

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PADAGIS US LLC,

Petitioner,

v.

NEURELIS, INC.,

Patent Owner.

Case No. IPR2025-00464

U.S. Patent No. 8,895,546

**REPLY DECLARATION OF MAUREEN DONOVAN, PH.D. IN SUPPORT OF
PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 8,895,546**

TABLE OF CONTENTS

I.	Introduction.....	4
II.	Legal Standards.....	5
III.	Level of Skill in the Art	5
IV.	Summary of Opinions	6
V.	The '558 Provisional Application Does Not Disclose Dodecyl Maltoside	7
VI.	The Claims of the '546 Patent Would Have Been Obvious to a POSA	7
VII.	Conclusion and Reservation of Rights.....	15

TABLE OF ABBREVIATIONS

Full Name of Cited Reference	Abbreviation	Exhibit No.
U.S. Patent No. 8,895,546	'546 patent	1001
Provisional Patent Application No. 61/040,558	'558 Provisional	1008
PCT Patent App. Pub. No. WO 2009/120933	Gwozdz	1009
U.S. Patent App. Pub. No. 2006/0046962	Meezan	1010
Final Written Decision issued in IPR 2019-00451 finding all claims of U.S. Patent No. 9,763,876 Unpatentable	'876 Patent FWD	1040
Declaration of Maureen Donovan, Ph.D. in Support of Petition for <i>Inter Partes</i> Review of U.S. Patent No. 8,895,546	Donovan Op. Decl.	1062
U.S. Provisional Pat. App. No. 61/040,281	Gwozdz Provisional	1064
U.S. Patent No. 9,763,876	'876 patent	1071
Expert Declaration of Professor Sveinbjorn Gizurarson in Support of Patent Owner's Response to Petition for <i>Inter Partes</i> Review of U.S. Patent No. 9,763,876	Gizurarson Decl.	1072
Certified Transcript of Deposition of Marc Brown, Ph.D. in <i>Padagis US LLC vs. Neurelis, Inc.</i> , IPR2025-00464, IPR2025-00465, IPR2025-00466 (March 17, 2026)	Brown Dep. Tr.	1077
Declaration of Mareen Donovan, Ph.D. in Support of Defendants' Responsive Claim Construction Brief, <i>Neurelis, Inc. v. Padagis LLC et al.</i> , 1:24-cv-562, D.I. 88-28 (D. Del. August 22, 2025)	Donvoan Claim Construction Decl.	2069
Expert Declaration of Dr. Marc Brown	Brown Decl.	2072

I. Introduction

1. I, Maureen Donovan, have been retained by Padagis US LLC (“Padagis” or “Petitioner”) to provide my expert opinions regarding the petition for *inter partes* review (“IPR”) of U.S. Patent No. 8,895,546 (“the ’546 patent”) set forth in the caption above. I previously submitted an expert declaration in this IPR on January 17, 2025 (“Donovan Op. Decl.”). *See generally* Ex. 1062.

2. In my opening declaration, I opined that all claims of the ’546 patent would have been obvious to a person of ordinary skill in the art (“POSA”). Specifically, I opined that all claims of the ’546 patent are unpatentable as obvious over Gwozdz (Ex. 1009) in view of Meezan (Ex. 1010); *See generally, e.g.*, Ex. 1062 at ¶¶ 95-246. It is still my opinion that the challenged claims of the ’546 patent are unpatentable as obvious over Gwozdz in view of Meezan, and for the reasons discussed in my opening declaration. I incorporate by reference my opinions set forth in my declaration signed on January 17, 2025, submitted in this proceeding as Ex. 1062.

3. In this reply declaration, I have been asked to reply to certain opinions set forth in the Expert Declaration of Dr. Marc Brown (Ex. 2072) submitted in support of Neurelis’s response to Padagis’s petition, as well as Neurelis’s Response to Padagis’s IPR. To the extent I do not expressly address any opinions or points raised by Dr. Brown or Neurelis, that does not mean I agree with or otherwise concede those points. Rather, I focus my opinions in this reply declaration on specific topics but otherwise maintain my opinion that all claims of the ’546 patent are unpatentable as obvious for the reasons discussed in my opening declaration.

4. My qualifications, list of testimony, and compensation were provided in my opening declaration and my *curriculum vitae*. *See, e.g.*, Ex. 1062 at ¶¶ 5, 7-16, Appendix A.

Further, the scope of my work and compensation remains the same since my opening declaration was submitted. My compensation does not depend on the outcome of this or any other proceeding.

II. Legal Standards

5. In my opening declaration, I discussed my understanding of various legal standards and principles relevant to my opinions, which I incorporate by reference in this reply declaration. *See, e.g.*, Ex. 1062 at ¶¶ 23-36.

III. Level of Skill in the Art

6. In my opening declaration, I discussed my understanding and definition of a POSA with respect to the '546 patent, which I incorporate by reference in this reply declaration. *See, e.g.*, Ex. 1062 at ¶¶ 17-22. Specifically, I opined that a POSA with respect to the '546 patent should be defined as follows:

[A] POSA would have been a pharmaceutical scientist, chemist, or biologist involved in the research and development of pharmaceutical formulations and/or delivery, and would have at least a Bachelor's degree with at least 5 years of experience, or a Master's, Ph.D. or Pharm.D. degree with several years of experience. In addition, it is my opinion that a POSA would have had knowledge of benzodiazepine structure and function, and would further have knowledge and practical experience working with intranasal and transmembrane formulations, including knowledge of the physiology and anatomy of the nasal cavity, with relevant experience in developing intranasal formulations.

Id. at ¶ 20.

7. I also understand from Dr. Brown's declaration that Neurelis contends that the POSA should be defined as follows:

[T]he skilled artisan holds a Master's degree with many years of experience, or a Ph.D. or Pharm.D degree with several years of experience or its equivalent experience in the field of pharmaceutical research and development. The skilled artisan would have knowledge of benzodiazepine structure and function, including physiochemical characteristics of benzodiazepines generally. The skilled artisan would further have knowledge and practical experience developing and working with intranasal formulations, including knowledge of the physiology and anatomy of the nasal cavity and methods of administering drugs intranasally. The skilled artisan also would have knowledge concerning clinical aspects of bioavailability,

tolerability, and patient acceptability of intranasal formulations and the difficulty of administering drugs by other routes during an event like a seizure.

See, e.g., Ex. 2072 (Brown Decl.) at ¶ 61.¹

8. While I disagree with Neurelis's POSA definition, and maintain that a POSA should meet the definition described in my opening declaration, I qualified as a POSA as of 2008 and am still a POSA today. The opinions in my opening declaration and this reply declaration are the same regardless of which POSA definition is ultimately adopted.

IV. Summary of Opinions

9. In forming the opinions set forth in this reply declaration, I considered and relied upon the materials cited in my opening declaration, the materials cited in Dr. Brown's declaration, and the materials cited in this reply declaration, including the materials identified in Appendix A to this declaration. My opinions and conclusions are also based on my education, experience, and knowledge of the relevant art.

10. Further, in my opening declaration, I opined that all claims of the '546 patent are unpatentable as obvious. *Id.* However, I was informed by counsel that after my opening declaration was submitted, Neurelis statutorily disclaimed all claims of the '546 patent except claims 17 and 22. I understand Dr. Brown has the same understanding. *See, e.g.*, Ex. 2072 at ¶ 29. Thus, in this reply declaration, I address claims 17 and 22 of the '546 patent ("the challenged claims"), which I understand are the only remaining claims of the '546 patent. Further, as discussed herein, it is my opinion that the '558 provisional does not disclose or support "dodecyl maltoside;" the challenged claims would have been obvious to a POSA, as Dr. Brown's arguments simply restate

¹ I note that while Dr. Brown discusses both proposed POSA definitions, he apparently takes no position about which POSA definition is correct or should be adopted in this proceeding.

previously unsuccessful positions, and Meezan clearly motivated a POSA to use n-dodecyl- β -D-maltoside with a reasonable expectation of success; and the antimicrobial properties of ethanol and benzyl alcohol would not be materially impacted by nonionic surfactants in a nasal spray formulation.

V. The '558 Provisional Application Does Not Disclose Dodecyl Maltoside

11. As explained in my opening declaration, it is my opinion that the claims of the '546 patent should be limited to a priority date of no earlier than March 27, 2009 (the filing date of the '439 application). *See, e.g.*, Ex. 1062 at ¶¶ 42-54. In addition, and as I explained in my opening declaration, it is my opinion that the '558 provisional application to which the '546 patent claims priority does not mention or disclose alkyl glycosides generally or dodecyl maltoside specifically. *Id.*

12. I have reviewed Dr. Brown's declaration and understand he did not opine that the claimed "dodecyl maltoside" is supported by the '558 provisional application, and thus he appears to agree that the priority date of the '546 patent is March 28, 2009. *See generally* Ex. 2072. Indeed, at his deposition, Dr. Brown confirmed that he has not offered any opinions about whether the claims of the '546 patent should be entitled to an earlier priority date, including the filing date of the '558 provisional application (i.e., March 28, 2008). *See, e.g.*, Ex. 1077 at 46:14-50:16.

13. Accordingly, for the reasons discussed in my opening declaration and by the PTAB in the '876 patent final written decision, which Dr. Brown does not dispute, it is my opinion that the '558 provisional application does not support or disclose the claimed formulations containing "dodecyl maltoside." *See, e.g.*, Ex. 1062 at ¶¶ 42-54.

VI. The Claims of the '546 Patent Would Have Been Obvious to a POSA

14. I have reviewed Dr. Brown's declaration and understand he opines that the claims of the '546 patent would not have been obvious to a POSA. While my original declaration

submitted in this IPR (Ex. 1062) addresses these arguments, there are a few specific issues below where I have provided additional discussion.

15. Dr. Brown opines about whether the claims of the '546 patent may contain water, including residual water associated with excipients like ethanol. *See, e.g.*, Ex. 2072 at ¶¶ 124-126, 133-139. Specifically, Dr. Brown points to a declaration I submitted in the district court proceeding involving the '546 patent and opines that my “opinions in the district court litigation . . . would seek to exclude even trace amounts of water from the scope of the claims.” *Id.* at ¶ 124-126.

16. While I disagree with Dr. Brown’s characterization of my opinions from the district court claim construction declaration, I understand from counsel that Padagis has agreed to adopt Neurelis’s proposed construction in the district court proceeding, and has withdrawn all claim construction briefing and my supporting declaration. In other words, I understand that the parties have now agreed in both the district court and this IPR proceeding that the phrase “consisting of” does not require an express construction.

17. As made clear in my original declaration, the obviousness analysis I provided applies the understanding that “consisting of” requires the claimed solution to “contain[] only” the claimed diazepam, vitamin E, ethanol, benzyl alcohol and dodecyl maltoside. *See, e.g.*, Ex. 1062 (Donovan Op. Decl.) at ¶ 138. Nowhere in the analysis of my original declaration or this supplemental declaration have I opined that “consisting of” requires the exclusion of trace amounts of water.

18. Dr. Brown opines that neither Gwozdz nor Meezan disclosed or would have motivated a POSA to use dodecyl maltoside. *See, e.g.*, Ex. 2072 at ¶¶ 178-199. For the reasons discussed in my opening declaration and below, I disagree with Dr. Brown.

19. As a threshold issue, I note that Dr. Brown points out that the Gwozdz provisional application does not include the phrase “penetration enhancers,” and he argues that this cuts against the motivation to combine Gwozdz and Meezan. *See, e.g.*, Ex. 2072 at ¶ 156. However, as established in my original declaration, there are numerous other rationales supporting a POSA’s motivation to combine that are unrelated to Gwozdz’s disclosure of “penetration enhancer.” *See* Ex. 1062 (Donovan Op. Decl.) at ¶¶ 95-100, 104-110.

20. Additionally, the passage from Gwozdz that I relied on states that other “pharmaceutically acceptable additives” maybe added to the Gwozdz formulations, including “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*’ to improve the efficacy.” Ex. 1062 (Donovan Op. Decl.) at ¶ 98 (emphasis added) (quoting Ex. 1009 (Gwozdz) at 10:12-16). While Dr. Brown and Neurelis assert that the “penetration enhancer” term is not supported by the Gwozdz Provisional, the “wetting...material” term is explicitly recited in the text of the Gwozdz Provisional. Ex. 1009 (Gwozdz) at 10:12-16. Additionally, Meezan states that the absorption enhancers described therein are surfactants, and that “[t]he term “surfactant” is any surface active agent that modifies interfacial tension of water...Broadly, the group includes soaps, detergents, emulsifiers, dispersing and *wetting agents*, and several groups of antiseptics.” Ex. 1010 (Meezan) at ¶ [0053] (emphasis added). In my opinion a POSA would have viewed Gwozdz’s disclosure of the inclusion of a “pharmaceutically acceptable additive,” including a “wetting material” as supporting the motivation to combine the teachings of Gwozdz and Meezan, as laid out in my original declaration. Ex. 1062 (Donovan Op. Decl.) at ¶ 98.

21. Further, Dr. Brown's own prior art publications demonstrate that a POSA would have understood that the use of penetration enhancers was beneficial in intranasal formulations. For example, Dr. Brown was listed as an author on a textbook chapter published in 2007 titled "Physiological Factors Affecting Nasal Drug Delivery." Ex. 1073. In his 2007 textbook chapter, Dr. Brown contradicted many of the opinions he has expressed in his declaration in this IPR. For example, Dr. Brown's 2007 textbook repeatedly emphasizes why a POSA would have been motivated to develop an intranasal formulation of lipophilic small molecule drug compounds (which would include diazepam) with a reasonable expectation of success. *See, e.g.*, Ex. 1073 at 18 ("More recently, drugs with systemic actions have been marketed for nasal delivery in preference to oral delivery or injection. This takes advantage of the potentially rapid and high systemic availability of nasally administered compounds"); 23 ("Lipophilic drug molecules are absorbed across the nasal epithelium by passive transcellular diffusion. For small, unionized molecules, this provides a rapid efficient transport mechanism, often resulting in plasma concentration profiles resembling that of intravenous injection and bioavailabilities of up to 100%"); 32 ("The nasal route is generating increasing interest as a route for the administration of local treatments and a cost-effective and patient-friendly alternative to injection for systemic delivery. The special advantages of nasal delivery make it attractive for (i) crisis treatment where rapid onset of action is desirable").

22. And, Dr. Brown's 2007 textbook dedicated a subsection of these formulation approaches to discussing the use of ***absorption enhancers***. *Id.* at 27. Thus, in my opinion, Dr. Brown's own prior art textbook, which specifically discusses *nasal* formulations and delivery of drugs, further supports my opinion that a POSA would have been motivated to use penetration enhancers in nasal formulations.

23. Further, Dr. Brown opines that even if a skilled artisan would have considered Meezan, there would have been no reason to modify Gwozdz to add alkyl glycosides, including dodecyl maltoside. Ex. 2071 (Brown Decl.) at ¶ 160. I disagree with Dr. Brown for a number of reasons, as explained below. Indeed, as I explained in my opening declaration, Meezan expressly discloses dodecyl maltoside as a preferred penetration enhancer. *See, e.g.*, Ex. 1062 (Donovan Op. Decl.) at ¶ 91.

24. Dr. Brown opines that “Meezan recommends using ‘highly branched’ alkyl glycosides” rather than linear alkyl glycosides. *See, e.g.*, Ex. 2072 at ¶ 180; *see also, e.g., id.* at ¶¶ 191, 196, 198; *see also* Brown Dep. Tr. at 174:8-17. As explained in my parallel declarations addressing the ’414 and ’786 patents, Dr. Brown’s opinions on this issue seemed to be focused on those patents’ recitation of “n-dodecyl-β-D-maltoside,” as opposed to “dodecyl maltoside” as claimed in the ’546 patent. Thus, it’s unclear to me how or why Dr. Brown even believes the chemistry and nomenclature issues he addresses in his ’414 and ’786 patent declarations are even relevant to the “dodecyl maltoside” limitation recited in the ’546 patent claims, particularly where he opines that “dodecyl maltoside” encompasses a genus of compounds, and because there is no question that Meezan discloses “dodecyl maltoside.”² Indeed, I understand the PTAB previously

² Because the chemistry and nomenclature issues raised by Dr. Brown are irrelevant to the ’546 patent, I do not include a technical discussion or analysis of those issues in this declaration. However, I refer and incorporate by reference those discussions, set forth in my reply declarations in the ’414 and ’786 patent IPRs here, to the extent they are somehow relevant or germane to the issues in the ’546 patent IPR.

found the “dodecyl maltoside” limitation in the claims of the ’876 patent unpatentable as obvious over Gwozdz in view Meezan. Ex. 1040 at 33-36.

25. In any case, Dr. Brown specifically cites to paragraph 149 of Meezan, which reads:

Stability of the alkyl glycoside depends, in part, on the number of carbon atoms, or **branching** of the alkyl chain, with tetradecylmaltoside (TDM) having the greatest effect; but other **highly branched** alkyl chains including DDM also have stabilizing effects. In contrast to Hovgaard-1, which described the preference for a high alkyl glycoside to drug ratio, the instant invention shows that this ratio is much lower. For example, alkyl glycosides in the range of about 0.01% to about 6% by weight result in good stabilization of the drug; whereas Hovgaard-1 shows stabilization is only achieved at much higher ratios of alkyl glycosides to drug (10:1 and 16: 1). Even more interesting, alkyl glycosides of the invention in the range of about 0.01% to about 6% have increased bioavailability (see FIG. 1). This is in sharp contrast to Hovgaard-2, which showed relatively low bioavailability (0.5-1%) at the high alkyl glycoside ratios (10:1 and 16:1).

Ex. 1010 (Meezan) at ¶ [0149] (emphasis added).

26. However, I understand Dr. Brown was relying on an *uncorrected* version of the Meezan specification. In fact, during prosecution, I understand Meezan’s specification was amended to **delete** the terms “branched” and “highly branched” and to replace those terms with “length” and “long,” respectively:

Stability of the alkyl glycoside depends, in part, on the number of carbon atoms, or ~~branching~~ length of the alkyl chain, with tetradecylmaltoside (TDM) having the greatest effect; but other ~~highly branched~~ long alkyl chains including DDM also have stabilizing effects. In contrast to Hovgaard-1, which described the preference for a high alkyl glycoside to drug ratio, the instant invention shows that this ratio is much lower. For example, alkyl glycosides in the range of about 0.01% to about 6% by weight result in good stabilization of the drug; whereas Hovgaard-1 shows stabilization is only achieved at much higher ratios of alkyl glycosides to drug (10:1 and 16:1). Even more interesting, alkyl glycosides of the invention in the range of about 0.01% to about 6% have increased bioavailability (see FIG. 1). This is in sharp contrast to Hovgaard-2, which showed relatively low bioavailability (0.5-1%) at the high alkyl glycoside ratios (10:1 and 16:1).

Ex. 1075 (Meezan Specification Amendment) at 6. Thus, in my opinion, Dr. Brown's repeated reliance on the incorrect "highly branched" language from Meezan underscores that his opinions on this issue are incorrect. Rather, the *correct* Meezan specification emphasizes and supports my opinions: a POSA would understand that Meezan discloses alkyl glycosides having straight-chain (i.e., "long") alkyl groups, *not* branched structures. Indeed, the corrected language above *specifically* emphasizes that "DDM" has a "long alkyl chain[]." *Id.*

27. Finally, I understand Dr. Brown opines that Meezan disclosed that TDM, not DDM, was the "most preferred" and best performing alkyl maltoside, and therefore a POSA would have been motivated to use TDM rather than DDM. *See, e.g.*, Ex. 2072 at ¶¶ 181-186. I understand from counsel that just because TDM purportedly outperformed DDM in Meezan's disclosure, that does not mean DDM would not have been obvious. Rather, I understand that where a prior art reference discloses several options in the form of preferred or non-preferred embodiments, they may all be considered obvious. Thus, I disagree with Dr. Brown's attempt to heighten the requirement for obviousness by arguing that a POSA would only ever consider or pursue the *best* performing ingredient.

28. In any case, as explained in my opening declaration, Meezan expressly disclosed dodecyl maltoside as a "preferred" alkyl glycoside and reported that it was effective at increasing the permeability of drugs. *See, e.g.*, Ex. 1010 at ¶¶ [0150]-[0151], [0157]-[0159], Table I. Thus, Meezan expressly disclosed that DDM was a preferred and effective absorption enhancer. The fact that TDM *may* have been more effective than DDM does not mean that DDM would not have been an obvious penetration enhancer to choose. Indeed, Meezan shows that it would have been an excellent choice. In particular, Example 3 of Meezan reported that dodecyl- β -D-maltoside concentrations of 0.25%, 0.375%, and 0.5% all achieved a dramatic improvement in absorption

and efficacy (as evidenced by the decreased blood glucose concentrations reported in Table I). EX1010 (Meezan) ¶[0158]. Although Dr. Brown relies heavily on his argument that Meezan did not demonstrate that a concentration of 0.125% dodecyl- β -D-maltoside was effective, this would not have discouraged a POSA from using dodecyl- β -D-maltoside in the greater concentrations that did show a significant improvement in absorption and efficacy. And, the challenged claims of the '546 patent would include concentrations of dodecyl- β -D-maltoside found to be effective in Meezan.

29. Thus, I reiterate my opinion, that a POSA would have been motivated by Meezan to use dodecyl maltoside as a penetration enhancer for small molecules, like diazepam. And it remains my opinion that a POSA would have been motivated to combine Gwozdz and Meezan, and that they would have had a reasonable expectation of success.

30. I understand that Neurelis and Dr. Brown have asserted that there would have been no motivation to combine Gwozdz and Meezan because the antimicrobial activity of the benzyl alcohol and ethanol components of Gwozdz might be reduced in the presence of a nonionic surfactant like dodecyl maltoside. POR 49-51; EX2074, ¶¶253-254. I disagree for several reasons.

31. First, an intranasal formulation (i.e., a nasal spray) as contemplated by Gwozdz would require a formulation in a final package that has virtually no bacteria present in the formulation. While the possibility of microbial contamination is always a consideration in pharmaceutical formulation development, for an emergency, one-time use product like a diazepam nasal spray, whether or not the antimicrobial properties of ethanol and benzyl alcohol are decreased or inactivated would not be seen as a limitation since single-use nasal spray devices able to deliver preservative-free nasal sprays were known in the art. These single-use devices would be also be suitable for the administration of diazepam in the emergency treatment of seizure.

32. However, even if a diazepam nasal spray formulation were intended to be used more than once, this would not impact the motivation to combine. A POSA would not expect that the very low concentrations of dodecyl- β -D-maltoside disclosed by Meezan (e.g., 0.25%, 0.375%, and 0.5%) would be sufficient to completely inactivate the antimicrobial properties of the relatively high concentrations of the combination of ethanol and benzyl alcohol utilized in the Gwozdz formulation.

33. Thus, in my opinion, any potential impact of the nonionic surfactant (including dodecyl- β -D-maltoside) on the antimicrobial properties of ethanol and benzyl alcohol does not change my opinion that a motivation existed to combine Gwozdz and Meezan.

VII. Conclusion and Reservation of Rights

34. For the reasons set forth above and in my opening declaration, it is my opinion that the challenged claims (i.e., claims 17 and 22) of the '546 patent are unpatentable as obvious.

35. I reserve the right to supplement and/or expand on the opinions in this declaration based on any new positions Neurelis advances, any additional information that is produced or offered in this IPR, based on any relevant claim construction, in response to any declarations submitted on behalf of Neurelis, or any other circumstances that impacts my opinions.

I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Dated: March 31, 2026

By:

A handwritten signature in black ink that reads "Maureen D. Donovan". The script is cursive and fluid, with the first letters of the first and last names being capitalized and prominent.

Dr. Maureen Donovan

APPENDIX A: MATERIALS CONSIDERED

Exhibit No.	Description
1001	U.S. Patent No. 8,895,546, Administration Of Benzodiazepine Compositions, filed June 13, 2012 (“’546 Patent”)
1002	File History for ’546 Patent, Ser. No. 13/495,942 (“’546 FH”) Part 1: Pages 1-350 Part 2: Pages 351-700 Part 3: Pages 701-1050 Part 4: Pages 1051-1400 Part 5: Pages 1401-1750 Part 6: Pages 1751-2100 Part 7: Pages 2101-2450 Part 8: Pages 2451-2681
1003	U.S. Patent No. 9,763,876, Administration Of Benzodiazepine Compositions, filed October 29, 2014 (“’876 Patent”)
1004	File History for 9,763,876 Patent, Ser. No. 14/527,613 (“’876 FH”) Part 1: Pages 1-270 Part 2: Pages 271-530
1005	Provisional Patent Application No. 61/497,017, filed June 14, 2011 (“’017 Provisional”)
1006	Provisional Patent Application No. 61/570,110, filed December 13, 2011 (“’110 Provisional”)
1007	File History for Non-Provisional Patent Application Serial No. 12/413,439, filed March 27, 2009 (“’439 FH”) Part 1: Pages 1-400 Part 2: Pages 401-800 Part 3: Pages 801-1200 Part 4: Pages 1201-1600 Part 5: Pages 1601-2000 Part 6: Pages 2001-2400 Part 7: Pages 2401-2800 Part 8: Pages 2801-3200 Part 9: Pages 3201-3488
1008	Provisional Patent Application No. 61/040,558, filed March 28, 2008 (“’558 Provisional”)
1009	Gwozdz et al., WO 2009/120933, Pharmaceutical Solutions And Method For Solubilizing Therapeutic Agents, published October 1, 2009, International Filing Date March 27, 2009 (PCT/US2009/038518) (“Gwozdz”)
1010	Meezan et al., U.S. Patent Application Publication No. US 2006/0046962, Absorption Enhancers for Drug Administration, Serial No. 11/127,786, published March 2, 2006 (“Meezan”)
1011	Ritschel, Handbook of Basic Pharmacokinetics, Chapter 36 (Bioavailability and Bioequivalence), Drug Intelligence Publications, Illinois, 1992 (“Ritschel”)

Exhibit No.	Description
1012	Osborne et al., Skin Penetration Enhancers Cited in the Technical Literature, Pharmaceutical Technology, November 1997 (“Osborne”)
1013	Lindhardt et al., Electroencephalographic effects and serum concentrations after intranasal and intravenous administration of diazepam to healthy volunteers, Blackwell Science Ltd Br J Clin Pharmacol, 52, 521-527, 2001 (“Lindhardt”)
1014	Illum L, Nasal drug delivery-possibilities, problems and solutions, Journal of Controlled Release 87 (2003) 187198 (“Illum I”)
1015	Ivaturi et al., Pharmacokinetics and tolerability of intranasal diazepam and midazolam in healthy adult volunteers, Acta Neurol Scand. 2009 Nov;120(5):353-7. Doi: 10.1111/j.1600-0404.2009.01170.x. Epub 2009 May 14 (“Ivaturi”)
1016	Rowe et al., editors, Handbook of Pharmaceutical Excipients, Fourth Edition (2003), Monographs for “Alcohol” (i.e., ethanol), “Alpha Tocopherol”, “Benzyl Alcohol”, “Glycerin”, “Olive Oil”, “Polyethylene Glycol”, “Propylene Glycol”, “Sesame Oil”, and “Triacetin”, American Pharmaceutical Association, Washington DC (“Rowe”)
1017	PDR 54th Edition 2000, DIASTAT® (diazepam rectal gel); MIACALCIN® (Calcitonin Nasal Spray); VALIUM® (diazepam injection), Physicians’ Desk Reference (“PDR”)
1018	Knoester PD, Jonker DM, Van Der Hoeven RT, et al. Pharmacokinetics and pharmacodynamics of midazolam administered as a concentrated intranasal spray. A study in healthy volunteers. Br J Clin Pharmacol. 2002; 53: 501-507 (“Knoester”)
1019	Florida Regional Common EMS Protocols Field Guide, Jones and Barlett Publishers, MA (2005) (“EMS”)
1020	Valium® Tablet Label, Roche, January 2008 (“Valium label”)
1021	Wolfe T, Macfarlane T. Intranasal midazolam therapy for pediatric status epilepticus. Am J Emerg Med 2006; 24:43-346 (“Wolfe”)
1022	Holsti M, Sill B, Firth S, et al., Prehospital intranasal midazolam for the treatment of pediatric seizures. Ped Emerg Care 2007; 23: 148-153 (“Holsti”)
1023	Greenblatt D, Gan L, Harmatz, et al. Pharmacokinetics and pharmacodynamics of single-dose triazolam: EEG compared with

Exhibit No.	Description
	digital symbol substitution test. Br J Clin Pharmacol 2005; 60: 244-248 (“Greenblatt”)
1024	O’Regan M, Brown J, Clarke M. Nasal rather than rectal benzodiazepines in the management of acute childhood seizures. Develop Med and Child Neurol 1996; 38: 1037-1045 (“O’Regan”)
1025	Bhattacharyya M, Kalra V, Gulati S. Intranasal midazolam vs rectal diazepam in acute childhood seizures. Pediatric Neurology 2006; 34: 355-359 (“Bhattacharyya”)
1026	SIGMA Chemical Company Catalog (1988) (“Sigma Catalog”)
1027	Wermeling DP, et al., Intranasal Delivery of Antiepileptic Medications for Treatment of Seizures, Neurotherapeutics: The Journal of the American Society for Experimental Neurotherapeutics, Vol. 6, 352-353, April 2009 (“Wermeling I”)
1028	Hardman, et al., Editors, Goodman & Gilman’s, The Pharmacological Basis of Therapeutics, 10th Edition (2001) (“Goodman & Gilman”)
1029	Loftsson T, Gudmundsdottir H, Sigurjonsdittur JF, et al. Cyclodextrin solubilization of benzodiazepines: formulation of midazolam nasal spray. Int J Pharm 2001; 212:29-40 (“Loftsson”)
1030	Gudmundsdottir H, Sigurjonsdottir JF, Masson M, et al. Intranasal administration of midazolam in a cyclodextrin based formulation: bioavailability and clinical evaluation in humans. Pharmazie 2001; 56: 963-966 (“Gudmundsdottir”)
1031	Dale O., Nilsen T., Loftsson T. Intranasal midazolam: a comparison of two delivery devices in human volunteers. J Pharmacy Pharmacol 2006; 58: 1311- 1318 (“Dale”)
1032	Burstein AH, Modica R, Hatton M, et al. Pharmacokinetics and pharmacodynamics of midazolam after intranasal administration. J Clin Pharmacol 1997; 37: 711-718 (“Burstein”)
1033	Wermeling, D, Record K, Kelly T, et al., Pharmacokinetics and safety of a new intranasal midazolam formulation in healthy volunteers. Anesth Analg 2006; 103:344-349 (“Wermeling II”)

Exhibit No.	Description
1034	Schols-Hendriks MWG, Lohman JJHM, Janknegt R, et al. Absorption of clonazepam after intranasal and buccal administration. Br J Clin Pharmacol, 1995; 39: 449-451 (“Schols-Hendricks”)
1035	Lau SWJ, Slattery JT. Intl J Pharmaceutics. Absorption of diazepam and lorazepam following intranasal administration. Int J Pharmaceutics 1989; 54: 171-174 (“Lau”)
1036	Wermeling DP, Miller JL, Archer SM, et al. Bioavailability and pharmacokinetics of lorazepam after intranasal, intravenous, and intramuscular administration. J Clin Pharmacol, 2001; 41: 1225-1231 (“WermelingIII”)
1037	Budavari, et al., Editors, The Merck Index, 12th Edition (1996) (“Merck Index”)
1038	USP 26/NF 21 2003, The Official Compendia of Standards, Ethanol, Copyright 2002 (“USP 26/ NF 21”)
1039	U.S. App. No. 12/413,439, filed March 27, 2009 (“439Application”)
1040	Final Written Decision issued in IPR 2019-00451 filed against U.S. Patent No. 9,763,876, August 6, 2020 (“IPR 2019-00451 Final Written Decision”)
1041	Lowenstein DH, Alldredge BK. Status epilepticus, N Eng J Med 1998; 338:970-976 (“Lowenstein I”)
1042	Lowenstein DH, Bleck T, Macdonald RL. It’s time to revise the definition of status epilepticus. Epilepsia 1999; 40:120-122 (“Lowenstein II”)
1043	Wang HC, Chang WN, Chang HW, et al., Factors predictive of outcome in 16osttraumatic seizures. J Trauma 2008; 64: 883-888 (“Wang”)
1044	Stavem K, Bjornaes H, Langmoen IA. Long-term seizures and quality of life after epilepsy surgery compared with matched controls. Neurosurgery 2008; 62: 326-334 (“Stavem”)
1045	Logroscino G, Hessdorffer DC, Cascino G, et al., Time Trends in incidence, mortality, and case-fatality after first episode of status epilepticus, Epilepsia 2001; 42:1031-1035 (“Logroscino”)
1046	Feen ES, Bershad EM, Suarez JI, Status Epilepticus, South Med J 2008; 101: 400-406 (“Feen”)

Exhibit No.	Description
1047	Pang T, Hirsch L, Treatment of convulsive and nonconvulsive status epilepticus, Cur Treat Options Neurol 2005; 7:247-259 (“Pang”)
1048	Smith B, Treatment of status epilepticus, Neurol Clin 2001; 19:347-369 (“Smith”)
1049	Ericksson K, Kalviainen R. Pharmacologic management of convulsive status epilepticus in childhood, Expert Rev Neurotherapeutics 2005; 5:777-783 (“Ericksson”)
1050	Meierkord H, Engelsen B, Gocke K, et al., EFNS guideline on the management of status epilepticus, Eur J Neurol 2006; 13: 445-450 (“Meierkord”)
1051	Prasad K, Krishman P, Al-Roomi K, et al., Anticonvulsant therapy for status epilepticus, Br J Clin Pharmacol 2007; 63:640-647 (“Prasad”)
1052	Illum L., Nasal Clearance in Health and Disease, J Aerosol Med 2006; 19:92-99 (“Illum II”)
1053	Constantino HR, Illum L, Brandt G et al., Intranasal delivery: Physicochemical and therapeutic aspects, Intl J Pharmaceutics 2007; 337:1-24 (“Constantino”)
1054	Rudy AC, Coda BA, Archer SM, et al., A multiple dose phase I study of intranasal hydromorphone hydrochloride in healthy volunteers, Anesth Analg 2004; 99:1379-1386 (“Rudy”)
1055	Mittal P, Manohar R, Rawat A, Comparative study of intranasal midazolam and intravenous diazepam sedation for procedures and seizures, Ind J Pediatrics 2006; 73:975-78 (“Mittal”)
1056	Mahmoudian T, Zadeh M, Comparison of intranasal midazolam with intravenous diazepam for treating acute seizures in children, Epilepsy and Behavior 2004; 5:253-255 (“Mahmoudian”)
1057	Lahat E, Goldman M, Barr J, et al., Comparison of intranasal midazolam with intravenous diazepam in treating febrile seizures in children: prospective randomized study, BMJ 2000; 321:83-87 (“Lahat”)
1058	Sharma S, et al., Permeation enhancers in the transmucosal delivery of macromolecules, Pharmazie 2006; 61(6): 495-504 (“Sharma”)

Exhibit No.	Description
1059	Ahsan F. et al., Effects of the permeability enhancers, tetradecylmaltoside and dimethyl- β -cyclodextrin, on insulin movement across human bronchial epithelial cells, Eur J Pharm Sciences 2003; 20:27-34 (“Ahsan”).
1060	U.S. Patent No. 5,661,130 to Meezan and Pillion (“Meezan II”)
1061	U.S. Patent No. 6,610,271 to Wermeling (“WermelingIV”)
1062	Declaration of Dr. Maureen Donovan, Ph.D.
1063	Complaint filed in Neurelis, Inc. v. Padagis LLC et al., Civil Action No. 1:24-cv-11637 (D. Mass) (complaint filed on June 25, 2024).
1064	U.S. Provisional Patent App. No. 61/040,281 (“281 Provisional”)
1065	NOT USED
1066	NOT USED
1067	NOT USED
1068	Neurelis, Inc. v. Aquestive Therapeutics, Inc., No. 2021-1038, (Fed. Cir. Oct. 7, 2021)
1069	Chart comparing claims 1-22 of the ’546 Patent to claims 1- 16 and 24-36 of the ’876 Patent
1071	US Patent No. 9,763,876 to Cartt (“’876 Patent”)
1072	Expert Declaration of Professor Sveinbjorn Gizurason in Support of Patent Owner’s Response to Petition for <i>Inter Partes</i> Review of U.S. Patent No. 9,763,876
1073	Lim et al., <i>Physiological Factors Affecting Nasal Drug Delivery</i> , in ENHANCEMENT IN DRUG DELIVERY (Elka Touitou & Brian W. Barry, 2007)
1074	US Patent No. 6,962,691 to Lulla
1075	File History for Non-Provisional Patent Application Serial No. 11/127,786, Response to Office Action and Amendments filed August 13, 2007

Exhibit No.	Description
1076	File History for Non-Provisional Patent Application Serial No. 13/371,274, Declaration of Dr. Edward T. Maggio filed September 19, 2013
1077	Certified Transcript of Deposition of Marc Brown, Ph.D. in <i>Padagis US LLC vs. Neurelis, Inc.</i> , IPR2025-00464, IPR2025-00465, IPR2025-00466 (March 17, 2026)
1079	Panico et al., A GUIDE TO IUPAC NOMENCLATURE OF ORGANIC COMPOUNDS, Recommendations (1993) (“IUPAC”)
1080	US Patent No. 8,278,292 to Brown (“’292 Patent”)
1083	Stipulation Regarding Claim Construction, <i>Neurelis, Inc. v. Padagis LLC et al.</i> , 1-24-cv-00562 (D.Del. May 8, 2024).
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 <i>Neurelis, Inc. v. Padagis LLC</i> , 1:24-cv-00562, D.I. 20 (D. Del. Aug. 28, 2024)
2003	Preliminary Invalidity Contentions served in <i>Neurelis, Inc. v. Padagis LLC</i> , 1:24-cv-00562 (D. Del. Dec. 20, 2024)
2004	Markman Order entered in <i>Gilead Sciences, Inc. v. Lupin Ltd.</i> , 1:22-cv-00615-MN, D.I. 280 (D. Del. Feb. 21, 2025)
2005	Markman Order entered in <i>Spinal Generations, LLC v. Depuy Synthes, Inc.</i> , 1:22-cv-01368 (MN), D.I. 147 (D. Del. Oct. 16, 2024)
2006	Orange Book Listing for U.S. Patent No. 8,895,546
2007	Declaration of Nicholas A. Peppas, Sc.D., dated December 6, 2018 in <i>Aquestive Therapeutics, Inc. v. Hale Biopharma Ventures, LLC</i> , IPR2019-00451, Exhibit 1041 (Jan. 29, 2019)
2008	Declaration of Daniel P. Wermeling, Pharm.D., dated January 27, 2020 in <i>Aquestive Therapeutics, Inc. v. Hale Biopharma Ventures, LLC</i> , IPR2019-00451, Exhibit 1150 (Jan. 28, 2020)
2013	Scheduling Oral Order entered in <i>Neurelis, Inc. v. Padagis LLC</i> , 1:24- cv-00562, D.I. 47 (D. Del. March 11, 2025) Order Granting Stipulation to Extend Certain Fact Discovery Deadlines entered in

Exhibit No.	Description
	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

Exhibit No.	Description
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”)
2049	Marc Brown Curriculum Vitae
2050	Joint Claim Construction Brief, Neurelis, Inc. v. Padagis LLC et al., 1:24-cv-00562, D.I. 87 (D. Del. August 15, 2025) (“Joint CC Brief”)
2051	Andrew Streitwieser, Introduction to Organic Chemistry (4th ed. 1992) (“Streitwieser”)
2052	David W. Oxtoby et al., Principles of Modern Chemistry (4th ed. 1999) (“Oxtoby”)
2053	European Pharmacopoeia 6.0, Vol 2 (6th ed. 2007) (“PhEur 6.0”)
2054	Panayiotis P. Constantinides et al., Advances in the Use of Tocols as Drug Delivery Vehicles, 23 Pharm Res. 243 (2006) (“Constantinides- 2006”)
2055	Rowe, Sheskey, & Owen, Handbook of Pharmaceutical Excipients, (6th ed. 2009) (“Rowe-2009”)
2056	Afaf Kamal-Eldin, Effect of Fatty Acids and Tocopherols on the Oxidative Stability of Vegetable Oils, 108 Eur. J. of Lipid Sci. & Tech. 1051 (2006) (“Kamal-Eldin-2006”)
2057	Branka Rozman & Mirjana Gašperlin, Stability of Vitamins C and E in Topical Microemulsions for Combined Antioxidant Therapy, 14 Drug Delivery 235 (2008) (“Rozman-2007”)
2058	Afaf Kamai-Eldin & Lars-Ake Appelqvist, The Chemistry and Antioxidant Properties of Tocopherols and Tocotrienols, 31 Lipids 671 (1996) (“Kamai-Eldin-1996”)
2059	March 2009 FDA Inactive Ingredient Database

Exhibit No.	Description
2062	C. Holvoet et al., Inclusion Complexation of Diazepam with Different Cyclodextrins in Formulations for Parenteral Use, 60 Pharmazie 598 (2005) (“Holvoet-2005”)
2063	Sila-On et al., Influence of Incorporation Methods on Partitioning Behavior of Lipophilic Drugs into Various Phases of a Parenteral Lipid Emulsion, 9 PharmSciTech 684 (2008) (“Sila-On-2008”)
2064	D. J. Van Drooge et al., Incorporation of Lipophilic Drugs in Sugar Glasses by Lyophilization using a Mixture of Water and Tertiary Butyl Alcohol as Solvent, 93 J. of Pharm. Sci. 713 (2004) (“Van Drooge-2004”)
2065	L. M. A. Monzon & L. M. Yudi, Voltammetric Analysis of Lipophilicity of Benzodiazepine Derivatives at the Water 1,2-dichloroethan Interface, 495 J. of Electroanalytical Chem. 146 (2001) (“Monzon-2001”)
2066	M. Molero-Monfort et al., Retention-activity Relationship Studies of Benzodiazepines by Micellar Liquid Chromatography, 13 Biomed. Chromatography 394 (1999) (“Molero-Monfort-1999”)
2067	M. Molero-Monfort et al., Micellar Liquid Chromatography for Prediction of Drug Transport, 870 J. of Chromatography 1 (2000) (“Molero-Monfort-2000”)
2068	Neurelis Patent Family Tree
2069	Declaration of Mareen Donovan, Ph.D. in Support of Defendants’ Responsive Claim Construction Brief, Neurelis, Inc. v. Padagis LLC et al., 1:24-cv-562, D.I. 88-28 (D. Del. August 22, 2025) (“Donovan-CC Decl.”)
2070	Certified transcription of December 10-11, 2025, Volume I and II Deposition of Maureen Donovan, Ph.D. in Padagis US LLC vs. Neurelis, Inc., IPR2025-00464, IPR2025-00465, IPR2025-00466 (“Donovan Transcript”)
2071	What is Log P and How Does It Predict Chemical Behavior?, Biology Insights, (August 16, 2025), https://biologyinsights.com/what-is-log-p-and-how-does-it-predict-chemical-behavior/ (“Log P”)