i>Aprepitant A Review of its Use in the Prevention of Nausea and Vomiting</i> , 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, <i>Casopitant: a novel NK1-receptor antagonist in the prevention of chemotherapy-induced nausea and vomiting</i> , 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

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

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

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	
2039	Navari et al, "Olanzapine for the Prevention of Chemotherapy-Induced Nausea and Vomiting", New England Journal of Medicine, 375(2), 134-142, 2016, https://doi.org/10.1056/NEJMoa1515725	X
2040	Reserved	
2041	Reserved	
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

Exhibit No.	Description	Previously Submitted
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

Exhibit No.	Description	Previously Submitted
2058	Shishido, Y. et al. "Discovery and stereoselective synthesis of the novel isochroman neurokinin-1 receptor antagonist 'CJ-17,493'." <i>Bioorganic & Medicinal Chemistry</i> 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." <i>Journal of Veterinary Pharmacology and Therapeutics</i> 30(4): 281-287 (2007)	X
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)	X
2061	Quartara, Laura and Altamura, Maria, "Tachykinin receptors antagonists: from research to clinic." <i>Current Drug Targets</i> 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-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)	X
2063	Shue, H. et al. "Cyclic urea derivatives as potent NK1 selective antagonists." <i>Bioorganic & Medicinal Chemistry Letters</i> 15(17): 3896-3899 (2005)	X
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)	X
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)	X

Exhibit No.	Description	Previously Submitted
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-piperidiny]-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	IPR2025-00945: Declaration of Rudolph Modesto Navari, M.D., Ph.D, F.A.C.P.	X
2068	Reserved	
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., <i>Comparison of an aprepitant regimen with a multiple-day ondansetron regimen, both with dexamethasone, for antiemetic efficacy in high-dose cisplatin treatment</i> , Annals of Oncology 17:1000-1006 (2006)	X
2074	<i>Emesis, Vomiting</i> , Black's Medical Dictionary (41 st ed. 2005)	X
2075	Bloechl-Daum, B. et al., <i>Delayed Nausea and Vomiting Continue to Reduce Patients' Quality of Life After Highly and Moderately Emetogenic Chemotherapy Despite Antiemetic Treatment</i> , J. Clin. Oncol. 24:4472-4478 (2006)	X
2076	Guidance for Industry, E9 Statistical Principles for Clinical Trials (Sept. 1998)	X
2077	Press Release – GSK provides update on regulatory filings for Zunrisa/Rezonic, September 27, 2009	X

Exhibit No.	Description	Previously Submitted
2078	Hamik, A. and Peroutka, S., <i>Differential interactions of traditional and novel antiemetics with dopamine D₂ and 5-hydroxytryptamine₃ receptors</i> , Cancer Chemother Pharmacol 24:307-310 (1989)	X
2079	Ison. P. and Peroutka, S., <i>Neurotransmitter Receptor Binding Studies Predict Antiemetic Efficacy and Side Effects</i> , Cancer Treatment Reports Vol. 70, No. 5, 637-641 (May 1986)	X
2080	January - March 2018 Potential Signals of Serious Risks/New Safety Information Identified from the FDA Adverse Event Reporting System (FAERS)	X
2081	Jordan, K. et al., <i>Chemotherapy-induced nausea and vomiting: current and new standards in the antiemetic prophylaxis and treatment</i> , European Journal of Cancer, 41 (2005) 199-205	X
2082	O'Brien, M.E.R. et al., <i>The role of metoclopramide in acute and delayed chemotherapy induced emesis: a randomised double blind trial</i> , Br. J. Cancer, 60 (1989) 759-763	X
2083	Peroutka, S., <i>Combination Antiemetics</i> , Cancer Treatment Reports, Vol. 66, No. 6, (June 1982) 1449	X
2084	Peroutka, S., <i>Chemotherapeutic agents do not interact with neurotransmitter receptors</i> , Cancer Chemother Pharmacol 19:131-132 (1987)	X
2085	Guidance for Industry, Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products (May 1998)	X
2086	Deposition transcript of Stephen J. Peroutka, taken on January 13, 2026	X
2087	Eric Roeland, MD, FASCO, FAAHPM Curriculum Vitae	X
2088	IPR2025-00945 - Declaration of Eric Roeland, MD, FASCO, FAAHPM	X
2089	RESERVED	

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

Exhibit No.	Description	Previously Submitted
2104	Declaration of Justin T. Fleischacker (Not Filed)	Served, Not filed

Helsinn's Patent Owner Response ("POR") showed that Azurity's Petition failed to prove that any challenged claim would have been obvious. Azurity's Reply ("Reply"), unaccompanied by expert testimony and lacking any attempt to rehabilitate the determinative deposition concessions from Dr. Peroutka cited throughout Helsinn's POR, fails to plug the numerous holes in the Petition's obviousness grounds.

I. AZURITY'S REPLY CONFIRMS NO MOTIVATION TO COMBINE

Azurity has not proven that a POSA would have been motivated to combine its cited prior art. *Endo Pharms. Sols., Inc. v. Custopharm Inc.*, 894 F.3d 1374, 1380-81 (Fed. Cir. 2018) (obviousness not proven where challenger had not "affirmatively demonstrate[d] that a skilled artisan would have been motivated to [follow the proposed path] despite no clear evidence of [a recognized problem]"). The Board can confirm patentability of each claim on this basis alone.¹

A. Azurity's Reply Confirms That the Petition's Legal Analysis Is Insufficient to Prove Obviousness

Helsinn's POR explained that, to prove obviousness, a patent challenger must identify the problem facing a POSA because "[o]nly after recognizing the existence of the problem would an artisan *then* turn to the prior art" to address this

¹ Azurity's Reply invokes unsupported claim construction positions (*see* Reply, 2-9, 12-13, 17-21), which are not material to Azurity's failure to prove a motivation to combine. These are addressed in Sections II and III, *infra*.

problem. (POR, 2, 26-29 (quoting *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1354 (Fed. Cir. 2013) (emphasis in original)².) Identifying this problem is not a performative exercise; it is fundamental to the motivation-to-combine analysis and guards against hindsight bias. This is because a skilled artisan would not have blindly combined different pieces of art in the abstract, but in pursuit of addressing a recognized problem. *See Leo Pharm.*, 726 F.3d at 1354 (“[B]ecause neither Dikstein nor Serup recognized or disclosed the stability problem, the record shows no reason for one of ordinary skill in the art to attempt to improve upon either Dikstein or Serup using Turi. The ordinary artisan would *first* have needed to recognize the problem . . .”).

Azurity's Reply implicitly concedes this to be the correct legal inquiry, disputing only how the problem facing a POSA should be defined. (Reply, 13-14.) But the Reply cannot identify *where* the Petition or Dr. Peroutka identified the problem facing a POSA and analyzed obviousness in view of any problem. (*Id.*, 1, 13-14; Ex. 2086, 108:4-10 (Dr. Peroutka testifying that he did not even understand the concept of the problem facing a POSA).) The Petition therefore failed to show that a POSA would have been motivated to combine the disparate disclosures of its references without hindsight. *Leo Pharm.*, 726 F.3d at 1354.

² Unless otherwise noted, all emphasis has been added, and all internal citations have been omitted.

B. The Reply's Belated Attempt to Identify the Problem Facing a POSA Should Be Rejected

On Reply, Azurity now contends that the Board identified the problem as “treating CINV.” (Reply, 14 (citing Decision, 25).) As an initial matter, “treating CINV” identifies no flaw in the MASCC/Herrstedt aprepitant treatment regimens that would guide a POSA to any alteration thereto. *See, e.g., Leo Pharm.*, 726 F.3d at 1354 (obviousness not proven where “the record shows no reason for one of ordinary skill in the art to attempt to improve upon either Disktein or Serup using Turi”). And when read in context, the Board used the phrase “problem of treating CINV” to paraphrase Helsinn’s POPR argument, not as a declaration of the problem facing a POSA. (Decision, 24-25.) Moreover, Azurity’s pivot to the Board’s Decision signals that its Petition lacks the required analysis, and its untimely argument should be disregarded. *E.g., Ariosa Diagnostics v. Verinata Health, Inc.*, 805 F.3d 1359, 1367-68 (Fed. Cir. 2015); *Sirona Dental Sys. GmbH v. Institut Straumann AG*, 892 F.3d 1349, 1356 (Fed. Cir. 2018).

Azurity’s reliance on the ’826 patent similarly fails. Azurity argues that the ’826 patent “defined the field broadly as ‘the use of centrally acting NK antagonists to treat nausea and vomiting’” (Reply, 13; *see also* Reply, 16 (relying on the claims).) But the specification excerpt cited by Azurity identifies the “Field of *the Invention*” (Ex. 1001, 1:17-24), and black-letter law dictates that “[i]n considering motivation in the obviousness analysis, the problem examined is

not the specific problem solved by the invention.” *Insite Vision Inc. v. Sandoz, Inc.*, 783 F.3d 853, 859 (Fed. Cir. 2015); *see also Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012).³

C. Even Under Its Proposed Problem Facing a POSA, Azurity Has Failed to Show a Motivation to Combine⁴

The Reply confirms Helsinn’s explanation that Azurity’s cited evidence fails to substantiate the motivation to combine prescribed by the Petition, Azurity’s own expert, and the Institution Decision. (*See, e.g.*, POR, 29-30, 36-42.)

Azurity concedes that its theories require a POSA looking to “treat[] CINV” (Reply, 14) in November 2009 to have believed (without the benefit of Helsinn’s clinical data) that netupitant represented a “new, *improved* drug[],” as compared to aprepitant (*id.*). (*See also* Petition, 17 (arguing netupitant to be “an improved NK₁

³ Azurity appears to imply that *Cytiva BioProcess R&D AB v. JSR Corp.*, 122 F.4th 876 (Fed. Cir. 2024) obviates the problem-facing-a-POSA analysis. (Reply, 16.) But the portion of *Cytiva* cited by Azurity merely instructed that “[a] lead-compound analysis is not required where the prior-art references expressly suggest the proposed modification.” *Cytiva*, 122 F.4th at 884. Here, Azurity’s obviousness theories rely on combining references in ways not disclosed by the references themselves—*i.e.*, altering the disclosed aprepitant regimen and incorporating netupitant.

⁴ On Reply, Azurity does not meaningfully allege that it has proven obviousness when applying the problem facing a POSA articulated by Helsinn and its expert. (*See* Reply, 13 (instead alleging that “[n]ausea was not the only problem confronting the POSA”).)

antagonist”), 22 (arguing netupitant to have an “improved profile” over “the older aprepitant”).) Azurity has not made this showing.

Each of Azurity’s grounds is rooted in the “MASCC” or “Herrstedt” references, which Azurity cites as describing a “three-drug” regimen that includes aprepitant, a 5-HT₃-receptor antagonist, and dexamethasone. (*E.g.*, Petition, 18.) By November 2009, this regimen was considered the “gold-standard” for treating patients suffering from CINV. (Ex. 2088, ¶62; *see also* Reply, 23.) But because MASCC and Herrstedt do not describe netupitant, Azurity’s obviousness grounds would require a POSA to *change* that gold-standard regimen and risk worse outcomes in a vulnerable patient population when looking to “treat[] CINV.” (Reply, 14.)

The expert testimony shows, however, that “a POSA would have no reason to alter aprepitant-based triple therapy . . . unless the POSA had reason to expect that this change would actually provide a better patient outcome.” (Ex. 2088, ¶219; Ex. 2086, 293:19-294:10 (Dr. Peroutka agreeing that a POSA “would not change the aprepitant triple therapy unless they believed that the change would provide at least similar or better patient outcome”).) But Azurity cites no evidence supporting—and has not proven—its allegation that a POSA would have considered netupitant to be a “new, improved drug[]” (Reply, 14) as compared to aprepitant, or even an equivalent thereof. It is undisputed that Azurity and its

expert did not directly compare aprepitant and netupitant (*e.g.*, for structural properties, biological activity, pharmacodynamics, or safety). Without any such comparison, Azurity necessarily failed to prove that a POSA would have recognized netupitant as an improvement over (or equivalent to) aprepitant. (POR, 30-31, 37-38, 40-42, 45-46; Ex. 2086, 240:25-241:3, 242:25-243:5, 253:7-255:15, 280:21-281:19.) Azurity cannot sustain the very motivation-to-combine burden that its Petition, its own expert, and its Reply self-prescribe.

D. Azurity's References Do Not Support a Motivation to Combine

Unable to counter the evidentiary gaps exposed by Helsinn's POR, Azurity's Reply glosses over key pieces of the motivation-to-combine analysis when discussing its chosen art. Azurity claims, for instance, that "Hoffman and Bös provide ample direction to those seeking an NK₁-inhibitor to employ *instead of aprepitant*." (Reply, 19.) But Azurity has not substantiated that a POSA would have been "seeking" to replace aprepitant at all. Indeed, the only mention in Azurity's Reply as to why a POSA would have been motivated to do so is "to enhance the efficacy of the existing combination with new, improved drugs" (*id.*, 14), which fails to point towards netupitant out of the "remarkable number of small molecule NK₁ receptor antagonists [that] were identified by many pharmaceutical companies" (Ex. 1011, 1362) before 2009. Azurity's own expert confessed that he had not considered the wealth of different NK₁ inhibitors known by November

2009, let alone shown that a POSA would have plucked netupitant out of that numerous bunch. (*See* POR, 35.)⁵

Likewise, the Reply (as with the Petition) relies on Hoffman and Bös without showing that a POSA would have been motivated to turn to those specific references. Azurity's obviousness arguments therefore would fail even if Azurity had proven that a POSA would have been motivated to alter the "gold-standard" aprepitant regimen. *See WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1337 (Fed. Cir. 2016) ("Whether a skilled artisan would be motivated to make a combination includes whether he would select particular references in order to combine their elements."). Azurity's expert conceded that he turned to these references because netupitant is "the subject of this patent dispute" (Ex. 2086, 127:5-10), but that hindsight-driven reconstruction of the claimed inventions is legally insufficient to support a motivation to combine. *See, e.g., Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH*, 139 F.3d 877, 881 (Fed. Cir. 1998) (warning against "improper hindsight in the selection of the prior art relevant to obviousness").

⁵ The availability of a "remarkable number of [other] NK₁ receptor antagonists" and lack of any motivation to combine Hoffman/Bos with MASCC/Herrstedt equally defeats Azurity's "obvious-to-try" allegations (Reply, 19). *See, e.g., Virtek Vision Int'l ULC v. Assembly Guidance Sys., Inc.*, 97 F.4th 882, 886-87 (Fed. Cir. 2024).

Given these fundamental flaws, Azurity's Reply attempts to read into its references more than they support. For example, Azurity alleges, "That a POSA could also pursue a quadruple (or more) therapy with all the additional costs and risk does not detract from the simple substitution that Hoffman suggested."

(Reply, 16.) But Hoffman suggests no substitution, let alone for the treatment of both nausea and vomiting induced by chemotherapy. Indeed, while Hoffman recounts that "MK-869 (aprepitant) was the first NK₁ receptor antagonist to receive marketing approval," Hoffman does not suggest that any of its 31 compounds (including netupitant) improve upon or are interchangeable with aprepitant. (*See* Ex. 2088, ¶172.)

**E. Unable to Show a Motivation to Combine,
Azurity's Reply Resorts to Irrelevant Misdirection**

First, Azurity argues that "[a] POSA does not require FDA approval [of netupitant] before attempting an otherwise promising substitution." (Reply, 15.) But the question is not whether netupitant was FDA-approved by November 2009, but if (as discussed above) a POSA would have believed that netupitant was a superior (or even equivalent) therapeutic option to the FDA-approved aprepitant. Without directly comparing the pharmacological properties of the two molecules (which Azurity has not done), Azurity cannot show a POSA would have considered replacing aprepitant with netupitant, let alone that this would be a "promising" substitution for vulnerable human patients. (Ex. 2088, ¶¶219-34.)

Second, Azurity cites inapposite caselaw stating that “[o]bviousness does not require that the motivation be the best option.” (Reply 16-17 (citing *Bayer Pharma AG v. Watson Labs., Inc.*, 874 F.3d 1316, 1328 (Fed. Cir. 2017).) *Bayer*, however, does not absolve Azurity from needing to show that a POSA would have been motivated to take the path urged by Azurity: **stopping** aprepitant therapy and replacing aprepitant with netupitant based on the belief netupitant would provide better clinical results. *See InTouch Techs., Inc. v. VGO Commc'ns, Inc.*, 751 F.3d 1327, 1352 (Fed. Cir. 2014) (obviousness not proven where challenger “failed to address why one of ordinary skill in the art *at the time of the invention*” would have been motivated to combine cited art).

Third, Azurity's suggestion that “a POSA would have reason to substitute netupitant for aprepitant simply expecting it to act suitably as an NK₁-inhibitor with dexamethasone and palonosetron” fails to support obviousness. (Reply, 17.) Membership in a large class of molecules says nothing about the comparative performance of two specific class members. (Ex. 2088, ¶ 232 (discussing differing NK₁ inhibitor properties); Ex. 2096, 1812-13 (“[I]t is very likely that tens of thousands of molecules have been prepared in the past decade as substance P antagonists, a large percentage of which likely exhibited sub-nanomolar potency at the NK-1 receptor, but only one has made it to market.”).) Moreover, applying Azurity's own logic, a POSA could have substituted any of the “remarkable

number of small molecule NK₁ receptor antagonists [that] were identified by many pharmaceutical companies” before November 2009 (Ex. 1011, 1362) and “expect[ed] [them] to act suitably” (Reply, 17). (*See, e.g.*, Ex. 2088, ¶¶232-33.) Therefore, mere classification as an NK₁ inhibitor would not have directed a POSA to netupitant specifically.

II. AZURITY’S REPLY CONFIRMS ITS FAILURE TO PROVE A REASONABLE EXPECTATION OF SUCCESS

Lacking data for netupitant, Azurity’s Reply (17-18) roots its expectation-of-success analysis in data for aprepitant and casopitant. But Azurity fails to reckon with the POR’s demonstration that Azurity has supplied no support for such a comparison. (*E.g.*, POR, 42-47.) Moreover, the Reply’s approach to claim 1—the claim for which Azurity supplies individualized analysis (*see* Reply, 19-21)—makes plain the fatal gaps in Azurity’s Petition with respect to the “reasonable-expectation-of-success” requirement.

A. Claim 1 Requires Treating “Both” Nausea and Vomiting⁶

Claim 1 recites a method of treating “a patient”⁷ in which, *inter alia*, “steps (a), (b) and (c) [(i.e., triple therapy with netupitant)] are effective to treat ***both***

⁶ Independent claim 19 likewise requires treatment of both nausea and vomiting.

⁷ Azurity incorrectly asserts that only one independent claim, claim 19, “requires a human subject.” (Reply, 17.) Claim 1, the other independent claim,

nausea and vomiting to a greater extent during the period defined by days one through 5 than steps (b) and (c) alone [(i.e., two-drug therapy)].”

Both experts agree that nausea and vomiting are “separate and distinct” afflictions. (Ex. 2088, ¶32; Ex. 2086 at 38:8-39:24.) Accordingly, a POSA would understand treating “both nausea and vomiting,” as recited in claim 1, to require that nausea is treated **and** vomiting is treated. (Ex. 2088, ¶175.) Any other reading of this phrase renders the claim term, “both,” “void, meaningless, or superfluous”—a “highly disfavored” outcome. *Intel Corp. v. Qualcomm Inc.*, 21 F.4th 801, 810 (Fed. Cir. 2021). Azurity’s suggestion that a “net improvement for these parameters together meets claim 1” (Reply, 4) is unfaithful to the claim language. Were Azurity correct, this limitation would be met where triple therapy worsens nausea, but improves vomiting to a slightly greater degree, which plainly would

recites a method of treating both nausea and vomiting . . . in a **patient** in need thereof.” (Ex. 1001, 21:39-40.) The specification makes clear that the claimed invention is directed to the “**clinical** effects of netupitant” (*id.*, 4:37-42) and to the **clinical** (i.e., human) “CINV patient population” (*id.*, 16:65-21:24). The specification makes no reference to any other type of patient, referring only to dosages applicable to human patients (e.g., *id.*, 17:4-33). *Cf. Eli Lilly & Co. v. Teva Parenteral Medicines, Inc.*, 2012 WL 2358102, at *7 (S.D. Ind. June 20, 2012) (“[POSA] would understand the term ‘patient’ when discussed in the context of a clinical trial [described in the specification] to involve a human undergoing medical treatment and not a mammal.”).

not constitute a treatment of “both” nausea and vomiting.⁸ *See Cat Tech LLC v. TubeMaster, Inc.*, 528 F.3d 871, 885 (Fed. Cir. 2008).

B. Claim 1 Requires a Statistically Significant Improvement in Both Nausea and Vomiting

Azurity alleges that “Helsinn also imports into claims 1 and 19 a requirement for statistically-significant efficacy for treatment (POR 18), but the express claim language and the specification contradict this assertion.” (Reply, 5.) Azurity, however, cites only one portion of the ’826 specification (column 8, lines 31-34). (*Id.*) That portion rebuts Azurity’s own argument, stating 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 upon its *statistical significance* relative to a baseline.” (Reply, 5 (quoting Ex. 1001, 8:28-31).) The specification then continues: “[W]hen a *treatment* is described herein, it will be understood that the treatment shows efficacy to a degree of *statistical significance*.” (Ex. 1001, 8:32-34.)

Claim 1 recites such a method of “treatment,” defined by the “measurable result or effect” of treating both nausea and vomiting. Claim 1 requires this

⁸ Azurity’s invocation (Reply, 4) of other FDA metrics (*i.e.*, “complete protection and reduced rescue medication,” *id.*) fails to track the “actual words of the claim” (“both nausea and vomiting”), which must control. *E.g.*, *Teleflex, Inc. v. Ficosa N. Am. Corp.*, 299 F.3d 1313, 1324 (Fed. Cir. 2002).

“treatment” to be “to a greater extent” than is provided by “steps (b) and (c) alone.” (Ex. 1001, 21:61-64.) Therefore, the ordinary meaning of “treatment” in the context of claim 1 requires treatment of both nausea and vomiting to a statistically significant degree, as compared to the recited “baseline.” *Phillips v. AWH Corp.*, 415 F.3d 1303, 1321 (Fed. Cir. 2005).

C. Azurity Has Not Shown a POSA Would Have Had a Reasonable Expectation of Success for at Least Claim 1

Azurity has failed to prove that a POSA would have reasonably expected a three-drug regimen (netupitant, palonosetron, and dexamethasone) to “treat *both* nausea and vomiting” to a statistically significant greater extent than a two-drug regimen (palonosetron and dexamethasone), as claimed. (POR, 42-53.)

Azurity's Petition merely invokes “superior response rates (complete response)” for a “combination lacking NK₁ antagonist.” (Petition, 50; Ex. 1009, ¶382; POR, 61-62.) Azurity's Reply, however, does not dispute Dr. Roeland's explanation that the complete response metric relied upon in the Petition does not “include nausea as a stated parameter.” (Ex. 2088, ¶53.) Further, the Reply invokes only an alleged “*numerical* improvement in nausea parameters”—not a statistically significant improvement—under the erroneous theory that a “statistically-significant improvement in nausea treatment” is not required. (Reply, 18-19 (emphasis in original); see POR, 49.)

Therefore, Azurity has offered no evidence that a POSA would have reasonably expected to use a three-drug regimen (including netupitant) to achieve the claimed statistically significant improvement in treating both vomiting and nausea, as compared to a two-drug regimen. *See OSI Pharmaceuticals, LLC v. Apotex Inc.*, 939 F.3d 1375, 1382 (Fed. Cir. 2019).

D. Azurity's Untimely "Restoration" Argument Fails

Perhaps recognizing the gaps in its Petition, Azurity's Reply appears to pivot to asserting that any required reduction in nausea is met by *dexamethasone*. Specifically, Azurity suggests—without any analysis of statistical significance—that a POSA would have expected the claimed anti-nausea benefits to be achieved “by restoring dexamethasone’s effectiveness against nausea from an ineffective half-dose back to a full-dose via NK₁-inhibitor enhancement.” (Reply, 3; *see id.*, 20-21.)

Azurity could have raised (but did not) this argument in its Petition. Instead, Azurity relied on measurements of “complete protection” (Petition, 42, 50-51) and its now-abandoned argument that “[a]prepitant show[ed] efficacy for nausea” (Petition, 59). Azurity's dexamethasone “restor[ation]” argument is therefore improper reply argument that should be disregarded. *E.g., Ariosa*, 805 F.3d at 1367.

Regardless, Azurity's new argument—citing to no evidence—fails. Azurity seems to be alleging that pairing an NK₁ antagonist with dexamethasone will *always* result in a statistically significant improvement in the treatment of nausea, as compared to an equivalent dose of dexamethasone without the NK₁ inhibitor. But this cannot be true, as Azurity's own expert testified that NK₁ antagonists can *cause* nausea, thus worsening nausea treatment. (Ex. 2086, 155:9-13, 156:10-17, 157:22-158:24, 159:21-160:5.)

Moreover, Azurity's contention that pairing dexamethasone with an NK₁ antagonist would always amplify the anti-nausea properties of dexamethasone to a statistically significant degree is rebutted by the prior art, which found “no difference in the nausea domain” between a therapy regimen with and without the NK₁ antagonist aprepitant. (Ex. 1048, 534; *see also* Ex. 2088, ¶¶87-151 (Dr. Roeland discussing prior art showing aprepitant was not effective against nausea).) And Azurity's own expert testified that a POSA would have expected “aprepitant and netupitant to achieve comparable anti-emetic and anti-nausea effects.” (Ex. 1009, ¶341.) A POSA would have thus expected similar failure, not success, in using a netupitant-based therapy to treat nausea to a statistically significant degree, just as with aprepitant. *OSI*, 939 F.3d at 1385.

III. AZURITY HAS FAILED TO SHOW THAT ITS CHOSEN ART DISCLOSES EVERY CLAIM LIMITATION

Azurity's Reply (Reply, 6-8, 19-21) fails to rebut Helsinn's showing that the prior art does not disclose at least two limitations of claim 1, defeating at least grounds 4-7. (POR, 57-63.) *See, e.g., PAR Pharm., Inc. v. TWI Pharms., Inc.*, 773 F.3d 1186, 1194 (Fed. Cir. 2014).

A. No Disclosure of a “Therapeutically Effective Amount” of Netupitant That Meets the “Striatum-Occupancy” Limitation

1. Azurity's Interpretation of This Limitation Is Legally Unsupported

Helsinn's Response explained that the cited references do not disclose administering a “therapeutically effective amount” of netupitant,” “which . . . crosses the blood brain barrier and occupies at least 70% of neurokinin-1 (NK₁) receptors in the striatum seventy-two hours after said administration.” (POR, 57-60; Ex. 2088, ¶¶188-98.) Azurity's retort that “[c]laim 1's striatum-occupancy element is descriptive” (Reply, 5, 16) and need not be disclosed in the prior art is meritless.

Azurity erroneously contends that “claim 1 does not specify a dosage.” (*Id.*; *see* POR, 22-24.) But the claim language requires that the dosage (*i.e.*, the “therapeutically effective amount”) in the recited method is one sufficient to “occup[y] at least 70% of the neurokinin-1 (NK₁) receptors in the striatum seventy-two hours after said administration.” (Ex. 1001, 21:43-46.) The “striatum-

occupancy” limitation (*i.e.*, the portion of the limitation beginning with “which”) dictates the amount of netupitant administered and thus defines claim scope. (*See* Ex. 1001, Fig. 5, 16:53-60.)

The specification confirms that the “striatum-occupancy” limitation defines the claim scope. The Federal Circuit has found similar clauses limiting where they are “part of the [claimed] process itself” or shown by the intrinsic record to be “material to patentability.” *See, e.g., Hoffer v. Microsoft Corp.*, 405 F.3d 1326, 1330 (Fed. Cir. 2005) (“This capability is more than the intended result of a process step; it is part of the process itself.”); *Allergan Sales, LLC v. Sandoz, Inc.*, 935 F.3d 1370, 1376 (Fed. Cir. 2019) (looking to intrinsic evidence); *L'Oreal USA, Inc. v. Olaplex, Inc.*, 844 F. App'x 308, 324 (Fed. Cir. 2021) (“[I]n requiring specific decreases (e.g., 5%, 10% . . .) in hair breakage, they state specific requirements”). Here, not only are the claimed receptor occupancy levels “part of the [claimed method] itself” (*i.e.*, defining the netupitant dosage to be administered), the specification describes the receptor occupancy benefits as an improvement over the prior art. (*See* Ex. 1001, 4:42-64.)

Azurity invokes *Minton v. Nat'l Ass'n of Sec. Dealers, Inc.*, 336 F.3d 1373 (Fed. Cir. 2003) (Reply, 7-8), but the Federal Circuit has found it inapplicable on

similar facts.⁹ In *Hoffer*, for instance, the court found *Minton* inapposite because, “when the ‘whereby’ clause states a condition that is material to patentability, it cannot be ignored in order to change the substance of the invention.” *Hoffer*, 405 F.3d at 1329; *see also Allergan Sales, LLC*, 935 F.3d at 1379 (Fed. Cir. 2019) (Prost, CJ., concurring) (distinguishing *Minton*). Applied here, the “striatum-occupancy” limitation defines the method claimed by dictating the therapeutically effective amount of netupitant to be administered, and *Minton* does not support “chang[ing] the substance of th[at] invention.” *Id.*

2. Azurity Has Not Shown the “Striatum-Occupancy” Limitation Is Expressly Taught or Inherently Present

Azurity’s Reply does not contest the POR’s showing that the Petition did not identify disclosure of the claimed “therapeutically effective amount of [netupitant].” (POR, 57-60; *see* Reply, 19-20.) Instead, Azurity points to *other* drugs and argues that “[T]he petition used Hargreaves to show that the art used striatum occupancy as a proxy for NK₁-inhibitor therapeutic effectiveness.” (Reply, 19-20.)

⁹ Azurity cites the dependent claims as purported support for its “striatum-occupancy” construction (Reply, 7-8), but they merely narrow the “therapeutically effective” netupitant dosages, and do not support Azurity’s attempt to read out this claim limitation.

In doing so, Azurity's Reply turns to inherency. (*Id.*, 20 ("Because netupitant is an NK₁-inhibitor, an effective amount of netupitant ***must*** meet Hargreaves receptor-occupancy threshold.")) While somewhat unclear, Azurity seems to be contending that any amount of any NK₁ inhibitor that treats both nausea and vomiting will ***necessarily*** "occup[y] at least 70% of neurokinin-1 (NK₁) receptors in the striatum seventy-two hours after" administration. But Azurity has not provided any evidence to substantiate such a broad proposition. (See Ex. 2088, ¶¶192-93.) Indeed, Azurity's own expert confirmed that he provided no explanation for why aprepitant dosing or receptor occupancy would inform the same for netupitant. (POR, 59.) That leaves only Azurity's attorney argument "say so," which is legally insufficient to show that every conceivable NK₁ receptor antagonist, at any dose, will necessarily and inevitably occupy the NK₁ receptors in the manner claimed. See, e.g., *Cytiva*, 122 F.4th at 889 n.15 ("Simply saying [a limitation is inherent] without sufficient evidence will not demonstrate unpatentability."); *PersonalWeb Techs., LLC v. Apple, Inc.*, 917 F.3d 1376, 1382 (Fed. Cir. 2019).

But even if Azurity's inherency theory were correct, it still would not support a finding of obviousness. Claim 1 and its dependent claims require a sufficient dose of netupitant that achieves the claimed receptor occupancy and specific treatment results. Hargreaves does not guide a POSA to any specific dose

of any NK₁ inhibitor beyond aprepitant, nor does any other prior art cited by Azurity. Hargreaves's study is rooted in aprepitant doses already determined to be effective (*i.e.*, the FDA-approved "125-mg/80-mg aprepitant regimen"). (Ex. 1012, 23.) No such dosing information was available for netupitant by November 2009. And confirming that Hargreaves's disclosures were not generally applicable to NK₁ receptor antagonists, a 300 mg dose of netupitant was ultimately approved for human use—nearly three times higher than the approved aprepitant dose. And as explained in the POR, Azurity's own expert testified that a given dose of netupitant may cause nausea, even if it provides emesis relief. (*See* POR, 51-52.)

B. No Disclosure of the "Improved Treatment" Limitation

As discussed above (Sections II.A-D), claim 1 requires treating both nausea and vomiting using a three-drug regimen to a degree that is statistically superior to a two-drug regimen (lacking netupitant). No prior art relied upon by Azurity discloses this limitation, either expressly or inherently. (POR, 60-63.) The MASCC/Herrstedt references disclose only treatment results with aprepitant (not netupitant) while the remainder of Azurity's references (*e.g.*, Hoffman/Bös) do not teach treating vomiting or nausea with netupitant.

**IV. AZURITY'S ATTORNEY ARGUMENT FAILS TO REBUT
THE OBJECTIVE INDICIA CONFIRMING NONOBVIOUSNESS**

Dr. Roeland explained that objective evidence, including unexpected results and skepticism, weighs heavily in favor of nonobviousness. (Ex. 2088, ¶¶251-68; POR, 63-66.) *In re Cyclobenzaprine Hydrochloride*, 676 F.3d 1063, 1079 (Fed. Cir. 2012). Azurity submitted no contrary expert testimony, and its attorney argument (Reply, 21-25) fails.

**A. Azurity's Response to Skepticism
Relies on Two Misstatements of the Record**

Azurity alleges that “Helsinn asserts skepticism in the prior art based solely on Dr. Roeland’s testimony.” (Reply, 24.) But Azurity’s *own* cited literature showed that nausea was considered to be “the main problem” associated with life-extending chemotherapy treatment by a “majority of patients” in 2009. (Ex. 1010, 143; POR, 6-8.) Azurity’s literature showed aprepitant’s failure to make a “difference in the nausea domain” led to the conclusion that “nausea is possibly related to some other neurotransmitters for which aprepitant has limited efficacy.” (Ex. 1048, 534; *see* Ex. 1034, 2828-29.) The invention of the ’826 patent overcame this skepticism by showing that an NK₁ antagonist could impact nausea, and that a netupitant-based regimen provides a statistically significant

improvement in nausea and significant nausea in human cancer patients.

(See Ex. 1001, 19-20 (Table 6).)¹⁰

Azurity suggests that prior art “skept[icism] about using NK1-inhibitors to treat nausea is a red herring because it does not correlate to the limitations of claims 1 and 19.” (Reply, 25.) Azurity’s position ignores that the claims plainly recite treating both nausea and vomiting. (Section II.A, *supra*.) Azurity also supplies no legal support for its contention that skepticism is “relevant” only where it correlates directly to the challenger’s (failed) motivation theory. (Reply, 25.)

**B. Helsinn Has Proven Unexpected Results,¹¹
Even Using the Test That Azurity’s Reply Prescribes**

Azurity’s Reply states that a patentee can prove unexpected results by showing “a difference in kind rather than a difference of degree.” (Reply, 22.) A patentee may make this showing by identifying “a new property dissimilar to the known property.” *Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.*, 752 F.3d

¹⁰ Azurity’s invocation of “generic industry skepticism” (Reply, 24-25) is unavailing where the relevant skepticism is not “generic to the field,” but “specific to the invention” (*i.e.*, the ability of an NK₁ antagonist to treat nausea). *Auris Health, Inc. v. Intuitive Surgical Operations, Inc.*, 32 F.4th 1154, 1159 (Fed. Cir. 2022).

¹¹ Much of Azurity’s unexpected results analysis rehashes its motivation and claim construction arguments. (Reply, 22-23.) To the extent these arguments are even relevant to the objective indicia inquiry, they fail for the same reasons discussed above.

967, 977 (Fed. Cir. 2014). Dr. Roeland's testimony confirms that Helsinn has demonstrated two such "new propert[ies]": the claimed methods' nausea-treatment benefits, and the synergy between netupitant and palonosetron. (Ex. 2088, ¶¶ 259-68.)

Controlling nausea: Azurity alleges that the "closest prior art" is "the aprepitant-palonosetron-dexamethasone treatment" (Reply 22-23) described in, for instance, Azurity's Herrington reference (Ex. 1016). Herrington evaluated three treatment "arms:" two that combined aprepitant/palonosetron/dexamethasone, and one with only palonosetron/dexamethasone. (*Id.*, 2081.) Herrington found that both the "incidence" and "severity" of nausea "was not different among the 3 arms" (Ex. 1016, 2084), meaning that addition of aprepitant to the palonosetron/dexamethasone combination conferred no anti-nausea benefits. (*See also* Ex. 1030, 5 (FDA-approved label for EMEND[®] (aprepitant) reporting no statistically significant improvement in nausea).)

Helsinn's POR explained that the '826 patent specification discloses, in contrast, that addition of netupitant to a palonosetron-dexamethasone combination did provide a statistically significant benefit in the treatment of nausea. (POR, 64-66.) Azurity's Reply did not contest this clinical data, and Azurity is incorrect in suggesting that Helsinn merely "points to percentage improvements (at best a difference of degree) from the substitution of netupitant for aprepitant."

(Reply, 23.) As the evidence makes clear, netupitant treats nausea, and aprepitant did not.¹²

Synergy: The inventors did not “hypothesize[] a synergy between netupitant and palonosetron” (Reply, 23), as Azurity alleges. Instead, the inventors proved that synergy with experimental evidence. (Ex. 2088, ¶¶266-67 (citing Ex. 1055, 343).) While Azurity postulates that palonosetron might show similar synergy “with any NK₁-inhibitor” (Reply, 23), it identifies no supportive testing or evidence. Indeed, while Azurity’s own cited literature reports “synergistic effects” between palonosetron and netupitant, it notes that “[i]t is not clear” whether palonosetron’s activity “would be synergistic, additive, or obscured when used in combination with [other] NK1 receptor antagonists.” (Ex. 1045, 2638.) These objective indicia further confirm Azurity’s failure to prove obviousness.¹³

¹² Azurity’s attempt to fault the specification for not reporting data with every possible netupitant dosage (Reply, 24) fails. *See Rambus Inc. v. Rea*, 731 F.3d 1248, 1257 (Fed. Cir. 2013) (“[W]e do not require a patentee to produce objective evidence of nonobviousness for every potential embodiment of the claim.”).

¹³ Azurity suggests that objective indicia of nonobviousness must fail where there is a purported motivation to combine. (Reply, 24.) But Azurity failed to prove any motivation to combine its cited art, which readily distinguishes Azurity’s cited *Allergan* case. Regardless, objective indicia can overcome even a facial showing of obviousness, which Azurity has not made here. *See, e.g., In re Cyclobenzaprine*, 676 F.3d at 1075-76.

**V. AZURITY FAILS TO REHABILITATE
DR. PEROUTKA'S QUALIFICATIONS**

Azurity's obviousness theory turns on whether a POSA would have "substitut[ed] netupitant as the NK1-inhibitor to treat CINV generally" with a reasonable expectation that such a treatment would successfully treat nausea and vomiting in a patient after chemotherapy. (Reply, 24.) Any POSA definition must therefore reflect experience in the treatment of CINV (*i.e.*, supportive cancer care). *See Best Med. Int'l, Inc. v. Elekta Inc.*, 46 F.4th 1346, 1354 (Fed. Cir. 2022).

Azurity wrongly suggests that what matters is "how a POSA would approach designing drug therapies" in the indication-agnostic abstract (Reply, 11). But what matters is how a POSA would go about treating this specific group of patients undergoing chemotherapy, including based upon real-world experience. Such a requirement is reflected in Helsinn's POSA definition, but not Azurity's. (POR, 12-13.)

Dr. Peroutka does not have any such experience in the treatment of CINV, and his testimony may properly be discounted. *Best Med.*, 46 F.4th at 1353. He has never treated patients for CINV, let alone prescribed the drug classes at issue

here or evaluated their effects. (Ex. 2086, 16:18-22, 18:12-20.) Dr. Roeland does have such experience, rendering his opinions far more credible.¹⁴

* * *

Respectfully submitted,

Dated: July 15, 2026

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

¹⁴ Azurity's critiques of Dr. Roeland fail. For example, Azurity's demand for a certain level of pre-priority experience (Reply, 11) is contrary to governing law. *Osseo Imaging, LLC v. Planmeca USA Inc.*, 116 F.4th 1335, 1341 (Fed. Cir. 2024). Moreover, the "collaborations" between Dr. Roeland and Helsinn cited by Azurity (Reply, 12) underscore Dr. Roeland's experience as a clinical investigator evaluating the effectiveness of drugs in cancer patients suffering from CINV—experience he has brought to consultations with more than a dozen pharmaceutical companies. (See Ex. 2088, ¶14.)

CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(d), the undersigned certifies that the foregoing Patent Owner's Sur-Reply contains, as measured by the word-processing system used to prepare this paper, 5,598 words. This word count does not include the items excluded by 37 C.F.R. § 42.24.

Respectfully submitted,

Dated: July 15, 2026

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

CERTIFICATE OF SERVICE

I certify that I served on the counsel identified below a true and correct copy of the foregoing Patent Owner's Sur-Reply by electronic means on July 15, 2026:

Richard Torczon (rtorczon@wsgr.com)
Jad A. Mills (jmills@wsgr.com)
Michael Rosato (mrosato@wsgr.com)
Wendy Devine (wdevine@wsgr.com)

4877-8318-2285@mail.vault.netdocuments.com

Respectfully submitted,

Dated: July 15, 2026:

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