

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 No. 8,623,826 B2

**PATENT OWNER'S BRIEF REQUESTING
DISCRETIONARY DENIAL OF INSTITUTION**

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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	
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	
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	
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	
2005	Akynzeo (netupitant/palonosetron) FDA Approval Letter, dated October 10, 2014, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/205718Orig1s000Approv.pdf	
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/	
2007	Heron Form 10-K, Feb. 27, 2025	
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	
2009	U.S. Patent No. 12,097,197 to Dubewar et al.	
2010	IDS Statement, Application No. 18/069,204, dated June 29, 2023	
2011	Press Release – CutisPharma Announces Acquisition of Silvergate Pharmaceuticals, Name Change to Azurity Pharmaceuticals, June 12, 2019, 6:00 ET	
2012	Press Release – Silvergate Pharmaceuticals Release: FDA Approves XATMEP, The First and Only Ready-To-Use Methotrexate Oral Solution, April 26, 2017	
2013	GLIADEL® WAFER label	

2014	Press Release - Azurity Pharmaceuticals Acquires Slayback Pharma, Sept. 27, 2023, available at https://azurity.com/azurity-pharmaceuticals-acquires-slayback-pharma/	
2015	U.S. Patent Application Publication No. 2024/0156829 A1	
2016	EMEND® label, March 2003	
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	
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	
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	
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	
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	
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	
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	
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	
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	
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	
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	
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	
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	
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	
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	
2032	U.S. Patent No. 5,202,333 to Berger et al.	
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	
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	
2035	AKYNZEO® label	

I. INTRODUCTION

Pursuant to Acting Director Stewart's March 26, 2025 Memorandum on Interim Processes for PTAB Workload Management ("March 26 Memorandum"), Patent Owner Helsinn Healthcare S.A. ("Helsinn" or "Patent Owner") submits this brief requesting discretionary denial of the petition for *inter partes* review ("Petition") filed by Petitioner Azurity Pharmaceuticals, Inc. ("Azurity" or "Petitioner") challenging claims 1-25 of U.S. Patent No. 8,623,826 ("the '826 patent"). As explained below, Azurity's Petition presents a straightforward case warranting the exercise of discretionary denial.

First, the '826 patent has been in force for more than ten years, which creates strong settled expectations as to its validity. No persuasive reason exists for disturbing this settled expectation given that, *inter alia*, the '826 patent has been commercialized by Helsinn in the form of its innovative drug product Akynzeo[®], which was first approved by the FDA in 2014 to treat chemotherapy-induced nausea and vomiting.

Second, Azurity has not identified any prior art that is more pertinent than what was already before the Office during prosecution. Azurity's two primary references, referred to as "MASCC" (Ex. 1013) and "Herrstedt" (Ex. 1010), differ from the prosecution prior art only in name, and not substance. And here, Azurity relies on MASCC and Herrstedt in the same way that the Office relied upon the

“Reddy” reference (Ex. 1021) during prosecution. (*See infra* Section IV.A.)

Specifically, the Office relied on Reddy for an alleged teaching of a three-drug regimen of aprepitant, palonosetron, and dexamethasone to treat nausea and vomiting. Because Azurity relies on MASCC and Herrstedt for the very same teaching, its invalidity ground merely repackages previously considered prior art, which is precisely what § 325(d) is designed to guard against.

Likewise, Azurity relies on two secondary references, referred to as “Hoffmann” (Ex. 1011) and “Bös” (Ex. 1014), for an alleged teaching of netupitant. But Reddy also disclosed netupitant as part of a longer list of NK-1 receptor antagonists. Bös is also expressly cited on the face of the ’826 patent, confirming that Azurity’s secondary references do not add anything beyond the prior art that was before the Office during prosecution.

Azurity also presents no basis for finding that the Office materially erred in allowing the ’826 patent claims. Azurity’s allegation that Helsinn misrepresented certain data during examination is demonstrably false, as confirmed by Azurity’s own cited art (*e.g.*, Herrington) and the data in the FDA-approval for a different drug product. (*See infra* Section IV.B.1.) In addition, Azurity fails to address, let alone persuasively challenge, the evidence of unexpected synergy between netupitant and palonosetron, which the Office referenced in its Notice of Allowance. (*See infra* Section IV.B.2.) Moreover, Azurity’s proposed motivation

for a POSA to combine the prior art—which hinges on its allegation that the prior art recognized netupitant as an “improved” NK-1 antagonist over aprepitant—finds no support in Azurity’s own cited art. (*See infra* Section IV.B.3.)

Third, the above-identified deficiencies also mean that Azurity has not presented a compelling challenge on the merits.

For at least these reasons, Helsinn respectfully requests that the Acting Director exercise discretion and deny institution.

II. BACKGROUND

A. State of the Art in 2009

Nausea and vomiting are common, but very serious, adverse events experienced by patients who are undergoing chemotherapy for the treatment of cancer. (Ex. 2001 at 1856.) Poorly controlled chemotherapy-induced nausea and vomiting (“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. (*Id.* at 1856.)

The term “CINV” is itself a misnomer, as treatments for CINV actually “do *not* need to demonstrate an effect on *nausea* to secure approval for this indication.” (Ex. 1005 at 347, ¶ 38 (emphases added).) Instead, “drug sponsors ... are 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.” (*Id.*, ¶ 38.) 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 treat than vomiting. (*See, e.g.*, Ex. 1010 at 143.)

As of September 2009, many different antiemetic agents from many different classes would have been known to a person of ordinary skill in the art (“POSA”). Some exemplary agents include benzodiazepines, cannabinoids, corticosteroids, dopamine antagonists, neurokinin-1 receptor antagonists (“NK-1 receptor antagonists”)¹, and serotonin 5-HT₃ receptor antagonists (“5-HT₃ receptor antagonists”). (Ex. 2001 at 1872 (Table XII).)

Aprepitant was the first NK-1 receptor antagonist to be marketed in the U.S. for the treatment of CINV, after Merck obtained FDA approval in 2003 for its oral

¹ Antiemetic medications are administered to block certain neurotransmitters from binding to receptors, with the hope of preventing vomiting. (Ex. 1010 at 144.) The chemical compounds within these medications that block neurotransmitters are referred to as “antagonists.” (*Id.* at 144.) For example, a chemical compound that blocks or inhibits an NK-1 receptor is referred to as an “NK-1 receptor antagonist.”

tablets of aprepitant marketed under the brand name Emend[®]. (Ex. 2002.) In 2008, Merck received FDA approval for the injectable prodrug of aprepitant (fosaprepitant dimeglumine), which was marketed as Emend[®] for Injection (“Emend[®] IV”). (Ex. 2004.)

Aprepitant was considered effective for treating vomiting, but did not show any statistically 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 . . .”).) And even four years after Merck introduced its oral tablets of aprepitant, nausea remained a significant concern in patients suffering from CINV. (*See, e.g.*, Ex. 1010 at 143 (“Today, a majority of patients consider nausea as the main problem.”).) Therefore, and notwithstanding the known efficacy of Emend[®] and Emend[®] IV in treating vomiting, there were no effective treatments for the nausea component of CINV in 2009. As discussed below, the ’826 patent invention covers the first effective treatment of the nausea component of CINV, which represents a significant and much-needed advance in supportive care for cancer patients undergoing chemotherapy.

**B. Unexpected Synergistic Effects of
Combining Netupitant and Palonosetron**

The '826 patent inventors discovered that, when the chemical compounds netupitant and palonosetron (a 5-HT₃ receptor antagonist) are combined, this produces unexpected synergistic effects in treating nausea by inhibiting a naturally occurring substance in the body known as “substance P.”² These synergistic effects of the innovative combination are far greater than the additive effects of netupitant and palonosetron when administered separately. Through their experiments, the inventors found that, while the “additive effect” of netupitant and palonosetron on inhibition of substance P might be expected to be “66 μ M (38 μ M for netupitant + 28 μ M for palonosetron),” the combination unexpectedly resulted in 970 μ M—a “*nearly 500-fold*” increase on substance P inhibition. (Ex. 1005 at 344, ¶¶ 22-23.³)

² Substance P binds to NK-1 receptors and plays a key role in triggering nausea. (Ex. 1010 at 146; Ex. 1005 at 342, ¶ 12.)

³ The “ μ M” values represent the “EC₅₀” of substance P. An EC₅₀ value is used to quantify the relationship between the concentration of a substance and the biological response it elicits.

The inventors further discovered that their innovative combination of netupitant and palonosetron provided “an unanticipated statistically significant effect *against nausea* . . . that [had] not previously been observed in clinical studies” of other NK-1 receptor antagonists in combination with other 5-HT₃ inhibitors. (Ex. 1005 at 345, ¶ 28 (emphasis added).) These controlled clinical trials had previously shown that aprepitant with 5-HT₃ receptor antagonists (ondansetron or palonosetron) did not provide significant relief for patients with “nausea” or “significant nausea” resulting from highly emetogenic chemotherapy or moderately emetogenic chemotherapy. (*Id.* at 345-47, ¶¶ 32-37; *see also* Ex. 2003 at 375 (reporting that “[t]hese drugs [5-HT₃ and NK-1 antiemetics] have had a huge impact in the protection from chemotherapy-induced vomiting, whereas the effect on nausea seems to be limited”).⁴) As a result, the inventors concluded that the combination of netupitant and palonosetron was especially effective in treating

⁴ Nausea can be assessed using a Visual-Analog scale (VAS), where patients must identify their feeling of nausea on a scale of 0-100 mm. No nausea and no significant nausea are typically defined as a VAS score < 5 mm and a VAS score < 25 mm, respectively. (*See, e.g.*, Ex. 1016 at 2081.)

nausea as compared to existing drug regimens involving aprepitant with either ondansetron or palonosetron. (Ex. 1005 at 345-47, ¶¶ 29-37.)

The inventors claimed their synergistic combination of netupitant and palonosetron in, *inter alia*, the '826 patent. Claim 1 of the '826 patent recites:

A method of treating both nausea and vomiting for five consecutive days in a patient in need thereof, comprising:

a) *administering to said patient on day one netupitant or a pharmaceutically acceptable salt thereof*, in a therapeutically effective amount which enters the systemic circulation, crosses the blood brain barrier and occupies at least 70% of neurokinin-1 (NK₁) receptors in the striatum seventy-two hours after said administration;

b) *administering to said patient on day one a therapeutically effective amount of palonosetron or a pharmaceutically acceptable salt thereof*; and

c) administering to said patient on day one a first dose of dexamethasone which is ineffective against chemotherapy induced nausea and vomiting (CINV) when administered alone, but effective against CINV when administered in combination with said netupitant

(Ex. 1001 at claim 1 (emphases added).)

C. In Granting Helsinn Several Patents, the Office Rejected Arguments Nearly Identical to Those Azurity Makes Here

As further discussed below in Section IV.A, Azurity’s Petition rehashes the nearly identical prior art arguments that the Office considered and rejected multiple times in allowing Helsinn’s claims. In determining that Helsinn’s claims were patentable, the Office recognized, *inter alia*, the synergy between the unique combination of netupitant and palonosetron, and found that this combination would not have been obvious to a POSA. (*Infra* Section IV.B.) In doing so, the Office relied on a Rule § 1.132 declaration by inventor Giorgia Rossi and Claudio Pietra (Ex. 1005 at 341-350 (“Rule 132 declaration”)), which showed “evidence of synergy (unexpected result) from the combination of netupitant and palonosetron in regard to the claimed method.” (Ex. 1005 at 369.) The Office made a similar finding in allowing another patent in the same family as the ’826 patent to issue, stating that the “applicant discovered that the combination [of] palonosetron and netupitant provides an unexpected result in regard to treating chemotherapy induced nausea and vomiting.” (Ex. 1008 at 286.)

III. THE PARTIES’ SETTLED EXPECTATIONS AND OTHER EQUITABLE CONSIDERATIONS WARRANT DENIAL

The Office has explained that, in seeking discretionary denial, “the parties are permitted to address all relevant considerations . . . bearing on the Director’s discretion.” *See* March 26 Memorandum at 2-3. “Settled expectation of the

parties, such as the length of time the claims have been in force,” is a relevant consideration the Director takes into account in exercising discretion. *Id.* Here, Helsinn’s settled expectation that the ’826 patent is valid and enforceable is dispositive.

A. The ’826 Patent Has Been in Force for More Than Ten Years, Creating “Strong” Settled Expectations

The challenged ’826 patent issued more than 11 years ago, on January 7, 2014. This patent has thus now been in force for more than “ten years, creating strong settled expectations” that the patent is valid and enforceable. *See, e.g., Samsung Elecs. Co. Ltd. V. Four Batons Wireless, Inc.*, IPR2025-00493, Paper 11 (July 17, 2025) (denying institution based on settled expectations); *see also Dabico Airport Solutions Inc. v. AXA Power APS*, IPR2025-00408, Paper 21 (June 18, 2025) (denying institution because “the challenged patent has been in force almost eight years, creating settled expectations”); *Intel Corp. v. Proxense LLC*, IPR2025-00327, Paper 12 (June 26, 2025) (denying institution because “the challenged patents have been in force over nine years, creating settled expectations”). Here, Helsinn’s ’826 patent has been in force even longer than the *Dabico* and *Intel* patents. “Although there is no bright-line rule on when expectations become settled, in general, the longer the patent has been in force, the more settled expectations should be.” *Dabico*, Paper 21 at 3.

**B. No Persuasive Reason Exists for
Disturbing Helsinn's Settled Expectations**

Helsinn's settled expectation in the validity and enforceability of the '826 patent should not be disturbed. When settled expectations exist, institution is inappropriate unless there is a persuasive reason to the contrary:

There may be persuasive reasons why the Board should review challenged claims several years after their issuance date. For example, a significant change in law may have occurred since the patent issued, and a petitioner can explain how that change in law directly bears on the patentability of the challenged claims. As another example, a patent may have been in force for years but may not have been commercialized, asserted, marked, licensed, or otherwise applied in a petitioner's particular technology space, if at all. These non-exclusive examples provide considerations that weigh against a patent owner's claim of settled expectations and bears on the Director's discretion. In the absence of any such information, however, such as in the present proceedings, the Office is disinclined to disturb the settled expectations of Patent Owner.

Intel, Paper 12 at 2-3. No persuasive reason exists here that would warrant upending Helsinn's settled expectations.

First, no significant change in law bearing on the patentability of the

challenged claims of the '826 patent has occurred since that patent issued. To allege invalidity, the Petition relies only on obviousness law, which has not significantly changed since the U.S. Supreme Court's decision in *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398 (2007). (See Petition at 1-3 (Grounds 1-7 relying solely on obviousness to assert that the '826 patent is invalid over combinations of seven references).) Indeed, the Petition premises its obviousness analysis on *KSR*. (See, e.g., Petition at 16-17.)

Second, and as explained further below, Helsinn has “commercialized, asserted, marked, licensed, or otherwise applied” the innovations claimed in the '826 patent for supportive cancer care (*i.e.*, CINV treatment) via its Akynzeo[®] product. See *Intel*, Paper 12 at 2.

- **Commercialization:** Akynzeo[®] was approved by the FDA for marketing in the United States on October 14, 2014, just months after the '826 patent issued on January 7, 2014. (Ex. 2005.) Since that time, Helsinn has spent significant resources further developing and commercializing its Akynzeo[®] product, which has become a major competitor in the global market for CINV treatment. (Ex. 2006; Ex. 2007 (Heron 10-K (2025)) at 27-28 (listing Akynzeo[®] as providing “significant competition”).)
- **Assertion:** Since 2009, Helsinn has protected its investment in

Akynzeo[®] by filing patent applications that cover various aspects of its innovative drug product. The '826 patent claims the benefit of U.S. Provisional Patent Application No. 61/262,470 filed on November 18, 2009. (Ex. 1001 at cover.) The FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (commonly known as "the Orange Book"), lists several Helsinn patents, including the '826 patent, as covering Akynzeo[®]. (Ex. 2034.) Helsinn previously asserted two of these Orange-book listed patents covering its Akynzeo[®] product, U.S. Patent No. 9,186,357 ("the '357 patent") and U.S. Patent No. 10,828,297 ("the '297 patent"), in a Hatch-Waxman litigation against Gland Pharma Limited, a generic drug company.⁵ *See Helsinn Healthcare S.A. v. Gland Pharma Limited*, No. 22-cv-04635 (D.N.J. July 18, 2022), ECF No. 1. The '357 and '297 patents are in the same family as the '826 patent, and likewise titled "Compositions and Methods for Treating Centrally Mediated Nausea

⁵ These two patents are at issue in other IPRs concurrently filed by Azurity. (See IPR2025-00946, -00947, -00949.)

and Vomiting.”⁶

Third, Azurity and its subsidiaries have been practicing in the same supportive cancer care space as Helsinn for many years. For example, on September 28, 2023, Azurity filed a new drug application for an aprepitant injectable emulsion that received tentative approval on July 25, 2024. (Ex. 2008 at 1 (Azurity Tentative Approval).) Azurity also holds patents and patent applications in the cancer supportive care space. For example, Azurity’s subsidiary Slayback Pharma LLC (“Slayback”)⁷ filed a patent application in December 2022 titled “Stable Liquid Compositions of Netupitant and Palonosetron” that claims priority to a December 21, 2021 Indian patent application. (See Ex. 2009 (U.S. Patent No.

⁶ The dispute between Helsinn and Gland was subsequently resolved via settlement on January 19, 2023. See *Helsinn Healthcare S.A. v. Gland Pharma Limited*, No. 22-cv-04635 (D.N.J. January 19, 2023), ECF No. 50.

⁷ Azurity acquired Slayback Pharma LLC in September 27, 2023, making Slayback a “wholly-owned subsidiary of Azurity.” (Ex. 2014 (<https://azurity.com/azurity-pharmaceuticals-acquires-slayback-pharma/>).)

12,097,197) at Cover.⁸) This patent application disclosed compositions “comprising netupitant and optionally palonosetron . . . and methods of using such compositions for prevention, treatment or management of nausea and vomiting.” (*See id.* at Abstract.) During prosecution of this patent application, Azurity cited Helsinn’s ’357 patent in an Information Disclosure Statement (“IDS”) dated June 29, 2023. (Ex. 2010.) The IDS statement demonstrates Azurity’s awareness of Helsinn’s patents, as early as June 2023.

Even before 2021, Azurity and its predecessors were practicing more generally in the cancer care space. Azurity was formed in June 2019, when

⁸ As a further example, in October 2023, Slayback filed another patent application directed to treatments for supportive cancer care. The application is titled “Stable Antiemetic Emulsions for Parenteral Administration” and claims priority to an October 31, 2022 Indian patent application. (*See* Ex. 2015 (U.S. Publication No. 2024/0156829) at Cover.) This application disclosed “compositions for parenteral administration comprising aprepitant . . . [and] aprepitant and palonosetron . . . useful for the prevention and control of acute and delayed *chemotherapy-induced nausea and vomiting (CINV)*” (*See id.* at Abstract (emphasis added).)

CutisPharma, Inc. acquired Silvergate Pharmaceuticals, Inc. (Ex. 2011.)

Silvergate Pharmaceuticals had been practicing in the cancer technology space since receiving approval in April 2017 for Xatmep (methotrexate) oral solution, which is indicated for treatment of a type of leukemia. (Ex. 2012.) Azurity subsequently acquired Arbor Pharmaceuticals in September 2021, which also practiced in the cancer technology space via its Gliadel wafer (carmustine implant) indicated for the treatment of certain brain and nervous system cancers. (Ex. 2013.) By practicing in the cancer space since at least 2017 without challenging the '826 patent until this year, Azurity and its affiliated entities have created a strong settled expectation that Helsinn's '826 patent is valid and enforceable.

Given Helsinn's settled expectations, and the lack of any persuasive reason to overturn them, institution of Azurity's IPR challenge should be denied.

**IV. DENIAL OF INSTITUTION IS ALSO
WARRANTED UNDER 35 U.S.C. § 325(d)**

In determining whether to institute an IPR, if another proceeding or matter involving the same patent is before the Office, “the Director may take into account whether, and reject the petition or request because, the same or substantially the same prior art or arguments previously were presented to the Office.” 35 U.S.C. § 325(d). The Office applies the two-part framework set forth in *Advanced Bionics* in evaluating whether to deny institution under § 325(d):

- (1) whether the same or substantially the same art previously was presented to the Office or whether the same or substantially the same arguments previously were presented to the Office; and
- (2) if either condition of first part of the framework is satisfied, whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims.

Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH, IPR2019-01469, Paper 6 at 8 (PTAB Feb. 13, 2020) (precedential); *see also Becton, Dickinson and Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 at 17-18 (PTAB Dec. 15, 2017) (precedential as to Section III.C.5, first paragraph) (listing factors to consider in evaluating the applicability of § 325(d), referred to herein as the *Becton-Dickinson* factors).

Azurity's Petition should be denied under § 325(d). Azurity has done no more here than present nearly identical arguments that the Office previously considered and rejected, using the same or substantially similar prior art that was already before the Office. Azurity does so without presenting any persuasive evidence that the Office made a material error in its consideration of the prior art.

A. Azurity Presents the Same or Substantially the Same Prior Art and Arguments Previously Considered by the Office

Azurity's Petition presents a nearly identical obviousness argument that Helsinn already overcame during prosecution of the '826 patent. Moreover, the prior art relied upon by Azurity differs from prior art before the Office only in name, rather than substance. (*See generally* Petition at 17-58.) As discussed below, the Petition's main prior art references (*i.e.*, the prior art upon which Azurity relies to allege the majority of its obviousness arguments) are either expressly cited on the face of the '826 patent, or are cumulative of the prior art that was considered by the Office.

Primary References (MASCC and Herrstedt): The Petition relies on MASCC as the primary reference in Grounds 1-3, and Herrstedt as the primary reference in Grounds 4-7. (Petition at 2-3.) Both references are, however, cumulative of the Reddy reference relied upon by the Office during the prosecution because Petitioner relies on them "in the same manner as the Examiner relied on

[Reddy] during prosecution.” *See Advanced Bionics*, Paper 6 at 15-16.

Specifically, the Office alleged that Reddy disclosed a three-drug regimen of aprepitant, palonosetron, and dexamethasone for the treatment of CINV. (*See, e.g.*, Ex 1005 at 284 (Reddy “teaches treatment of chemotherapy-induced nausea and vomiting (CINV) by administering a Neurokinin-1 (NK-1) Antagonist, i.e. aprepitant, in combination with . . . [a] 5-HT₃ antagonist and dexamethasone,” where the “5-HT₃ antagonist is palonosetron.”).) The Petition relies upon MASCC and Herrstedt for the same alleged teaching of a three-drug regimen of aprepitant, palonosetron, and dexamethasone for the treatment of CINV. (*See, e.g.*, Petition at 18 (“MASCC recommends treating acute-phase nausea after HEC with 5-HT₃ antagonist (ondansetron or palonosetron), NK₁ antagonist (aprepitant), and dexamethasone”); *id.* at 31 (“Herrstedt teaches treating both nausea and vomiting for five days, by administering therapeutically-effective amounts of NK₁ antagonist (aprepitant), 5-HT₃ antagonist (e.g., palonosetron), and a first (sub-therapeutic) dose of dexamethasone on day 1.”).) Azurity’s repackaging of prior art and arguments is precisely the type of IPR challenge that §325(d) was meant to disallow.

Secondary References (Hoffmann and Bös): Next, the Petition offers two secondary references, Hoffmann and Bös, to allege that it would have been obvious to a POSA to use netupitant in place of aprepitant in MASCC or Herrstedt’s

aprepitant-based, three-drug regimen for treating CINV. (*See* Petition at 19 (“Hoffmann provides ample reason to substitute netupitant in MASCC’s 3-drug regimen with palonosetron and dexamethasone and reasonably expect success based on netupitant’s excellent efficacy.”); *id.* at 25 (“Bös provides ample reason to replace MASCC’s aprepitant with Bös’ new, improved netupitant.”); *id.* at 32 (“A POSA would have known to try an improved NK₁ antagonist (netupitant) instead of aprepitant in Herrstedt’s combination.”) But the Office considered substantially the same argument during prosecution: whether it would have been obvious to a POSA to use netupitant instead of aprepitant in Reddy’s three-drug regimen. (Ex. 1005 at 284-285.)

Neither Hoffmann nor Bös is materially different from the prior art considered during prosecution. Azurity relies on Hoffmann and Bös in the same way that the Office relied on Reddy for disclosure of “***netupitant*** as a suitable NK-1 antagonist.” (Ex. 1005 at 284 (emphasis in original).) In fact, Bös *was* squarely before the Office during prosecution. (*See* Ex. 1005 at 287 (listing Bös in

References Considered).⁹) And while Hoffmann is not listed on the face of the '826 patent, it is the “same or substantially the same prior art” as Bös and Reddy under the first prong of *Advanced Bionics*.

First, Hoffmann is cumulative of both Bös and Reddy in terms of its alleged disclosure of netupitant as an NK-1 receptor antagonist that may be substituted for aprepitant. Like with Bös, Azurity relies on Hoffmann for an alleged teaching of netupitant and a motivation for a POSA to use netupitant in place of aprepitant. (*Compare* Petition at 19 *with id.* at 24-25.)

Second, the Office expressly considered both Reddy and Hoffmann during prosecution of a related patent claiming a “regimen of palonosetron, netupitant and dexamethasone” for treatment of CINV. (Ex. 1002 at Cover (citing Reddy and Hoffmann) and claim 1.) But the Office *still* found the claimed three-drug regimen patentable despite Hoffman’s teachings regarding netupitant. So even when

⁹ While the Office did not issue any rejection over Bös, or otherwise discuss that reference during prosecution, Bös is listed on the cover of the '826 patent and thus was “previously presented to the Office” under the *Advanced Bionics* framework. *Ecto World, LLC v. RAI Strategic Holdings, Inc.*, IPR2024-01280, Paper 13 at 4 (PTAB May 19, 2025) (precedential).

Hoffmann was considered along with both Reddy and Bös, the Office did not find the claimed palonosetron-netupitant-dexamethasone drug regimen obvious. (Ex. 1006 at 241-42, 342; Ex. 1002 at Cover; *see also* Ex. 1006 at 327-331 (Notice of Allowance).) Therefore, Hoffmann should be considered the “same or substantially the same prior art” for the ’826 patent given its consideration in a related patent with similar limitations to the ’826 patent.

Tertiary References (Herrington, Aloxi, Hargreaves): Azurity relies on MASCC, Herrstedt, Bös, and Hoffmann to address the ***bulk*** of the challenged claim limitations. Azurity thus cannot overcome the first prong of *Advanced Bionics* by injecting tertiary references such as “Herrington” (Ex. 1016), the “Aloxi[®] Label” (Ex. 1015), and/or “Hargreaves” (Ex. 1012) into one or more grounds of its Petition to address certain dependent claims. *See Kayak Software Corp. v. IBM*, CBM2016-00075, Paper 16 at 10 (PTAB Dec. 15, 2016) (informative) (holding that Petitioners’ citation of a reference not previously considered by the Office solely for “additional subject matter of certain dependent claims, is insufficient to persuade us that exercising our discretion under 35 U.S.C. §325(d) is inappropriate”). Regardless, none of these tertiary references, separately or together, establish that “there are ‘significant and material differences between the prior art asserted in this Petition and the prior art evaluated during prosecution.’” *Advanced Bionics*, Paper 6 at 16.

First, Herrington is listed on the face of the '826 patent, and thus deemed considered by the Office under *Advanced Bionics*. (Ex. 1001 at Cover.)

Second, Azurity cites the Aloxi[®] Label, for example, as allegedly “teach[ing] administering before chemotherapy a therapeutically-effective amount of palonosetron salt.” (Petition at 28.) The Office, however, alleged that the prior art during the prosecution of the '826 patent purportedly disclosed this claim limitation, and nonetheless allowed the claims to issue. (Ex. 1005 at 284-85.) Therefore, Azurity cannot credibly allege that the Aloxi[®] Label is materially different from “the prior art evaluated during prosecution.” *Advanced Bionics*, Paper 6 at 16. And importantly, the Aloxi[®] drug product itself is expressly mentioned in the '826 patent's specification. (Ex. 1001 at 1:42-45.)

Finally, the Petition cites Hargreaves as allegedly teaching that “a therapeutically-effective amount occupies at least about 75% of striatum NK₁ receptors” to allege obviousness of the limitation in challenged claim 1 that “netupitant or a pharmaceutically acceptable salt thereof . . . occupies at least 70% of neurokinin-1 (NK) receptors in the striatum” (Petition at 34-35.) The Office considered similar claim language during prosecution of the '826 patent and alleged that the prior art before it discloses “wherein said netupitant occupies at least 80% of NK₁ receptors in the striatum” (Ex. 1005 at 285) and nonetheless

allowed the claims to issue. Accordingly, Hargreaves does not add anything to the prior art that was before the Office.

B. Azurity Fails to Demonstrate that the Office Erred in a Manner Material to the Patentability of the Challenged Claims

In considering the second prong of the *Advanced Bionics* framework, the PTAB evaluates “whether the petitioner has demonstrated a material error by the Office.” *Advanced Bionics*, Paper 6 at 10. “[I]f reasonable minds can disagree regarding the purported treatment of the art or arguments, it cannot be said that the Office erred in a manner material to patentability.” *Id.* at 9. Azurity does not and cannot show that the Office materially erred in allowing the claims of the ’826 patent.¹⁰

¹⁰ Helsinn respectfully requests that the Director review the arguments set forth in Section IV.B in conjunction with its arguments in the forthcoming Patent Owner Preliminary Response, which will further show why Azurity’s contentions here fail. See FAQ 12, *FAQs for Interim Processes for PTAB Workload Management* (“FAQs”), available at <https://www.uspto.gov/patents/ptab/faqs/interim-processes-workload-management> (“[T]he Director will consider the merits in the merits briefing if the parties ask the Director to do so. Parties should not repeat their

1. Helsinn Did Not Mischaracterize Data During Examination

Here, Azurity contends that Helsinn allegedly misrepresented certain data during examination, including the data submitted as part of the Rule 132 declaration to show the unexpected synergistic effects of the combination of netupitant and palonosetron. (Petition at 8, 63-66). But even a cursory review of Azurity’s arguments demonstrates that the only misrepresentations are Azurity’s. As explained briefly below—and as Helsinn will more fulsomely show in the forthcoming Patent Owner’s Preliminary Response—Helsinn’s arguments accurately characterized the underlying data.

Azurity contends in its Petition that, contrary to Helsinn’s representations to the Office, the “experimental data shows a POSA knew aprepitant treats nausea effectively.” (Petition at 59-60.) Azurity then claims that Helsinn mischaracterized the Emend® (aprepitant) label as showing that aprepitant did not achieve “statistically significant reduction in either nausea or significant nausea.”

merits arguments verbatim but should briefly explain why the merits are relevant.”).

(*Id.* at 60 (citing the Emend[®] label (Ex. 1030)¹¹).) But as confirmed by the following two tables taken directly from the Emend[®] label (Ex. 1030), Helsinn was correct in stating that the effect of aprepitant on nausea or significant nausea is ***not*** statistically significant, as indicated by “NS**” provided for the p-Value:

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.

¹¹ Azurity cites the Emend[®] label from 2008. But during examination, Helsinn referenced the Emend[®] label from **2003** (*see, e.g.*, Ex. 1005 at 346 (TABLE 2 referring to Ref. E), 350 (describing Ref. E as the March 27, 2003 Emend[®] label)), which is attached herewith as Exhibit 2016.

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).) Helsinn’s characterization of the Emend[®] label is also consistent with the Herrington prior reference that Azurity relies upon. Citing the Emend[®] label, Herrington states that “[a]ccording to its package insert, *aprepitant fails to demonstrate* improved efficacy over placebo for the prevention of nausea” (Ex. 1016 at 2086.)

Rather than address the p-value column for the “nausea” and “significant nausea” data in the tables from the Emend[®] label, Azurity instead focuses on the “complete protection” row in the Emend[®] label. (Petition at 61.) But as discussed above, the only information in Emend[®]’s label that is specifically directed to nausea unequivocally indicated that aprepitant had no significant impact. (See Ex.

1005 at 347, ¶ 38; Ex. 1030 at 4-5; *see also* Ex. 1005 at 330.)

Azurity also posits that Helsinn’s data presented in Table 2 of its Rule 132 declaration submitted during prosecution was “lacking.” (Petition at 64-66.) For example, Azurity alleges that Helsinn never provided the Office with the “underlying data for any palonosetron-netupitant combination.” (*Id.* at 64.) But contrary to this allegation, Helsinn did provide the internal data for the palonosetron-netupitant combination in columns 1 and 3 of Table 2 (reproduced below) of its Rule 132 declaration, and also cited specific Helsinn internal studies (NETU-07-07 and NETU-08-18) as the source of that data. (*See* Ex. 1005 at 346.) If the Office had believed that an evaluation of the underlying data was merited, the Office simply could have asked Helsinn for the data, 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 ^{res}	30.6	59.9 ^{res}
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 ^{res}	66.1	91 ^{res}
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

^{res} 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 346.)

2. Azurity Fails to Rebut the Office's Finding Regarding the Unexpected Synergy Between Netupitant and Palonosetron

Azurity completely fails to address the underlying evidence of synergistic effects that the Office referenced in its Notice of Allowance for the '826 patent. Overlooking this key part of prosecution is fatal to its obviousness arguments and

also fatal to any allegation that the Office committed material error.¹²

As referenced above in Section II.C, Helsinn submitted a Rule 132 declaration during prosecution of the '826 patent. This declaration contained data demonstrating the unexpected synergistic effects of the netupitant-palonosetron combination in inhibiting substance P response. (See Ex. 1005 at 334-338 (Helsinn's Remarks on synergistic effects, citing the Rule 132 declaration).) As the Rule 132 declaration explains, "[a]t concentrations where neither individual molecule increased the EC₅₀ of substance P [*i.e.*, 1 nM netupitant and 0.2 nM palonosetron], the combination of molecules increased the EC₅₀ of substance-P from 2 μM to 120 μM, a **sixty-fold increase** in the EC₅₀ of substance-P. **The additive increase should have been zero.**" (Ex. 1005 at 344, ¶ 21 (emphases added).) Additionally, for 30 nM netupitant and 6 nM palonosetron, Helsinn "observed an increase in EC₅₀ to 970 μM, **nearly 500-fold**," again, **when the increase should have been zero.** (*Id.*, ¶ 23 (emphases added).) The data upon which Helsinn relies in support of these statements is expressly set forth in Table 1

¹² The Office stated that Helsinn showed, *inter alia*, "evidence of synergy (unexpected result) from the combination of netupitant and palonosetron in regard to the claimed method." (Ex. 1005 at 369.)

below, which was also included in the Rule 132 declaration.

TABLE I

Inhibition of SP response in NC108-15 cells by netupitant (netu) and palonosetron (palo).

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

(Ex. 1005 at 343, ¶ 17.)

Azurity's Petition ignores these results under the pretext that "the specification neither defines nor discusses 'synergy' withing the claims' context or purported unexpected results." (Petition at 66-67.) In doing so, Azurity fails to dispute the unexpected impact of the netupitant-palonosetron combination on *substance P activity*. Instead, Azurity baldly asserts that the netupitant-palonosetron combination had no notable beneficial effect on nausea over other known combinations (e.g., palonosetron with aprepitant). (Petition at 67-68.)

3. Azurity's Proposed Motivation to Combine Is Factually Unsupported

As discussed above, Azurity's obviousness challenge relies on either

(i) MASCC or Herrstedt as the primary reference that discloses the “triple therapy” of aprepitant, palonosetron, and dexamethasone for the treating CINV, and (ii) Bös or Hoffmann as the secondary reference to provide an alleged motivation for substituting netupitant for aprepitant. (*See generally* Petition at 17-58.) Azurity’s underlying evidence, however, does not show that a POSA would have been motivated to substitute aprepitant in MASCC or Herrstedt for netupitant based on the actual disclosures of either Hoffmann or Bös.

Azurity’s proposed motivation for a POSA to have substituted the NK-1 antagonist netupitant for a different NK-1 antagonist (aprepitant) has no support. Azurity argues that “Hoffmann teaches [netupitant] has favorable characteristics, including high affinity, excellent penetration into the central nervous system (CNS), and excellent oral NK₁-antagonist activity,” and similarly that “Hoffmann teaches netupitant as an *improved* NK₁ antagonist.” (Petition at 13, 17 (citing Ex. 1011 (Hoffmann) at 1364).) Azurity similarly argues that Bös “provides ample reason to replace MASCC’s aprepitant with Bös’ new, *improved* netupitant.” (*Id.* at 25 (emphasis added).) But neither Azurity’s Petition nor the declaration of its expert Dr. Peroutka contains any evidence that netupitant was recognized as an “improved” NK-1 receptor antagonist compared to aprepitant. And while Dr. Peroutka states that netupitant is an “‘excellent’ alternative to aprepitant,” his cited reference (Hoffmann) includes no comparison between aprepitant and netupitant at

all. (Ex. 1009 at ¶ 135 (citing Ex. 1011 (Hoffmann), Abstract); *see also* Petition at 19 (citing Ex. 1009 at ¶ 135).) Likewise, Hoffmann’s statement that netupitant has “high affinity and excellent CNS penetration” sheds no light as to how or whether netupitant is an “improved” NK-1 antagonist over aprepitant.

Dr. Peroutka’s reliance on Bös is similarly misplaced. For example, Dr. Peroutka opines that “a POSA would have been motivated to substitute the new NK₁ receptor antagonist (netupitant) described in Bös 2001” because “CNS penetration . . . was highly desirable in NK₁ receptor antagonists.” (Ex. 1009 at ¶ 175.) But like Hoffmann 2006, Bös does nothing to compare the CNS penetration of netupitant and aprepitant that would indicate netupitant’s properties are in any way improved over aprepitant. As another example, Dr. Peroutka opines that, in Bös, “netupitant was shown ‘to potently inhibit NK₁ agonist-induced foot tapping . . . after oral administration’ which was indicative of successful NK₁ receptor antagonism.” (Ex. 1009 at ¶ 160 (citing Ex. 1014 (Bös), 1:15-2:65, 14:9-38, 18:42-19:25).) But Bös makes no reference to aprepitant at all—let alone contain comparative data or analysis between netupitant and aprepitant. Without any valid data or analysis, there would have been no reason for a POSA to believe that netupitant offered any properties beyond what aprepitant already possessed.

The above arguments will be elaborated upon further in Helsinn’s forthcoming POPR. But as Helsinn’s arguments here already make clear, Azurity

cannot show material error by the Office. Azurity's Petition should be denied accordingly under § 325(d).

**V. THE PETITION DOES NOT PRESENT A
COMPELLING UNPATENTABILITY CHALLENGE**

For at least the reasons set forth above in Section IV.B and those set forth in the forthcoming Preliminary Response, Azurity has not presented a compelling merits challenge.

VI. CONCLUSION

For the foregoing reasons, Helsinn respectfully requests that the Acting Director exercise her discretion to deny the Petition.

Dated: August 4, 2025

Respectfully submitted,

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CERTIFICATE OF COMPLIANCE

Pursuant to Acting Director Stewart's March 26, 2025 Memorandum on Interim Processes for PTAB Workload Management, the undersigned certifies that the foregoing Patent Owner's Brief Requesting Discretionary Denial of Institution contains, as measured by the word-processing system used to prepare this paper, 6,201 words. This word count does not include the items excluded by 37 C.F.R. § 42.24.

Dated: August 4, 2025

Respectfully submitted,

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CERTIFICATE OF SERVICE

I certify that I caused to be served on the counsel identified below a true and correct copy of the foregoing Patent Owner's Brief Requesting Discretionary Denial of Institution by electronic means on August 4, 2025:

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