

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AZURITY PHARMACEUTICALS, INC.,
Petitioner,

v.

HELSINN HEALTHCARE S.A.,
Patent Owner.

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

**PATENT OWNER'S 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> , <i>Drugs</i> 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> , <i>Therapeutics and Clinical Risk Management</i> 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, <i>ihealthcareanalyst</i> , 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 1-23 of U.S. Patent No. 9,943,515 ("the '515 patent"). As explained below, Azurity's Petition presents a straightforward case warranting the exercise of discretionary denial.

First, the '515 patent has been in force for more than seven years, which creates strong settled expectations as to its validity. No persuasive reason exists for disturbing this settled expectation given that, *inter alia*, the '515 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 relies on four references across its two grounds. Two of those four references, "Bös" (Ex. 1014) and "Herrington" (Ex. 1016), were considered by the Office during prosecution. A third reference, "Herrstedt" (Ex. 1010), is relied upon in the same way that the

Office relied upon the “Reddy” reference (Ex. 1021) during prosecution: for an alleged teaching of a three-drug regimen including aprepitant to treat nausea and vomiting. The fourth reference, “Hargreaves” (Ex. 1012), is relied upon in only one of the two grounds. Hargreaves is also relied upon by Azurity for a limitation that the Office alleged as disclosed or suggested by the prior art; Hargreaves is thus cumulative of the prior art that was before the Office. Azurity’s unpatentability grounds thus repackage the same or substantially the same prior art that was considered by the Office, which is precisely what § 325(d) is designed to guard against.

Even though it recycles the prosecution prior art, Azurity’s Petition is silent as to any error—let alone material error—by the Office in its examination of the prior art. Any future argument by Azurity alleging any such error would be meritless. For example, as discussed below in Section IV.B, Helsinn amended the claims to include a limitation relating to a single, one-time dose of netupitant before allowance. But Azurity’s cited prior art for this limitation—the previously considered Bös and Herrington references—is entirely silent on this single, one-time netupitant dose. (*Infra* Section IV.B.1.) 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 the Bös reference cited by Azurity for that

proposition. (*Infra* Section IV.B.2.)

Third, 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.*)

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.*) 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 tablets of aprepitant marketed under the brand name Emend[®]. (Ex. 2002.) In 2008, Merck received FDA approval for the injectable prodrug of aprepitant

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.*) For example, a chemical compound that blocks or inhibits an NK-1 receptor is referred to as an “NK-1 receptor antagonist.”

(fosaprepitant dimeglumine), which was marketed as Emend[®] for Injection (“Emend[®] IV”). (Ex. 2004.) Aprepitant was considered effective for treating emesis, 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.”).) Thus, 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 ’515 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. A Single Dose of Netupitant Is Effective In Treating Both Nausea and Vomiting

The ’515 patent inventors discovered that (1) “netupitant is active against nausea” and (2) “that a single dose of netupitant is able to treat nausea and vomiting in response to highly and moderately emetogenic chemotherapy for five consecutive days.” (Ex. 1003 at 4:55-60.) This unexpected discovery follows

from netupitant's "unexpectedly . . . unique binding habits to the NK₁ receptors in the brain." (*Id.* at 4:60-62.)

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

(*Id.* at 4:62-66.) As directed by the Emend[®] (aprepitant) label, aprepitant must be administered for CINV over three days. (Ex. 2016 (Emend[®] Label) at 11 ("EMEND is given for 3 days as part of a regimen that includes . . . 125 mg orally 1 hour prior to chemotherapy treatment (Day 1) and 80 mg once daily in the morning on Days 2 and 3."); Ex. 1016 at 2081 ("FDA-approved 3-day regimen of aprepitant 125 mg orally on Day 1 followed by 80 mg orally per day on Days 2 and 3").) And even when this FDA-approved dosing schedule is followed, "aprepitant fails to demonstrate improved efficacy over placebo for the prevention of nausea" (Ex. 1016 at 2086.)

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

A method of treating nausea and vomiting from an emesis-inducing event for a period of five consecutive days in a patient in need thereof, comprising

administering to said patient netupitant or a pharmaceutically acceptable salt thereof, in a therapeutically effective amount which is effective to treat nausea and vomiting during the acute and delayed phases of emesis, and which enters the systemic circulation, crosses the blood brain barrier and occupies 70% or more of NK1 receptors in the striatum seventy-two hours after said administration,

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

(Ex. 1003 at claim 1 (emphasis added).)

The Office allowed the claims after Helsinn added the bolded, italicized limitation to the claims to clarify that “one single dose of netupitant is administered over a five-day period of time, and the single dose is effective to prevent nausea

and vomiting during the entire five-day period.” (Ex. 1007 at 324, 328, 342.) As discussed below, none of Azurity’s prior art discloses or suggests this limitation.

III. 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 ’515 patent is valid and enforceable is dispositive.

A. The ’515 Patent Has Been in Force for More Than Seven Years, Creating “Strong” Settled Expectations

The challenged ’515 patent issued more than 7 years ago, on April 7, 2018. This has created “strong” settled expectations that the patent is valid and enforceable. *See, e.g., Amgen, Inc. v. Bristol-Myers Squibb Co.*, IPR2025-00601, Paper 9 at 3 (Director July 24, 2025) (“In particular, the challenged patents have been in force for seven and six years, respectively, creating strong settled expectations for Patent Owner”) (citing *Dabico Airport Solutions Inc. v. AXA Power ApS*, IPR2025-00408, Paper 21 at 2-3 (Director June 18, 2025)).

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

Helsinn’s settled expectation in the validity and enforceability of the ’515 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 Corp. v. Proxense LLC, IPR2025-00327, Paper 12 at 2-3 (June 26, 2025);

Amgen, Paper 9 at 3 (holding that settled expectations should not be disturbed

without “persuasive reasoning why an *inter partes* review is an appropriate use of

Board resources”). 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 ’515 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 generally Petition at 1-2 (all grounds relying solely on obviousness).) Indeed, the Petition premises its obviousness analysis on *KSR*. (See, e.g., Petition at 14.)

Second, and as explained further below, Helsinn has “commercialized, asserted, marked, licensed, or otherwise applied” the innovations claimed in the ’515 patent for supportive cancer care (*i.e.*, CINV treatment) via its Akynzeo[®] product. *Intel*, Paper 12 at 2-3.

- **Commercialization:** Akynzeo[®] was approved by the FDA for marketing in the United States on October 14, 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 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. For example, the '515 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 '515 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.² 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 '515 patent, and likewise titled "Compositions and Methods for Treating Centrally

² These two patents are at issue in other IPRs concurrently filed by Azurity. (See IPR2025-00946, -00947, -00949.)

Mediated Nausea and Vomiting.”³

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. Azurity’s subsidiary Slayback Pharma LLC (“Slayback”)⁴ also 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.

³ 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.

⁴ Azurity acquired Slayback Pharma LLC in September 27, 2023, making Slayback a “wholly-owned subsidiary of Azurity.” (Ex. 2014.)

12,097,197) at Cover.⁵) 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 CutisPharma, Inc. acquired Silvergate Pharmaceuticals, Inc. (Ex. 2011.)

⁵ 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 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).)

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 '515 patent until this year, Azurity and its affiliated entities have created a strong settled expectation that Helsinn's '515 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 presents the same or substantially the same prior art that the Office previously considered during prosecution. 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 Previously Considered by the Office

The prior art relied upon by Azurity is virtually identical to the prior art already considered by the Office. Two out of the four prior art references relied upon by Azurity (*see, e.g.*, Petition at 2) are listed on the face of the '515 patent. The other two references are cited for limitations the Office previously alleged as

disclosed by the prosecution prior art. Thus, none of Azurity’s cited 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.

The Petition’s first ground relies on Herrstedt, Bös, and Herrington, while its second ground adds Hargreaves to these three references. (Petition at 2.) Bös and Herrington were squarely before the Office during prosecution and thus previously presented to the Office under the *Advanced Bionics* framework. (See Ex. 1007 at 317 (listing Herrington in References Considered), 530 (listing Bös in References Considered).⁶) Azurity relies upon these two references as allegedly suggesting the claim limitation directed to administration of a single dose for netupitant for a five-day period, which was added to the claims just before allowance. (See *infra* Section IV.B.1.) But neither Bös nor Herrington discloses or suggests this

⁶ While the Office did not issue any rejection over Bös or Herrington, or otherwise discuss them during prosecution, they are listed on the cover of the ’515 patent and are “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).

limitation, confirming no error (let alone material error) was made by the Office.

(*See id.*)

Herrstedt, which is Azurity's base reference, is cumulative of Reddy because Azurity relies on it "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 1007 at 212 (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 Herrstedt for the same alleged teaching of an aprepitant-based three-drug regimen for treating CINV. (*See, e.g.*, Petition at 16-17 ("Herrstedt reports studies treating highly-emetogenic chemotherapy patients with a triple-drug combination including an NK₁ antagonist (aprepitant)."))

Hargreaves, in turn, is cited by Azurity as allegedly teaching that "a therapeutically-effective amount of NK₁ antagonist occupies at least about 75% . . . of NK₁ receptors in the striatum" to address claim 1's limitation that "netupitant or a pharmaceutically acceptable salt thereof . . . occupies 70% or more of NK₁ receptors in the striatum seventy-two hours after said administration." (Petition at

35-37.) The Office considered similar claim language during prosecution of the '515 patent and alleged that the prior art before it discloses “wherein said netupitant occupies at least 80% of NK1 receptors in the striatum,” (Ex. 1007 at 212-213), but nonetheless allowed the claims to issue. Accordingly, Hargreaves is not materially different from the prior art that was before the Office.

B. Azurity Fails to Demonstrate 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.” *See 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 '515 patent by overlooking or misapprehending the prior art. *Id.* at 8 n.9 (“An example of a material error may include misapprehending or overlooking specific teachings of the relevant prior art where those teachings impact patentability of the

challenged claims.”).⁷

1. Azurity’s Cited Art Does Not Disclose the Claimed Single, One-time Dose of Netupitant

Here, the Office allowed the ’515 patent after Helsinn amended the claims to specify that “one single dose of netupitant is administered over a five-day period of time, and the single dose is effective to prevent nausea and vomiting during the entire five-day period.” (Ex. 1007 at 324, 328, 342.) Azurity relies on Bös and Herrington as teaching or suggesting this limitation. (*See, e.g.*, Petition at 20 (relying on Bös’s teaching of a 30 hour “half-life”); *id.* at 20-21 (relying on Herrington for teaching “a single dose of aprepitant” has “similar effectiveness” as

⁷ Helsinn respectfully requests that the Director review the arguments set forth below 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 merits arguments verbatim but should briefly explain why the merits are relevant.”).)

“dosing aprepitant three times”).) But neither reference discloses any dosing regimen for netupitant, much less that administering a *single dose* of netupitant is effective in treating *nausea* and vomiting for five consecutive days after an emesis-inducing event, as claimed.

The Office did not err when issuing the claims of the '515 patent over the disclosures in Bös. For example, Bös is silent on how many times netupitant should be administered. In addition, Bös discloses a large genus that covers millions of compounds (in addition to netupitant), as well as uses for such compounds generally. (*See generally* Ex. 1014.) In Bös’s brief description of various *in vivo* animal studies that included netupitant, Bös stated that netupitant’s “antagonism . . . had a functional half life of 30 hours” in one study, while in other studies “the compound has a terminal half life of 24 hours” and “18 hours.” (*Id.* at 18:64-19:37.) Based solely on these statements, Azurity concludes without any support that a half-life of 30 hours is a “*large* half-life value” that provides “reason to omit subsequent NK1-antagonist dosing.” (Petition at 20 (emphasis added).) Its expert then repeats this conclusory attorney argument without further explanation. (*Compare id.*, with Ex. 1009 at ¶ 522.)

Azurity’s superficial analysis fails to show any error by the Office here, let alone a material one. *First*, Azurity provides no explanation regarding why or how a 30-hour half-life suggests that administering netupitant would be effective against

nausea and vomiting for five consecutive days (120 hours). This lack of explanation is particularly conspicuous given that netupitant was found to have a shorter half-life (24 and 18 hours) in other studies.

Second, Azurity ignores that Bös did not evaluate netupitant’s impact on nausea. Instead, Bös’s studies were limited to emesis. (*See* Ex. 1014 at 19:10-30.) But claim 1 of the ’515 patent recites that the “single dose of netupitant or pharmaceutically acceptable salt thereof if [sic] effective to treat said *nausea* and vomiting for said five consecutive days.” (Ex. 1003 at claim 1 (emphasis added).) Azurity offers no explanation for why a POSA would have believed a drug that is allegedly effective against emesis would also have been effective against nausea. Indeed, and as discussed above in Section II.A, the evidence confirms that a POSA would not have been believed that to be the case.

Azurity’s analysis of Herrington likewise fails to show any material error by the Office. Azurity cites Herrington for its alleged disclosure that a single dose of aprepitant has similar effectiveness as compared to a three-day dosing regimen. (Petition at 20.) But Herrington does not even mention netupitant, and the only studies it discusses pertain to aprepitant. (*See generally* Ex. 1016.) Azurity assumes that Herrington’s aprepitant results are equally applicable to a drug regimen involving netupitant, but provides no basis for why a POSA would have made such an assumption. In fact, the evidence shows that such an assumption

would have been wrong because netupitant had unexpectedly superior properties over aprepitant. (*Supra* Sections II.A-B.)

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

Azurity's failure to show disclosure or suggestion of the limitation that was added to the claims before the Notice of Allowance (*see supra* Section IV.B.1) confirms that the Office did not materially err in allowing the challenged claims. But this is not the only deficiency in Azurity's obviousness challenge. For example, as discussed below, Azurity fails to factually support its alleged motivation to combine the teachings of Herrstedt and Bös.

Azurity relies on Herrstedt as allegedly disclosing a "triple-drug combination including an NK₁ antagonist (aprepitant)" for treating CINV, (*see, e.g.*, Petition at 16-17, 32-33), and on Bös as a secondary reference providing an alleged motivation for substituting netupitant for aprepitant. (*See, e.g., id.* at 17-18, 33-35). Azurity contends that Bös recognizes netupitant as an "*improved* NK₁ antagonist." (Petition at 31 (emphasis added); *see also id.* at 18 (alleging that Bös recognizes netupitant as a "potent and selective NK₁ antagonist").) Based on this alleged recognition, Azurity concludes that "[a] POSA had good reason to substitute Bös' newer NK₁ antagonist (netupitant) for the existing NK₁ antagonist aprepitant in Herrstedt's combination and reasonably expect the combination to work as well or

better.” (*Id.* at 31.) But neither Azurity’s Petition nor the declaration of its expert Dr. Peroutka, which merely *parrots* the Petition, contains any evidence that netupitant was recognized as an “improved” NK-1 receptor antagonist compared to aprepitant.

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. 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 cited portions of Dr. Peroutka’s declaration do not shed any additional light on why a POSA would substitute netupitant for aprepitant in Herrstedt’s three-drug regimen. Indeed, they are virtually identical to the Petition, (*compare* Petition at 18, *with* Ex. 1009 at ¶ 516; *compare* Petition at 31, *with* Ex. 1009 at ¶ 599), and thus deficient for the above-identified reasons.

These exemplary deficiencies in Azurity’s obviousness challenge 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 also 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, 4,870 words. This word count does not include the items excluded by 37 C.F.R. § 42.24.

Dated: August 4, 2025

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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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