UNITED STATES PATENT AND TRADEMARK OFFICEP

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Padagis US LLC,
Petitioner

v.

Neurelis, Inc.,
Patent Owner

Case No. IPR2025-00466
Patent No. 11,793,786

PATENT OWNER'S PRELIMINARY RESPONSE

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37 C.F.R. §42.23(b) 26

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EXHIBIT LIST

Exhibit	Description
2001	*Clinical Superiority Findings*, U.S. FOOD & DRUG ADMIN. (Dec. 18, 2024) https://www.fda.gov/industry/designating-orphan-product-drugs-and-biological-products/clinical-superiority-findings
2002	Scheduling Order entered in *Neurelis, Inc. v. Padagis LLC*, 1:24-cv-00562, D.I. 20 (D. Del. Aug. 28, 2024)
2003	Preliminary Invalidity Contentions served in *Neurelis, Inc. v. Padagis LLC*, 1:24-cv-00562 (D. Del. Dec. 20, 2024)
2004	Markman Order entered in *Gilead Sciences, Inc. v. Lupin Ltd.*, 1:22-cv-00615-MN, D.I. 280 (D. Del. Feb. 21, 2025)
2005	Markman Order entered in *Spinal Generations, LLC v. Depuy Synthes, Inc.*, 1:22-cv-01368 (MN), D.I. 147 (D. Del. Oct. 16, 2024)
2006	Orange Book Listing for U.S. Patent No. 11,241,414
2007	Declaration of Nicholas A. Peppas, Sc.D., dated December 6, 2018 in *Aquestive Therapeutics, Inc. v. Hale Biopharma Ventures, LLC*, IPR2019-00451, Exhibit 1041 (Jan. 29, 2019)
2008	Declaration of Daniel P. Wermeling, Pharm.D., dated January 27, 2020 in *Aquestive Therapeutics, Inc. v. Hale Biopharma Ventures, LLC*, IPR2019-00451, Exhibit 1150 (Jan. 28, 2020)
2009	Application No. 18/782,666 ("'666 Application")
2010	Information Disclosure Statements filed with the Application No. 18/782,666 ("'666 Application") Prosecution History
2011	Sai H. S. Boddu, Sneha Kumar, *A Short Review on the Intranasal Delivery of Diazepam for Treating Acute Repetitive Seizures*. Pharmaceutics 2020; 12, 1167

2012	Cornett et al., *VALTOCO® (Diazepam Nasal Spray) for the Acute Treatment of Intermittent Stereotypic Episodes of Frequent Seizure Activity*, Neurology International 2021; 13:64–78
2013	Scheduling Oral Order entered in *Neurelis, Inc. v. Padagis LLC*, 1:24-cv-00562, D.I. 47 (D. Del. March 11, 2025) Order Granting Stipulation to Extend Certain Fact Discovery Deadlines entered in *Neurelis, Inc. v. Padagis LLC*, 1:24-cv-00562, D.I. 65 (D. Del. May 15, 2025)
2014	Jacqueline A. French, Timothy A. Pedley, *Initial Management of Epilepsy*, New England Journal of Medicine 2008; 359:166-76 ("French & Pedley 2008")
2015	Penovich et al., *Burden of Seizure Clusters on Patients With Epilepsy and Caregivers*, The Neurologist 2017; 22: 207-214
2016	Cloyd et al., *Overcoming the Challenges of Developing an Intranasal Diazepam Rescue Therapy for the Treatment of Seizure Clusters*, Epilepsia 2021; 62:846-856
2017	Hogan, R.E., et al., *Bioavailability and Safety of Diazepam Intranasal Solution Compared to Oral and Rectal Diazepam in Healthy Volunteers*, Epilepsia, 61:455-464 (Feb. 2020)
2018	Lindsay M. Higdon and Michael R. Sperling, *A Review of a Diazepam Nasal Spray for the Treatment Of Acute Seizure Clusters and Prolonged Seizures*, J Expert Review of Neurotherapeutics 2021; 21(11):1207-1212
2019	Bechgaard et al., *Solubilization of Various Benzodiazepines for Intranasal Administration, a Pilot Study*, Pharmaceutical Development and Technology 1997; 2(3):293-296

2020	Gizurarson, S., et al., *Intranasal Administration of Diazepam Aiming at the Treatment of Acute Seizures: Clinical Trials in Healthy Volunteers*, Biol. Pharm. Bull., 22(4):425-427 (Apr. 1999)
2021	Ivaturi, V.D., et al., *Bioavailability and Tolerability of Intranasal Diazepam in Healthy Adult Volunteers*, Epilepsy Res., 84:120-126 (2009)
2022	Schrier, L., et al., *Pharmacokinetics and Pharmacodynamics of a New Highly Concentrated Intranasal Midazolam Formulation for Conscious Sedation*, Brit. J. Clin. Pharmacol., 83:721-731 (Apr. 2017)
2023	Penovich et al., *Benzodiazepines for the Treatment of Seizure Clusters*, CNS Drugs 2024; 38:125-140
2024	Kapoor et al., *A Review of Intranasal Formulations for the Treatment of Seizure Emergencies*, Journal of Controlled Release 2016; 237: 147-159
2025	Rabinowicz et al., *Improvement of Intranasal Drug Delivery with Intravail® Alkylsaccharide Excipient as a Mucosal Absorption Enhancer Aiding in the Treatment of Conditions of the Central Nervous System*, Drugs in R&D 2021; 21:361-369
2026	Acorda Therapeutics, Letter to Plumiaz Clinical Trial Participants, May 20, 2016
2027	U.S. Patent No. 6,193,985 ("Sonne")
2028	Corrected Opening Brief for Appellee Aquestive Therapeutics, Inc. in *Neurelis, Inc. v. Aquestive Therapeutics, Inc.* (Fed. Cir. 21-1038), dated March 31, 2021 (D.I. 21)
2029	Certified transcription of October 5, 2021 oral hearing in *Neurelis, Inc. v. Aquestive Therapeutics, Inc.* (Fed. Cir. 21-1038)

I. INTRODUCTION

Padagis's Petition anchors itself to a primary reference, the Gwozdz PCT, that is not prior art because the challenged claims have perfected priority to a provisional application filed a year before the Gwozdz PCT. Without this reference, the single obviousness ground the Petition advances must fail. Even with this reference, the obviousness ground must fail for a separate and independent reason. Gwozdz PCT supplies the only evidence on which the Petition relies to substantiate a motivation to combine. But the critical date of this subject matter upon which Padagis relies is too late for it to be available to a skilled artisan as prior art to the challenged claims regardless of which priority date is accorded to those claims. Without the undelying subject matter or its support of a motivation to combine, the Petition's obviousness ground collapses. Either of these reasons prevents Padagis from establishing a reasonable likelihood of prevailing as to even one challenged claim and therefore suffices to deny institution. Together, they mandate denial.

II. PRELIMINARY STATEMENT

In the past patients with epilepsy suffering from seizure clusters needed an acute rescue therapy that they or their caregivers could administer without help from medical professionals. Benzodiazepines, particularly diazepam, were effective and could be administered intravenously in the emergency room but not at school, home,

or work, where most seizure episodes occur. The only diazepam rescue product approved for seizure clusters and that could be used outside the medical clinic was a gel that had to be administered rectally. The discomfort and social embarrassment of this route of administration compromised utilization. Some environments refused to administer it at all due to perceived legal risks and privacy restrictions. Nevertheless, this product remained the only marketed rescue therapy for seizure clusters for more than twenty years due to the difficulty of developing alternatives.

Patent Owner Neurelis solved that problem. Neurelis developed a tailored class of pharmaceutical solutions for nasal administration that could be used in any setting, without medical assistance, to deliver a highly effective, well-tolerated dose of diazepam to a patient before, during, or after a seizure cluster. Neurelis researchers found that dissolving diazepam in vitamin E, benzyl alcohol, and ethanol yielded a concentrated, stable, and well-tolerated nasal spray that possessed physicochemical properties (*e.g.*, viscosity) that were ideally suited for intranasal administration to avoid first-pass metabolism. They also believed the addition of the absorption enhancer n-dodecyl beta-D-maltoside could increase diazepam absorption across the nasal mucosa. The Patent Office recognized this innovation and awarded Neurelis several patents directed to pharmaceutical solutions, including the challenged U.S. Patent No. 11,793,786 (the "'786 Patent"). This patent covers Neurelis's anti-seizure product, Valtoco, which FDA awarded Orphan Drug

Exclusivity due to its clinical superiority that provides "a major contribution to patient care." 21 C.F.R. §316.3(b)(3)(iii); EX2001, 4.

The obviousness ground this Petition advances should be denied for its threshold deficiencies:

First, institution should be denied because Gwozdz PCT is not prior art to the '786 Patent for several independent reasons. Relevant here, every claim of the '786 Patent is entitled to the March 28, 2008 priority date of the '558 Provisional, as the Office explicitly found during the earlier prosecution of the child of the '786 Patent, U.S. Patent No. 11,241,414 (the "'414 Patent"). Since that is the same day as the earliest filing date to which any subject matter in Gwozdz PCT can be accorded, Gwozdz PCT is not prior art to the '786 Patent.

The Petition asserts that collateral estoppel prevents Neurelis from disputing that the '558 Provisional "does not provide adequate written description support for the 'alkyl glycoside' limitation" of the claims, without which – the Petition asserts – the earliest priority date for the '786 Patent would be in 2009. Petition, 8-9. On its face this assertion is irrelevant to the claims of the '786 Patent, which nowhere recite "alkyl glycoside." Rather, every claim specifically recites "n-dodecyl beta-D-maltoside." That was a known compound identified by name in the '558 Provisional. This disclosure satisfies written description as a matter of law. *See, e.g.*, *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1350 (Fed. Cir. 2010)

(*en banc*) ("adequate written description requires a precise definition, such as by structure, formula, ***chemical name***, physical properties, or other properties . . . sufficient to distinguish" the subject matter) (emphasis added).

Knowing that this infirmity exists in its Petition, Padagis responds that ***the way*** the '558 Provisional discloses n-dodecyl beta-D-maltoside is inadequate because it was incorporated by reference in the '558 Provisional via a page from a catalogue of the Sigma Chemical Company. Petition, 12-15. Relying on authority that is irrelevant to priority claims, Padagis alleges that a patent application cannot rely on "essential material" included by reference in a priority document, including a provisional application. Padagis's response is legally insupportable. Both caselaw and the MPEP specifically permit an application (like that issuing as the '786 Patent) "to rely upon the filing date of an earlier application, ***even if the earlier application itself incorporates essential material by reference to another document***." MPEP §608.01(p)(1)(B) (citing *Ex parte Maziere*, 27 U.S.P.Q.2d 1705, 1706-07 (B.P.A.I. 1993)) (emphasis added).

Thus, the Office concluded during the prosecution of Neurelis's '414 Patent that the claims of that patent – which like the claims that issued in the '786 Patent all recited "n-dodecyl beta-D-maltoside" – "receive a priority date of March 28, 2008. As such, Gwozdz [PCT] . . . does not qualify as prior art." EX1004 , 28. The '414 Patent was prosecuted and issued before the '786 Patent, and was reviewed by

the same Examiner.[1] The Office's conclusion during the '414 Patent's prosecution is equally relevant to the '786 Patent; it deals the Petition a fatal blow.

Second, the Petition fails to provide prior art evidence of a motivation for a person of ordinary skill to combine Gwozdz PCT with Meezan. The only evidence on which the Petition relies to establish a motivation to combine these references is subject matter in Gwozdz PCT referring to the option to include "penetration enhancers" in certain embodiments of the disclosed compositions. *See* Petition, 29, 31-32, 41. But this subject matter – the concept of "penetration enhancers" – was first disclosed in Gwozdz PCT, itself (*i.e.*, the March 27, 2009 Gwozdz PCT application). The Gwozdz Provisional omits that element.

A provisional application must provide support for subject matter carried forward into a published application and used in a patentability challenge for that subject matter to be entitled to the filing date of the provisional. *See In re Riggs*, 131 F.4th 1377, 1384 (Fed. Cir. 2025) ("to claim priority to the provisional filing date, the portion of the application relied on . . . as prior art must be supported by the provisional application."). *See also Ex parte Robert A. Mann & Eric Colaviti*, 2016

[1] The '414 Patent was prosecuted on a faster timeline and issued before the '786 Patent, even though it was a child application of the '786 Patent, because the '414 Patent was prosecuted under the Track One prioritized examination provisions (*see* EX1004, 117), whereas the '786 Patent was prosecuted under standard provisions.

WL 7487271, at *5 (PTAB Dec. 21, 2016). The Gwozdz Provisional does not support the "penetration enhancer" disclosure on which the Petition relies for a motivation to combine, and so that subject matter is not prior art. Aside from that disclosure, the Petition fails to articulate a rationale for combining Gwozdz PCT and Meezan and thus cannot carry its threshold burden of showing a reasonable likelihood that at least one claim of the '786 Patent is unpatentable. *In re NuVasive, Inc.*, 842 F.3d 1376, 1382-83 (Fed. Cir. 2016) ("Our precedent dictates that the PTAB must make a finding of a motivation to combine when it is disputed."); *see also* 35 U.S.C. §314(a).

For these and other reasons below the Board should not institute.

III. FACTUAL BACKGROUND

The facts are from the Petition and Exhibits (EX) filed by Padagis and by Neurelis.

A. Rescue Therapy for Seizures Before March 2008

1. Therapeutic Rationale

Millions of Americans suffer from epilepsy. EX2014, 1 (6-8 per 1000 Americans). While treatments exist for epileptic seizures, about 30% of patients have uncontrolled seizures despite treatment with antiepileptic drugs. EX2015, 1. Some of these patients may experience bouts of seizure clusters. *Id.* Patients suffering from seizure clusters are at risk for brain or neuronal damage, psychosis,

and higher mortality relative to patients without clusters. *Id*. These bouts "must be treated quickly and effectively to interrupt the cluster and prevent the progression to prolonged seizures and/or status epilepticus." EX2016, 2.

For many years patients suffering from seizure emergencies received intravenous benzodiazepines, including diazepam. *Id.*; EX1001, 1:61-67. Intravenous administration "is not practical for nonmedical caregivers." EX2016, 2; *see also* EX1001, 1:61-67. Most seizure clusters occur outside the hospital environment. EX2016, 2. And a seizing patient "suffers from rigid muscles and uncontrollable movement" which can make "intravenous administration difficult or inconvenient." EX1001, 16:17-20. "Patients need readily available, easily administered, nonintravenous rescue therapies" for quick use outside the hospital. EX2016, 2.

The first out-of-hospital treatment for seizure clusters was a gel formulation of diazepam (called "Diastat"), approved in the U.S. in 1997, which must be administered rectally. *Id.*, 2-3. Despite its reasonable efficacy, it has many drawbacks. "[M]any adults and older children find this route of administration socially embarrassing, which leads to underutilization." *Id.* Some environments, including schools, refuse to administer this product "citing purported legal restrictions, the child's privacy, and ignorance about dosing." *Id.*, 3. Rectal

diazepam also exhibits marked variability in bioavailability "with some subjects showing negligible diazepam plasma levels." EX2017, 8.

Other routes of administration were considered for benzodiazepines, but all presented problems. Insertion into the mouth, including oral, buccal, and sublingual administration is complicated by the seizure process. "[D]ue to the nature of seizures and muscle spasms, it can be extremely difficult for either a patient or a care-giver to administer the benzodiazepine drug orally." EX1001, 1:58-60. Oral administration also risks choking. EX2017, 8. And oral administration requires longer times and larger doses to overcome first pass metabolism and reach therapeutically relevant concentrations in the bloodstream. EX1001, 1:50-57.

In view of these limitations, intranasal administration was investigated. In principle, intranasal administration "has a number of theoretical advantages" including that this route "is noninvasive and easy to access, may allow rapid onset of effect, avoids first-pass metabolism, does not require patient cooperation, and is socially acceptable." EX2016, 3. But implementing a solution for nasal administration of benzodiazepines posed many problems.

2. Problem of Concentration

Intranasal administration requires working with the anatomical limits of the nose, including small surface area such that drug delivery is limited to about 100-200 μL to avoid leakage or swallowing. *Id*. Initial attempts at intranasal

administration used the available (dilute) intravenous benzodiazepine formulations as nasal drops. This approach had several drawbacks. First, the solutions were too dilute, requiring 10-to-20-fold more fluid than the mucosa can support (1-2 mL) to deliver a potentially therapeutic dose. *E.g.*, EX1018, 502. Portions of such volumes drip out or are swallowed (EX2016, 3), confounding dosing and consistent bioavailability. Second, administration of such formulations has never "been rigorously designed or tested to ensure adequate absorption nor is duration of action known." EX2018, 3. Third, such administration required the intercession of a medical professional. *See* EX1019, 54, Back Cover (all actions, including use of nasal spray device require EMT or paramedics, and also require contact with "medical control"). Fourth, administering drops "require patient to hold their head back so as not to lose drug to environment or throat," which is infeasible in a seizing patient. EX2017, 7. Finally, these drops were not well tolerated. *See, e.g.*, EX1032, 712 (nasal irritation requiring anesthesia with lidocaine); EX1018, 502 (large volume "may account for the lacrimation, burning and general discomfort"). More concentrated solutions were needed.

3. Problem of Solubility

Aqueous drug solutions are typically used for treatments because they are well-tolerated. But "most benzodiazepines are so slightly soluble in water that a therapeutically effective amount cannot be dissolved in a volume of aqueous solvent

that is amenable to application to a mucosal membrane." EX1001, 15:61-65. One way of addressing this problem that academic researchers pursued was to add various organic solvents or co-solvents that could improve benzodiazepine solubility. *E.g.*, EX2019, 3, Table 1 (testing solubility of diazepam in various glycols); EX1035, 172 (testing diazepam solubility in seven non-aqueous solvents). But solvents are often intolerable, or even toxic.

4. Problem of Tolerability

Theoretically, the addition of organic solvents could improve solubility of benzodiazepines. But attempts to do so rendered the resulting solution intolerable to patients. Organic solvents tend to irritate the nasal mucosae. EX1035, 172 (six solvents "found to be irritating and unsuitable for intranasal application"). They also are often toxic. EX2016, 6, Table 2).

Many researchers observed this problem and recognized that it limited clinical opportunity. *See, e.g.*, EX2020, 2 (majority of subjects felt some irritation); EX2021, 6 ("The tolerability scores indicate that the intranasal formulation caused considerable, but transient, pain"), 1 ("not well tolerated"); EX1015, 357 (discomfort "a major limitation"); EX2022, 8 ("substantial nasal toxicity"). Acorda Pharmaceuticals's attempt to develop a commercial intranasal diazepam product also showed similar problems. EX2016, 7 ("Adverse events that may have been related to the use of the organic solvent included dysgeusia (25.8%), nasal

discomfort (22.6%), increased lacrimation (16.1%), nausea (16.1%), rhinorrhea (16.1%), somnolence (16.1%), oropharyngeal pain (12.9%), paranasal sinus hypersecretion (12.9%), and tongue injury (12.9%).").

5. Problem of Bioavailability

Bioavailability refers to the extent a drug is absorbed by the body and therefore can affect the body. Bioavailability of a benzodiazepine is correlated with its efficacy, such that bioavailability can be used as supporting evidence for efficacy. *See* EX2023, 8. Drugs administered intravenously are definitionally 100% bioavailable. *See* EX2016, 4, Table 1 (comparing percentage bioavailability versus intravenous, also known as "absolute bioavailability"). Thus, attempts to develop other routes of administering benzodiazepines seek to approach intravenous bioavailability.

The intranasal route requires both avoiding first-pass metabolism and traversing the mucosa, which can be difficult. EX2017, 7 ("nasal mucosal permeability of diazepam present[s a] unique challenge[] for consistent drug delivery."). Mucosal and ciliary clearance mechanisms provide a challenge to intranasal delivery, because they "control[] the contact time of inhaled drug with nasal epithelia, thereby influencing the extent of drug absorption." EX2024, 4. As well, nasal cell anatomy is constructed with tight cell-cell junctions to block foreign

agents from entering through the cell wall, which can impede introduction of therapeutics. EX2025, 3-4; EX2016, 8.

Inadequate and highly variable bioavailability was commonly observed by researchers and industry alike. For example, Lindhardt and colleagues observed that their polyethylene glycol based intranasal solution provided only 42-45% bioavailability of diazepam versus intravenous. EX1013, 521. A few years later, Acorda Pharmaceuticals sought FDA approval for an intranasal diazepam product, Plumiaz, conducting several clinical studies of it. *See* EX2024, 3, Table 2 (showing five clinical studies underway). But development was "discontinued after a study in patients found suboptimal nasal absorption compared with rectal diazepam." EX2016, 7; EX2026.

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The combined need for a small administration volume, high concentration, high tolerability, and high bioavailability resulted in the fact that more than twenty years elapsed between FDA approval of rectal diazepam and FDA approval of intranasal diazepam for the acute treatment of seizure clusters. EX2016, 3.

B. The '876 IPR

In January 2019, Aquestive Therapeutics filed a petition for *inter partes* review against every claim of Neurelis's '876 Patent. *Aquestive Therapeutics, Inc. v. Hale Biopharma Ventures, LLC*, IPR2019-00451, Paper 1 (Jan. 29, 2019). The

'876 Patent claimed methods for administering pharmaceutical compositions that included, *inter alia*, "alkyl glycosides." The petition asserted two grounds for invalidity, for obviousness over Gwozdz PCT in view of Meezan (claims 1-16 and 24-36) or for obviousness over Gwozdz PCT in view of Meezan and Cartt (claims 17-23). *Id.* at 5. In the '876 IPR, there was no dispute that Meezan was prior art, and for purposes of that IPR, Patent Owner did not contest that Gwozdz PCT was entitled to the filing date of its provisional application. EX1040, 14. There was a dispute as to the priority date of the '876 Patent. The Board found that at the preliminary stage, Neurelis had failed to carry its burden of production to show that all of the '876 claims were supported throughout the priority chain. *Aquestive Therapeutics,* IPR2019-00451, Paper 14 at 5-6 (Sept. 27, 2019). Consequently, the Board instituted on all claims.

As the Board noted, the '876 Patent set forth one independent claim (claim 1), from which all the other claims depended. EX1040, 4-5. That claim recited, in addition to other elements, "an alkyl glycoside." *Id.* The Board construed every claim of the '876 Patent to require "an alkyl glycoside." *Id.* at 14, n.6. The Board found that the disclosure in the '558 Provisional "is not sufficient to provide written description support for the 'alkyl glycoside' limitation in the claims." *Id.* at 19, n.7. Consequently, the Board found that Patent Owner had failed to perfect priority of the '876 Patent's claims to the '558 Provisional, and as a result Gwozdz PCT was

prior art. *Id.* at 23. The Board then evaluated whether the '876 Patent's claims were obvious in view of the cited art and found that the petitioner had proven by a preponderance of the evidence that every '876 claim was unpatentable. *Id.* at 68. This decision was affirmed without decision by the Federal Circuit.

C. The '786 Patent

1. Prosecution History

The '786 Patent issued from a U.S. application No. 17/228,514, ("the '514 Application,") that claims priority – through a continuation – to the '439 Application, filed March 27, 2009, and to the '558 Provisional, filed March 28, 2008. None of the then-pending claims of the '514 Application, which issued as the claims of the '786 Patent, recited "an alkyl glycoside." Instead, every claim recited "n-dodecyl beta-D-maltoside." See EX1002, 176-78.

When it filed the '514 Application, Neurelis submitted all the art on which this Petition relies (specifically including Meezan and Gwozdz PCT). *Id.*, 487-515. Neurelis also submitted the entire record from the '876 IPR on which the Petition relies, including the '876 IPR Petition, Petitioner and Patent Owner briefs, expert declarations and other exhibits, Institution Decision and requests for rehearing of it, the Final Written Decision, and appellate briefs. *Id*., 374-94.

The Office considered all those documents. *Id*., 72-100.

The obviousness argument on which Padagis relies (Gwozdz PCT and Meezan) had ***previously*** been specifically discussed with the ***same Examiner*** during an interview in the prosecution of the '414 Patent, on November 5, 2021. EX1004, 29. The '876 IPR also was discussed at that time. *Id.* The question of whether priority of the then-pending claims had been perfected to the '558 Provisional was addressed. *Id.* ("Examiner discussed the priority of the recitation of n-dodecyl beta-D-maltoside. Applicant[']s representative pointed out where Applicants believed that priority existed in the priority documents."). After review, in the subsequent Notice of Allowance the Examiner agreed that priority existed for the '414 claims, all of which recited n-dodecyl beta-D-maltoside. *Id.* at 27-28 ("Reasons for Allowance"). Examiner Milligan stated that "Applicants['] claims are considered to be supported in the priority documents" and "[t]he provisional Application incorporates a listing of n-dodecyl β-D-maltoside by reference to a Sigma Catalog" and that as a consequence "[t]he instant claims receive a priority date of March 28, 2008. As such Gwozdz [PCT] (WO 2009-120933) does not qualify as prior art." *Id.*

Like the claims of the '414 Patent, every claim of the '786 Patent requires n-dodecyl beta-D-maltoside. EX1001, 36-37.

Furthermore, Examiner Milligan also issued a rejection of the then-pending claims during prosecution of the '786 Patent based on Meezan (EX1010), on which this Petition relies, and Sonne (U.S. 6,193,985). EX1002, 66. Following that

rejection, Neurelis's counsel discussed these matters with the Examiner, including discussing the withdrawal of the '876 Patent due to the '876 IPR. *Id.*, 59. This IPR had been the subject of previous discussion with Examiner Milligan in the '414 prosecution, as discussed above. Neurelis overcame the obviousness rejection based in part on Meezan (*id.,* 43-46), and the Examiner withdrew it, allowing the claims (*id.*, 20-22).

2. The Claimed Invention

The '786 Patent claims pharmaceutical solutions of diazepam for nasal administration having several specific characteristics. Claim 1, below, is exemplary:

> 1. A pharmaceutical solution for nasal administration consisting of:
>
> > a therapeutically effective amount of diazepam or a pharmaceutically acceptable salt thereof;
> >
> > one or more natural or synthetic tocopherols or tocotrienols selected from the group consisting of α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, α-tocotrienol, β-tocotrienol, γ-tocotrienol, δ-tocotrienol, tocophersolan, any isomers thereof, any esters thereof, and any combinations thereof, in an amount from 30% to 95% (w/w);
> >
> > one or more alcohols in an amount from 10% to 70% (w/w), wherein the one or more alcohols comprises benzyl alcohol; and
> >
> > n-dodecyl beta-D-maltoside.

EX1001, claim 1. Certain characteristics of the claimed invention are detailed below.

a. Use of a Solvent System of Vitamin E and Alcohols

Vitamin E and other tocopherols and tocotrienols (collectively "tocols") provide some solubility for diazepam and are highly tolerable but are too viscous for a nasal spray standing alone. Consequently, when vitamin E had been used as a carrier in the prior art, it was as a component of suspensions and emulsions. *E.g.*, EX2027, 4:1–7:12. These had drawbacks. They were hard to create and to stabilize. EX1001, 30:47-49. They left an oily residue. *Id.*, 30:49-50. Alcohols had good capacity to dissolve diazepam but were considered undesirable for intranasal use due to their tendency to cause irritation and intolerability. EX2027, 3:1-4, 3:65-67.

Neurelis's inventors discovered that the addition of alcohols, such as benzyl alcohol and often ethanol, to vitamin E maintained diazepam solubility while lowering the viscosity of the composition. EX1001, 35:27-37. Unexpectedly, the inventors also discovered that ethanol and benzyl alcohol could be used in surprisingly large amounts without irritating the patients' nasal mucosae. *Id.*, 30:50-62.

b. Inclusion of n-dodecyl beta-D-maltoside

The Neurelis inventors also explored the use of absorption enhancers to enhance the transit of diazepam across the nasal mucosa. One such agent they explored was n-dodecyl-β-D-maltoside. *Id.*, 3:39-43, 5:3-7, 8:6-10, 13:56-61, 31:50-32:18, 37:16-32. This component was thought to increase bioavailability "by

transiently and reversibly loosening tight junctions between cells" in the nasal mucosae. EX2016, 8.

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The combination of these components provides a pharmaceutical solution for nasal administration of diazepam that Neurelis provides to patients as Valtoco. Every challenged claim of the '786 Patent covers Valtoco. This product can be administered nasally in an acute therapeutic environment to treat seizure cluster victims. EX1001, 18:64-19:3. Valtoco was approved in January 2020 and was awarded Orphan Drug Exclusivity because it possesses clinical superiority and provides "a major contribution to patient care." 21 C.F.R. §316.3(b)(3)(iii); EX2001, 4. This superiority has met with industry praise and has supported substantial commercial success.

D. Padagis's Petition

Padagis filed this Petition on January 17, 2025, along with two other petitions. Petition 1 asserts invalidity of the '414 Patent, which is the child of the '786 Patent, on substantially the same bases as this Petition asserts: Gwozdz PCT in view of Meezan.[2] *Padagis US, LLC v. Neurelis, Inc.*, IPR2025-00465, Paper No. 2 (PTAB

[2] The instant Petition adds to Gwozdz PCT and Meezan an additional reference to Cartt (EX1065) with respect to claims 20-21, and a reference to USP (EX1066) with respect to claims 26-27. Petition, 6, 61-67. Neurelis's arguments in this

Jan. 17, 2025). Petition 3 asserts invalidity of the related '546 Patent, which also claims priority to the '439 Application and the '558 Provisional, on substantially the same bases as this Petition asserts. *Padagis US, LLC v. Neurelis, Inc.*, IPR2025-00464, Paper No. 2 (PTAB Jan. 17, 2025).

All three petitions rely on declarations from Dr. Maureen Donovan, which are substantially identical to each other, and which substantially reiterate the language included in the petitions. *See Padagis US, LLC v. Neurelis, Inc.*, IPR2025-00464, Paper 2 (PTAB Jan. 17, 2025); *Padagis US, LLC v. Neurelis, Inc.*, IPR2025-00465, Paper 2 (PTAB Jan. 17, 2025); EX1062.

The Petition proposes a construction for the term "vitamin E" as it appears in claims 10 and 26-27 of the '786 Patent. Petition, 17. Petitioner contends that no construction is required, as this term has a plain and ordinary meaning to a person of ordinary skill in the art.

The Petition proposes a definition of the person of ordinary skill in the art. Petition, 26. Although Neurelis does not acquiesce to that definition, solely for the purpose of evaluating whether the Petition should be instituted, Neurelis does not dispute that definition.

Preliminary Response are equally relevant to these grounds, and are unaffected by the additional references included within them.

IV. ARGUMENT

The institution decision is given entirely to the Board's discretion. *See, e.g.*, *Harmonic Inc. v. Avid Tech., Inc*., 815 F.3d 1356, 1367 (Fed. Cir. 2016) ("[T]he PTO is permitted, but never compelled, to institute an IPR proceeding."). The law permits institution of an IPR only if the petitioner demonstrates that "there is a reasonable likelihood that the petitioner would prevail with respect to at least one of the claims challenged in the petition." 35 USC §314(a). Padagis fails to cross this threshold. Padagis's Petition bases itself almost entirely on an erroneous assertion of collateral estoppel, and a teaching not available in the prior art. Amongst other requirements, a party can be estopped on an issue only if that issue is 1) identical to one that was 2) previously litigated. Padagis fails to establish either of these necessary predicates on multiple issues on which their obviousness argument is based. As the Office explicitly found during its previous prosecution of the '414 Patent, claims reciting "n-dodecyl beta-D-maltoside" are entitled to priority on March 28, 2008. This reasoning applies equally to the '786 Patent's claims, disqualifying the key reference, Gwozdz PCT, from being prior art. Moreover, the only support the Petition cites for a purported motivation to combine is subject matter that cannot be prior art regardless of which priority date one accords the '786 Patent.

Thus, Padagis's Petition is both procedurally and substantively infirm. Institution should be denied.

A. Gwozdz PCT Is Not Prior Art to the '786 Patent

Every claim of the '786 Patent is directed to a pharmaceutical solution consisting of diazepam, vitamin E or other tocols, benzyl alcohol, optionally one or more additional alcohols (such as ethanol), and n-dodecyl beta-D-maltoside. The '786 Patent claims priority to the '558 Provisional, filed on March 28, 2008. As the Office explicitly found during previous prosecution of the '414 Patent, claims reciting "n-dodecyl beta-D-maltoside" are "supported in the priority documents" and therefore "receive a priority date of March 28, 2008." EX1004, 27-28. Every claim of the '786 Patent likewise requires "n-dodecyl beta-D-maltoside," and so the Office's prior conclusion that this element finds support in the '558 Provisional is equally applicable to the '786 Patent's claims.

The earliest priority date that can be accorded any subject matter in the cited Gwozdz PCT reference on which this Petition relies is also March 28, 2008. Consequently, and as the Office also explicitly found, Gwozdz PCT "does not qualify as prior art." *Id.* at 28. Without Gwozdz PCT, the Petition's obviousness allegations fail.

Padagis's responds by asserting that Neurelis is estopped from disputing that the '558 Provisional "does not provide adequate written description support for the

'alkyl glycoside' limitation." Petition, 8-9. This issue is irrelevant, because no claim of the '786 Patent recites or requires the inclusion of "alkyl glycoside." Thus, this finding in the '876 IPR is irrelevant to the '786 Patent and Padagis has failed to carry its burden of proving collateral estoppel applies. *See Purdue Pharma L.P. v. Iancu*, 767 F. App'x. 918, 922 (Fed. Cir. 2019) ("The Restatement (Second) of Judgments (1982) has guided [the Federal Circuit]'s application of collateral estoppel") (citing *Voter Verified, Inc. v. Election Sys. & Software LLC*, 887 F.3d 1376, 1383 (Fed. Cir. 2018)); *see also* Restatement (Second) of Judgments, §27 (1982) comment *f* ("[t]he party contending that an issue has been conclusively litigated and determined in a prior action has the burden of proving that contention").

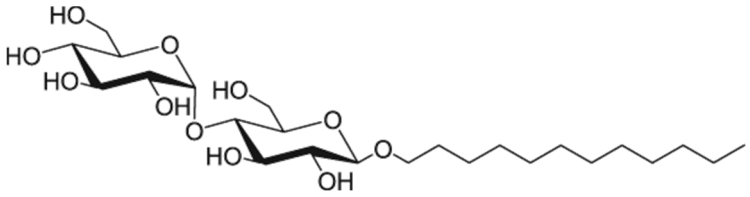
As an alternative to the imposition of collateral estoppel, Padagis argues that the '558 Provisional does not disclose "alkyl glycoside" (Petition, 13-16) but again, this contention is irrelevant because this limitation is nowhere stated in the '786 Patent's claims. In addressing the relevant question to ***these*** claims – whether the '558 Provisional discloses "n-dodecyl beta-D-maltoside" – Padagis contends that its verbatim incorporation by reference is improper and that the Office erred in finding otherwise. Petition, 14-16. This contention is in equal parts legally incorrect and disingenuous.

1. Gwozdz PCT Is Not Prior Art Because the '786 Patent Is Entitled to the Priority Date of the '558 Provisional

a. Padagis Fails to Show That Collateral Estoppel Applies to the Priority Date of the '786 Patent

Assertion of collateral estoppel requires the proponent to satisfy four factors: (1) the issue is identical to one decided in the first action; (2) the issue was actually litigated in the first action; (3) resolution of the issue was essential to a final judgment in the first action; and (4) the party against whom collateral estoppel is being asserted had a full and fair opportunity to litigate the issue in the first action. *In re Freeman*, 30 F.3d 1459, 1465-1467 (Fed. Cir. 1994).

Every claim of the '786 Patent specifically requires n-dodecyl beta-D-maltoside as a component of the pharmaceutical solution. This is a particular chemical substance with a specific chemical structure:



In contrast, in the '876 IPR, the Board addressed patentability of claims broadly covering "an alkyl glycoside," not n-dodecyl beta-D-maltoside:

> Claim 1 requires 'an alkyl glycoside.' Ex. 1001, 63:34. Since all of the remaining claims of the '876 patent depend, directly or indirectly, from Claim 1, ***they also require the presence of 'an alkyl glycoside.'*** "

EX1040, 14, n.6 (emphasis added). *See also id* at 19, n.7 (discussing "the 'alkyl glycoside' limitation in the claims"), 23 ("we find that the '558 provisional does not provide adequate written description support for the 'alkyl glycoside' limitation. Therefore, the claims of the '876 patent are not entitled to the benefit of priority to the '558 provisional.").

The Board stated that every claim of the '876 patent included the phrase "an alkyl glycoside." This statement obviously is not true of any claim of the '786 Patent. Consequently, the patentability issue here – whether the '558 Provisional supports "n-dodecyl beta-D-maltoside" – differs from that to which Padagis asserts collateral estoppel applies – whether the '558 Provisional "provide[s] adequate written description support for the 'alkyl glycoside' limitation." Petition, 8-9. Since the patentability issue differs, collateral estoppel does not apply.

Padagis may argue that there were claims of the '876 Patent that required "dodecyl maltoside," and so the Board should interpolate that the priority issue relevant to the '786 Patent was decided. First, on its face this is a different issue, because no claim of the '876 patent – and every claim of the '786 patent – requires "n-dodecyl beta-D-maltoside," not "dodecyl maltoside." Second, and notably, nowhere does the Petition identify a location where the Board in the '876 IPR decided whether the '558 Provisional provides adequate written description for "n-dodecyl beta-D-maltoside." Padagis does not identify this material because it does

not exist. Third, the petitioner in the '876 IPR recognized this fact, and on that basis argued to the Federal Circuit that "Neurelis waived any argument that the listing of dodecyl maltoside in the SIGMA catalog provides adequate written description support." EX2028, 64. A predicate of this argument was the argued failure of the parties to join battle on – or the Board to make specific findings concerning – whether the '558 Provisional supported "dodecyl maltoside."

The relevant priority issue to the '786 Patent was not addressed in the previous IPR because the claims there differed. This difference in scope distinguishes the priority issue here from the previously-litigated issue, resulting in a different conclusion: every claim of the '786 Patent is entitled to priority of the '558 Provisional, which eliminates Gwozdz PCT as prior art.

b. The '786 Patent Is Entitled to the March 28, 2008 Priority Date of the '558 Provisional

The only argument the Petition raises why the '786 Patent should not be entitled to the priority date of the '558 Provisional is a purported lack of written description support for the "n-dodecyl beta-D-maltoside" element. Petition, 12-16. On that element, the '558 Provisional states that "enhancing agents that are appropriate include . . . biological detergents listed in the SIGMA Catalog, 1988, page 316-321 (which is incorporated herein by reference)." EX1008, ¶152. It is bedrock patent law that material incorporated by reference "is effectively part of the

host document as if it were explicitly contained therein." *Advanced Display Sys., Inc. v. Kent State Univ.*, 212 F.3d 1272, 1282 (Fed. Cir. 2000). The Sigma Catalogue excerpt incorporated by reference in the '558 Provisional, in turn, not only specifically identifies n-dodecyl beta-D-maltoside, but shows that it was commercially available:

BIOLOGICAL DETERGENTS

Sigma offers a wide range of detergents useful to the biochemist for the solubilization of proteins and membrane components. This section is organized into the four major detergent categories:

n-Decyl β-D-glucopyranoside	2.2	—	320.4
Digitonin	—	6	1229.3
n-Dodecyl β-D-glucopyranoside	0.19	—	348.5
n-Dodecyl β-D-maltoside	0.16	—	348.5
n-Heptyl β-D-glucopyranoside	70 (est.)	—	278.4
n-Octyl β-D-glucopyranoside	25	27	292.4
n-Octyl α-D-glucopyranoside	10	—	292.4
Nonidet P-40	0.29	—	602.8
n-Nonyl β-D-glucopyranoside	6.5	—	306.4
Triton X-100	0.24	140	624.9

EX1026, 19 (annotation added). This excerpt provides verbatim written description of the n-dodecyl beta-D-maltoside element claimed in the '786 Patent. It is indisputable that this disclosure satisfies the written description requirement.[3] *See,*

[3] In passing the Petition mentions an "enabling" disclosure and "undue experimentation." Petition, 16. Nowhere does the Petition develop or state a lack-of-enablement argument; that argument is waived. *See, e.g.*, *Intelligent Bio-Sys. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1369 (Fed. Cir. 2016) (finding late argument in reply improper under 37 C.F.R. §42.23(b) and stating "It is of the utmost importance that petitioners in the IPR proceedings adhere to the requirement that the initial petition identify 'with particularity' the 'evidence that

e.g., *Ariad*, 598 F.3d at 1350; *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, (Fed. Cir. 1991) (adequate written description of a chemical invention requires a precise definition distinguishing it from other materials, such as by chemical name, structure, formula, or physical properties, and not merely a wish or plan for obtaining the chemical invention claimed) (citing *Oka v. Youssefyeh*, 849 F.2d 581, 583 (Fed. Cir. 1988)). During its previous prosecution of the '414 Patent, the Office determined as much. *See supra* Section III(C)(1). *See also Ecto World, LLC v. Rai Strategic Holdings, Inc.*, IPR2024-01280, Paper 13 at 4-5 (PTAB May 19, 2025) (precedential) (institution inappropriate where the art on which the Petition relies was considered by the Office and no legitimate error in that consideration is identified).

Padagis responds that under 37 C.F.R. §1.57(d) matter incorporated by reference in a provisional application cannot support "essential matter" recited in the claims. Petition, 15-16. This contention is both incorrect and disingenuous. It is incorrect because Section 1.57(d) does not apply to the priority issue here. Not only

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supports the grounds for the challenge to each claim.'") (citing 35 U.S.C. §312(a)(3)). In any event, the disclosures in the '558 Provisional of commercial availability of n-dodecyl beta-D-maltoside (from, *e.g.*, Sigma, EX1008, ¶152), its specific utility ("to increase absorption across the mucosa," *id.* at ¶150) and amount ("up to 20%," *id.* at ¶152), and the specific utility of the composition (*e.g.*, to treat seizures, *id.* at ¶002) establish enablement that supports the priority claim. *See, e.g.*, *In re Bundy*, 642 F.2d 430, 434 (C.C.P.A. 1981).

is there no rule against a provisional providing disclosure through incorporation by reference – the MPEP ***approves*** of doing just that:

> The limitations on the material which may be incorporated by reference in U.S. patent applications which are to issue as U.S. patents do not apply to applications relied on only to establish an earlier effective filing date under 35 U.S.C. 119 or 35 U.S.C. 120. Neither 35 U.S.C. 119(a) nor 35 U.S.C. 120 places any restrictions or limitations as to how the claimed invention must be disclosed in the earlier application to comply with 35 U.S.C. 112(a). Accordingly, ***an application is entitled to rely upon the filing date of an earlier application, even if the earlier application itself incorporates essential material by reference to another document***. *See Ex parte Maziere*, 27 USPQ2d 1705, 1706-07 (Bd. Pat. App. & Inter. 1993).

MPEP §608.01(p)(I)(B) (emphasis added).

Padagis's contention is disingenuous because the incorporation by reference was found ***sufficient*** in the very IPR on which Padagis pins its hopes.

> CHIEF JUDGE MOORE: . . . You agree that the Board's original conclusion in the [P]etition that this wasn't incorporated by reference was modified in the final decision. And the Sigma disclosure, these six pages, are considered incorporated by reference. . .
>
> DANIEL SCOLA [Petitioner]: Yes, Your Honor

EX2029, 12:3-8. Janus-like, Padagis argues that the issues here were all resolved previously by the Board and should be found preclusive, but that the Board should ignore the other evidence presented in the IPR that does not support their position.

There is additional evidence that the '558 Provisional supported the addition of absorption enhancers, such as n-dodecyl beta-D-maltoside. For example, the '558

Provisional discloses including "enhancers" or "enhancing agents" in the formulation. EX1008, ¶¶16, 152. "Enhancing agents," in turn, are defined as "any material which acts to increase absorption across the mucosa and/or increases bioavailability." *Id.* at ¶150. And claims 17 and 35 both cover compositions including enhancers. *Id.* at 38, 40.

There is also very substantial evidence that the remaining elements of the challenged claims are supported by the '558 Provisional and are carried forward into the subsequent priority documents. Although the Petition raises no question in this regard, Patent Owner sets forth in the table below *exemplary* support the '558 Provisional provides for each of the elements of the challenged claims:

Claim Elements	**Exemplary Support in EX1008**
1. A pharmaceutical solution for nasal administration consisting of:	¶009, ¶173, claims
a therapeutically effective amount of diazepam or a pharmaceutically acceptable salt thereof;	¶010, ¶025, claims
one or more natural or synthetic tocopherols or tocotrienols selected from the group consisting of α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, α-tocotrienol, β-tocotrienol, γ-tocotrienol, δ-tocotrienol, tocophersolan, any isomers thereof, any esters thereof, and any combinations thereof, in an amount from 30% to 95% (w/w);	¶009, claims
one or more alcohols in an amount from 10% to 70% (w/w), wherein the one or more alcohols comprises benzyl alcohol; and	¶009, ¶120, ¶141, claims

n-dodecyl beta-D-maltoside.	¶150, ¶152, claims 17 & 35
2. The pharmaceutical solution of claim 1, wherein the therapeutically effective amount of diazepam or pharmaceutically acceptable salt thereof is present in the pharmaceutical solution in a concentration from 1 to 20% (w/v).	¶013
3. The pharmaceutical solution of claim 1, wherein the therapeutically effective amount of diazepam or pharmaceutically acceptable salt thereof is present in the pharmaceutical solution in a concentration from 10 mg/mL to 250 mg/mL.	¶140
5. The pharmaceutical solution of claim 1, wherein the one or more natural or synthetic tocopherols or tocotrienols is in an amount from 45% to 85% (w/w).	¶014
6. The pharmaceutical solution of claim 5, wherein the one or more natural or synthetic tocopherols or tocotrienols is in an amount from 60% to 75% (w/w).	¶014
7. The pharmaceutical solution of claim 1, wherein the one or more alcohols is benzyl alcohol and a second alcohol selected from ethanol, propyl alcohol, butyl alcohol, pentanol, any isomers thereof, and any combinations thereof.	¶012, ¶020, ¶120
8. The pharmaceutical solution of claim 1, wherein the one or more alcohols are in an amount from 15% to 55% (w/w).	¶015, ¶020, ¶120
9. The pharmaceutical solution of claim 8, wherein the one or more alcohols are in an amount from 25% to 40% (w/w).	¶015, ¶020, ¶120
11. A pharmaceutical solution for nasal administration consisting of:	¶009, ¶173, claims
a therapeutically effective amount of diazepam or a pharmaceutically acceptable salt thereof;	¶010, ¶025, claims

one or more natural or synthetic α-tocopherols selected from the group consisting of tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, tocophersolan, any isomers thereof, any esters thereof, and any combinations thereof, in an amount from 30% to 95% (w/w);	¶009, claims
one of more alcohols in an amount from 10% to 70% (w/w)), wherein the one or more alcohols comprises benzyl alcohol; and	¶009, ¶141, claims
n-dodecyl beta-D-maltoside.	¶150, ¶152, claims 17 & 35
12. The pharmaceutical solution of claim 11, wherein the therapeutically effective amount of diazepam or pharmaceutically acceptable salt thereof is present in the pharmaceutical solution in a concentration from 1 to 20% (w/v).	¶013
13. The pharmaceutical solution of claim 11, wherein the therapeutically effective amount of diazepam or pharmaceutically acceptable salt thereof is present in the pharmaceutical solution in a concentration from 10 mg/mL to 250 mg/mL.	¶140
15. The pharmaceutical solution of claim 11, wherein the one or more natural or synthetic tocopherols is in an amount from 45% to 85% (w/w).	¶014
16. The pharmaceutical solution of claim 15, wherein the one or more natural or synthetic tocopherols is in an amount from 60% to 75% (w/w).	¶014
17. The pharmaceutical solution of claim 11, wherein the one or more alcohols is benzyl alcohol and a second alcohol selected from ethanol, propyl alcohol, butyl alcohol, pentanol, any isomers thereof, and any combinations thereof.	¶012, ¶020, ¶120
18. The pharmaceutical solution of claim 11, wherein the one or more alcohols are in an amount from 15% to 55% (w/w).	¶015, ¶020, ¶120

19. The pharmaceutical solution of claim 18, wherein the one or more alcohols are in an amount from 25% to 40% (w/w).	¶015, ¶020, ¶120
20. The pharmaceutical solution of claim 1, wherein the therapeutically effective amount of diazepam or pharmaceutically acceptable salt thereof present in the pharmaceutical solution is from about 5 to about 20 mg.	¶140, ¶142
21. The pharmaceutical solution of claim 11, wherein the therapeutically effective amount of diazepam or pharmaceutically acceptable salt thereof present in the pharmaceutical solution is from about 1 mg to about 20 mg.	¶126
22. The pharmaceutical solution of claim 1, wherein the n-dodecyl beta-D-maltoside is present in the pharmaceutical solution in an amount from about 0.01% (w/v) to about 1% (w/v).	¶152
23. The pharmaceutical solution of claim 11, wherein the n-dodecyl beta-D-maltoside is present in the pharmaceutical solution in an amount from about 0.01% (w/v) to about 1% (w/v).	¶152
24. The pharmaceutical solution of claim 1, wherein the n-dodecyl beta-D-maltoside is present in the pharmaceutical solution in an amount from about 0.125% (w/v) to about 0.5% (w/v).	¶152
25. The pharmaceutical solution of claim 11, wherein the n-dodecyl beta-D-maltoside is present in the pharmaceutical solution in an amount from about 0.125% (w/v) to about 0.5% (w/v).	¶152
26. The pharmaceutical solution of claim 1, wherein the α-tocopherol is Vitamin E USP.	¶116
27. The pharmaceutical solution of claim 11, wherein the α-tocopherol is Vitamin E USP.	¶116

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As the Office found when evaluating the claims that ultimately issued in the '414 Patent – in view of the full '876 IPR record and after discussing that proceeding with Neurelis's counsel – the claims of the '414 Patent "receive a priority date of March 28, 2008. As such, Gwozdz [PCT] (WO 2009120933) does not qualify as prior art." EX1004, 28. That conclusion applies equally to the '786 Patent, and is well-supported by the law and facts. Padagis's contention to the contrary is legally unsupportable. Without Gwozdz PCT, the Petition fails to show a reasonable likelihood that its challenge will prevail on even a single claim. Institution should be denied.

B. The "Motivation to Combine" That the Petition Advances Is Not Prior Art Because the Critical Date of the Subject Matter is March 27, 2009

The Petition relies solely on a disclosure in Gwozdz PCT concerning "penetration enhancers" to argue that a skilled artisan would have been motivated to combine Gwozdz with Meezan (Petition, 29, 31-32, 41). But the Gwozdz PCT disclosure on which the Petition relies to support the motivation to combine was not present in the Gwozdz Provisional application to which Gwozdz PCT claims priority. That subject matter, thus, is not available as prior art regardless of which priority date one accords the '786 Patent.

Padagis asserts that Neurelis cannot dispute that "Gwozdz [PCT] is entitled to the filing date of the '281 Provisional." Petition, 8-9. But, as the Board stated in the '876 IPR, this issue was not litigated previously. *See* EX1040,14 ("Patent Owner does not contest that Gwozdz [PCT] is entitled to this filing date."). Therefore, collateral estoppel cannot apply.

Next, Padagis asserts that if collateral estoppel is not imposed, the Gwozdz PCT is entitled to the priority date of the Gwozdz Provisional for two reasons. Petition, 21-23. First, Padagis argues that Gwozdz PCT is entitled to the provisional application's priority date because the claims in the 2009 PCT are identical to those stated in the Gwozdz Provisional. *Id.*, 21-22. Second, Padagis argues that the disclosures from the 2009 PCT on which the Petition relies are supported by the Gwozdz Provisional. *Id.*, 22. The first contention is irrelevant; the second is incorrect.

1. Collateral Estoppel Does Not Apply Because the Priority Date of Gwozdz Was Not Actually Litigated

The Petition states that collateral estoppel applies to the question whether Gwozdz PCT is entitled to the filing date of the Gwozdz Provisional. This assertion is both incorrect and irrelevant. The application of collateral estoppel requires that an issue be actually litigated in a prior proceeding. *In re Freeman*, 30 F.3d at 1465-66. But the Board's Final Written Decision in the '876 IPR explicitly states that the

issue of Gwozdz's applicable priority date was not disputed. *See* EX1040, 14 ("Patent Owner does not contest that Gwozdz [PCT] is entitled to this filing date" of the Gwozdz Provisional). Failure to contest an issue – or even ***stipulating*** to an issue – does not comprise litigating that issue for collateral estoppel purposes. *See Purdue Pharma L.P. v. Iancu*, 767 F. App'x. at 922 ("The Restatement (Second) of Judgments (1982) has guided [the Federal Circuit]'s application of collateral estoppel. . . . [Which] states that '[a]n issue is not actually litigated . . . if it is a stipulation between the parties…. [or] a judgment entered by confession, consent, or default….") (citing *Voter Verified, Inc.*, 887 F.3d at 1383).

Moreover, whether some subject matter of Gwozdz PCT may be entitled to claim priority to the Gwozdz Provisional is irrelevant to the passage discussing "penetration enhancers," which, as detailed below, indisputably is not supported by the Provisional and thus is not prior art.

2. The Purported Motivation to Combine Is Not Prior Art Regardless of the '786 Patent's Priority Date

The obviousness combination on which the Petition relies requires combining the pharmaceutical solution of Gwozdz PCT – including diazepam, vitamin E or other tocopherols or tocotrienols, and one or more alcohols – with the mucosal absorption enhancer, n-dodecyl beta-D-maltoside that Meezan discloses. Petition, 26-30. In relying on a combination of references to argue obviousness, the Petition

must provide a motivation for a skilled artisan to have made that combination at the priority date. *See, e.g.*, *In re NuVasive, Inc.*, 842 F.3d at 1382-83 ("Our precedent dictates that the PTAB must make a finding of a motivation to combine when it is disputed").

The only argument that the Petition makes for why a skilled artisan would have combined the absorption enhancer of Meezan with the pharmaceutical solution of Gwozdz PCT relies on a passage in Gwozdz PCT referring to the inclusion of "additives, including . . . '***penetration enhancers***' . . . ." Petition, 41 (citing EX1009, 10:12-16) (emphasis added), 29, 31-32. On this basis Padagis argues that a skilled artisan would have been motivated to incorporate "compounds that increase the absorption (i.e., absorption enhancers) and bioavailability of drug compounds." *Id.*, 29.

The phrase "penetration enhancers," however, does not appear in the Gwozdz Provisional. Rather, that phrase first appears in the March 27, 2009 Gwozdz PCT application. Indeed, its absence from the Gwozdz Provisional application is glaring and intentional when viewed in context:

solubilizing agent such as Cremophor. Such pharmaceutical compositions may further contain other pharmaceutically acceptable additives such as, but not limited to, acidifying, alkalizing, buffering, chelating, complexing and solubilizing agents, antioxidants and antimicrobial preservatives,{ }humectants, suspending and/or viscosity modifying agents, tonicity and wetting or other biocompatible materials.

2008 Gwozdz Provisional (EX1064), 10:10-17 (annotation added)

solubilizing agent such as Cremophor. Such pharmaceutical compositions may further contain other pharmaceutically acceptable additives such as, but not limited to, acidifying, alkalizing, buffering, chelating, complexing and solubilizing agents, antioxidants and antimicrobial preservatives,{ penetration enhancers,} humectants, suspending and/or viscosity modifying agents, tonicity and wetting or other biocompatible materials.

2009 Gwozdz PCT (EX1009), 10:9-16 (annotation added)

Nowhere does the Gwozdz Provisional disclose the inclusion of absorption or penetration enhancers. And notably, reference to "penetration enhancers" appears

to be ***the only text*** added to the PCT when compared to the Gwozdz Provisional, indicating the specific importance placed on this addition by the applicant.

The Petition contends that Gwozdz PCT is entitled to the 2008 priority date of the Gwozdz Provisional because the claims of the Gwozdz PCT are identical to those of the Gwozdz Provisional. Petition, 21-22 (citing *Dynamic Drinkware, LLC v. Nat'l Graphics, Inc*., 800 F.3d 1375 (Fed. Cir. 2015)). But a provisional application must provide support for ***subject matter*** carried forward into a published application and used in a patentability challenge for that subject matter to be entitled to the filing date of the provisional. *See In re Riggs*, 131 F.4th at 1384. *See also Ex parte Robert A. Mann & Eric Colaviti*, 2016 WL 7487271, at *5. "This subject matter test is ***in addition to*** the comparison of claims required by *Dynamic Drinkware*." *Id.* (emphasis added). The Petition tacitly concedes as much in going on to assert (and attempt to support the premise) that "all of the disclosure Petitioner relies on from Gwozdz [PCT] is supported by the [Gwozdz] '281 Provisional." Petition, 22-23.

The Gwozdz Provisional does not support the "penetration enhancers" disclosure on which the Petition relies for a motivation to combine. Consequently, that subject matter is not available to cite against the '786 Patent until the filing date of the Gwozdz PCT, *i.e.*, March 27, 2009. The '786 Patent claims priority to the '439 Application, filed on the same day. Therefore, the "penetration enhancer"

subject matter is not available as prior art against the '786 Patent regardless of which priority date is accorded to the patent. And since this subject matter provides the sole support the Petition advances for a motivation to combine (in both the Petition and its supporting expert declaration), the Petition fails to articulate a prior art rationale for combining Gwozdz PCT and Meezan.

It is also notable that the passage on which the Petition relies concerning "penetration enhancers" is relevant solely to "a pharmaceutical composition for injection," not for intranasal administration as the '786 Patent requires. *See* EX1009, 10:3-7. Gwozdz PCT addresses compositions for intranasal administration elsewhere and nowhere mentions adding penetration or absorption enhancers or other additives. *Id.*, 8:32-10:2. Thus, neither Gwozdz PCT nor the Petition supplies a motivation to combine with Meezan for a second and independent reason.

Finally, it is rich for Padagis simultaneously to argue that Gwozdz Provisional provides written description support for penetration enhancers, when that subject matter is absent from the document, and to argue the '558 Provisional lacks written description support for that concept when there is verbatim disclosure of the claimed element. This argument belies credibility and should be discarded.

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The Petition relies on one piece of purported evidence that a skilled artisan would have had a motivation to combine Gwozdz PCT with Meezan. That evidence

is not prior art subject matter and thus is unavailable as evidence of a purported motivation to combine. Nor would it have been relevant to pharmaceutical solutions for intranasal administration even if it were available as prior art. For that very reason, the Petition relies on the single statement made in the Gwozdz PCT, which is not prior art. Institution should be denied.

C. Other Limitations Not Addressed

At this preliminary stage, Patent Owner addresses those deficiencies in the prior art which clearly show a lack of reasonable likelihood of the petition's success. Patent Owner's decision not to address certain other deficiencies at this preliminary stage in no way reflects Patent Owner's agreement with the Petition or lack of dispute as to these additional deficiencies.

V. CONCLUSION

For the foregoing reasons, the Board should deny institution of Padagis's proposed ground for *inter partes* review.

Respectfully submitted,

Date: June 17, 2025

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CERTIFICATION OF WORD COUNT

The undersigned hereby certifies that the portions of the above-captioned PATENT OWNER PRELIMINARY RESPONSE specified in 37 C.F.R. § 42.24 have 8,296 words, in compliance with the 14,000 word limit set forth in 37 C.F.R. § 42.24. This word count was prepared using Microsoft Word 365 V.2503.

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CERTIFICATION OF SERVICE

The undersigned hereby certifies that the foregoing PATENT OWNER'S PRELIMINARY RESPONSE and all supporting EXHIBITS 2001-2029 were served by filing the documents through the Patent Trial and Appeal Case Tracking System (P-TACTS) and courtesy copies were also served via electronic mail, in their entireties on the following:

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