UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PADAGIS US LLC,

Petitioner,

v.

NEURELIS, INC.,

Patent Owner.

Case No. IPR2025-00465
U.S. Patent No. 11,241,414

REPLY DECLARATION OF MAUREEN DONOVAN, PH.D. IN SUPPORT OF PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 11,241,414

TABLE OF CONTENTS

I. Introduction 4

II. Legal Standards 5

III. Level of Skill in the Art 5

IV. Summary of Opinions 6

V. Technical Background and State of the Art 7

A. Chemical Structures and Nomenclature: Alkanes 7

B. Chemical Structures and Nomenclature: n-dodecyl-β-D-maltoside 14

C. Chemical Structures and Nomenclature: Saccharides and Glycosides 15

VI. The ’558 Provisional Application Does Not Disclose Alkyl Maltosides, Dodecyl Maltoside, or n-dodecyl-β-D-maltoside 16

VII. The Claims of the ’414 Patent Would Have Been Obvious to a POSA 18

A. Dr. Brown’s Obviousness Opinions Merely Reiterate the Same Obviousness Arguments Raised by Neurelis in the ’876 Patent IPR 18

B. Meezan Disclosed and Would Have Motivated a POSA to use n-dodecyl-β-D-maltoside with a Reasonable Expectation of Success 19

C. Antimicrobial Properties of Ethanol and Benzyl Alcohol Would Not Be Materially Impacted by Nonionic Surfactants in a Nasal Spray Formulation 28

VIII. Conclusion and Reservation of Rights 29

TABLE OF ABBREVIATIONS

Full Name of Cited Reference	Abbreviation	Exhibit No.
U.S. Patent No. 11,241,414	’414 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
SIGMA Chemical Company Catalog (1988)	Sigma Catalog	1026
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 *Inter Partes* Review of U.S. Patent No. 11,241,414	Donovan Op. Decl.	1062
U.S. Provisional Pat. App. No. 61/040,281	Gwozdz Provisional	1064
U.S. Publication No. 2008/0279784 to Cartt et al.	Cartt	1065
USP 23/NF 18 1995, The Official Compendia of Standards, Vitamin E, Copyright 1994	USP 23/NF 18	1066
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 *Inter Partes* Review of U.S. Patent No. 9,763,876	Gizurarson Decl.	1072
Lim et al., *Physiological Factors Affecting Nasal Drug Delivery*, *in* ENHANCEMENT IN DRUG DELIVERY (Elka Touitou & Brian W. Barry, 2007)	Brown Textbook	1073
U.S. Patent No. 6,962,691	’691 patent	1074
File History for Non-Provisional Patent Application Serial No. 11/127,786, Response to Office Action and Amendments filed August 13, 2007	Meezan Spec. Amendment	1075
File History for Non-Provisional Patent Application Serial No. 13/371,274, Declaration of Dr. Edward T. Maggio filed September 19, 2013	Maggio Decl.	1076
Panico et al., A GUIDE TO IUPAC NOMENCLATURE OF ORGANIC COMPOUNDS, Recommendations (1993)	IUPAC 1993	1079
U.S. Patent No. 8,278,292	’292 patent	1080
Certified Transcript of Deposition of Marc Brown, Ph.D. in *Padagis US LLC vs. Neurelis, Inc.*, IPR2025-00464, IPR2025-00465, IPR2025-00466 (March 17, 2026)	Brown Dep. Tr.	1077
Andrew Streitwieser, Introduction to Organic Chemistry (4th ed. 1992)	Streitwieser	2051
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)	Donvoan Claim Construction Decl.	2069
Expert Declaration of Dr. Marc Brown	Brown Decl.	2073

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. 11,241,414 ("the '414 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 '414 patent would have been obvious to a person of ordinary skill in the art ("POSA"). Specifically, I opined that all claims of the '414 patent are unpatentable as obvious over Gwozdz (Ex. 1009) in view of Meezan (Ex. 1010). *See generally, e.g.*, Ex. 1062 at ¶¶ 117-204. It is still my opinion that the challenged claims of the '414 patent are unpatentable as obvious in view of the combinations of references listed above, 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. 2073), submitted in support of Neurelis's response to Padagis's petition, as well as Neurelis's Response to Padgais'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 '414 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. In addition to the legal principles described in my opening declaration, I was informed of additional details related to certain legal principles relevant to my opinions.

6. As I discussed in my opening declaration, I understand that to be entitled to an earlier priority date, each claim limitation must be expressly, implicitly, or inherently supported in the originally filed disclosure. *Id*. at ¶¶ 41-42. I was also informed that claim limitations may be considered "essential" or "non-essential" material. I understand that "essential material" is material that is necessary to provide a written description of the claimed invention whereas "non-essential material" generally refers to background material or material that is relevant to the state of the art in the context of the claimed invention.

III. Level of Skill in the Art

7. In my opening declaration, I discussed my understanding and definition of a POSA with respect to the '414 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 '414 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.

8. 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. 2073 (Brown Decl.) at ¶ 61.[1]

9. 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

10. 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

[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.

to this declaration. My opinions and conclusions are also based on my education, experience, and knowledge of the relevant art.

11. I disagree with Dr. Brown that the prior art references I rely on to form my obviousness opinions do not disclose, and would not have motivated a POSA to use, n-dodecyl-β-D-maltoside. Specifically, Dr. Brown opines that Meezan does not disclose and would not have motivated a POSA to use n-dodecyl-β-D-maltoside as an ingredient in a diazepam nasal solution. In my opinion, as explained in my opening declaration and again in this reply declaration, Meezan both discloses n-dodecyl-β-D-maltoside and would have motivated a POSA to use n-dodecyl-β-D-maltoside in the non-aqueous diazepam nasal solutions disclosed by Gwozdz with a reasonable expectation of success. *See, e.g.*, Ex. 1062 (Donovan Op. Decl.) at ¶¶ 133-139. Further, as discussed herein, it is also my opinion that the '558 provisional does not disclose or support "n-dodecyl-β-D-maltoside;" the claims of the '414 Patent would have been obvious to a POSA, as Dr. Brown's arguments simply restate 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.

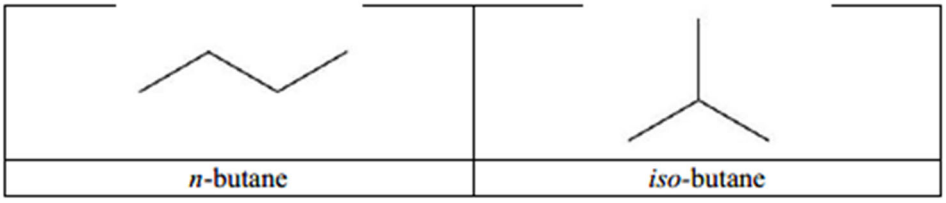
V. Technical Background and State of the Art

A. Chemical Structures and Nomenclature: Alkanes

12. Dr. Brown begins his discussion of the n-dodecyl-β-D-maltoside argument by addressing "some basic principles of chemistry and biochemistry." *See*, *e.g.*, Ex 2073 at ¶ 63-67. For example, Dr. Brown explains generally that "[o]rganic compounds are structured around carbon-carbon (C-C) and carbon-hydrogen (C-H) bonds, although they may include other elements, particularly oxygen, nitrogen, and sulphur." *Id*. at ¶ 65. And he explains that the

chemical bonds and structures that form organic compounds can be represented in different ways. *Id*. at ¶¶ 66-67.

13. Dr. Brown next discusses alkanes, which he explains "are a type of hydrocarbon compound that are made entirely of carbon (C) and hydrogen (H) atoms, and in which all the carbon-carbon bonds are single bonds." *Id*. at ¶ 68. Dr. Brown notes that "[a]lkanes of four or more carbons can form different ***isomers***." *Id*. at ¶ 69 (emphasis in original). And he discusses butane as an example, noting that "[b]oth isomers have the same number of carbons and hydrogens, but they have different structures":



Id. at ¶ 70.

14. According to Dr. Brown, "[t]he 'n-' nomenclature refers to the 'normal' or ***linear*** isomer." *Id*. And he opines that "[i]n contrast to *n*-alkanes, the other category of isomer is ***branched***." *Id*. Dr. Brown goes on to discuss isomers and structures of alkanes having different numbers of carbon atoms, explaining that alkanes with higher numbers of carbon atoms are capable of forming a larger number of isomers (i.e., one straight or unbranched structure and a number of branched-chain structures). *Id*. at ¶¶ 71-73. Thus, Dr. Brown opines that an alkane (or alkyl group) should be named with the "n-" prefix when referring to a straight-chain alkane. *Id*.

15. I disagree with Dr. Brown that the "n-" prefix is necessary in the context of chemical nomenclature to understand when an alkane is a straight-chain isomer as opposed to a branched isomer. Indeed, the Streitwieser textbook that Dr. Brown relies on to support his opinions discusses *n*-alkanes as a general class of straight-chain alkanes (as opposed to branched alkanes),

but does not state or recommend that straight-chain alkanes must or should always be named with the "n-" prefix. *See, e.g.*, Ex. 2051 (Streitwieser) at 9. For example, Streitwieser explains that "[t]he normal alkanes are named according to the number of carbon atoms in the chain (Table 3.2)," but does not state that the "n-" prefix should be used. *Id*. Indeed, Table 3.2 of Streitwieser identifies the normal alkanes by their "name" *without* using the "n-" prefix:

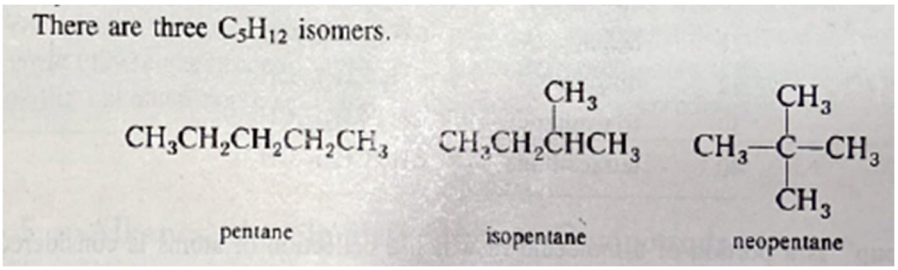
TABLE 3.2

n	Name	Formula
1	methane	CH_4
2	ethane	CH_3CH_3
3	propane	$CH_3CH_2CH_3$
4	butane	$CH_3CH_2CH_2CH_3$
5	pentane	$CH_3(CH_2)_3CH_3$
6	hexane	$CH_3(CH_2)_4CH_3$
7	heptane	$CH_3(CH_2)_5CH_3$
8	octane	$CH_3(CH_2)_6CH_3$
9	nonane	$CH_3(CH_2)_7CH_3$
10	decane	$CH_3(CH_2)_8CH_3$
11	undecane	$CH_3(CH_2)_9CH_3$
12	dodecane	$CH_3(CH_2)_{10}CH_3$
13	tridecane	$CH_3(CH_2)_{11}CH_3$
14	tetradecane	$CH_3(CH_2)_{12}CH_3$
15	pentadecane	$CH_3(CH_2)_{13}CH_3$
20	eicosane	$CH_3(CH_2)_{18}CH_3$
21	heneicosane	$CH_3(CH_2)_{19}CH_3$
22	docosane	$CH_3(CH_2)_{20}CH_3$
30	triacontane	$CH_3(CH_2)_{28}CH_3$
40	tetracontane	$CH_3(CH_2)_{38}CH_3$

Id. at 9-10. When presented with this table at his deposition, Dr. Brown referenced a notation to the right-hand margin of the page where Table 3.2 appears in Streitweiser that states "n-Alkanes, the Simplest Organic Compounds," implying that the "n-" prefix was somehow not required in naming the alkanes in the table in light of that notation. Ex. 1077 (Brown Dep. Tr.) at 94:12-16.

But, that notation on the right-hand margin of the page is just referencing the section within the textbook that the page appears in: "SEC. 3.5 n-Alkanes, the Simplest Organic Compounds." Ex. 2051 (Streitwieser) at 9. That can be clearly seen by looking at the margin comments on each page of Streitwieser, which alternate between identifying the chapter that the page appears in (*see*, *e.g.*, *id.* at 7, 9, 11, 14) and the section number and section heading that the page appears in (*see*, *e.g.*, *id.* at 6, 8, 10, 12, 13, 15). In light of that, a POSA would not interpret the notation on the right-hand margin next to Table 3.2 as signifying anything other than the section that the page appears in.

16. As described in Streitwieser, a POSA would understand that "pentane" (i.e., named without the "n-" prefix) refers to the straight-chain isomer having the number of carbon atoms indicated by "penta-" (meaning "five" in Greek). Indeed, Streitweiser does just that when it discusses the three isomers of pentane:



Id. at 11. It is the *branched* alkanes that are appended with an appropriate prefix to specify *which* branched structure is being identified (e.g., "iso" and "neo" are added as prefixes to denote specific branched structures of a five-carbon alkane). When presented with the manner in which Streitwieser refers to pentane at his deposition, Dr. Brown suggested that it could be a typographical error given that Streitwieser also refers to "*n*-butane" two paragraphs above. Ex. 1077 (Brown Dep. Tr). at 111:15-24. But, what this shows a POSA is that there is no

requirement to use the "n-" prefix when referencing an alkane that is a straight-chain isomer, which is consistent with Table 3.2 and the remainder of the discussion in Streitwieser.

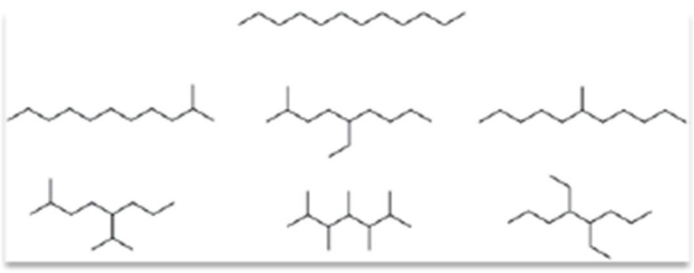
17. Streitwieser reiterates exactly that point when discussing the large number of potential isomers that alkanes with more carbon atoms may have: "With more carbons the number of possible isomers increases rapidly … [i]t is obviously not possible to coin a set of unique prefixes like iso- and neo- to name all of the dodecane isomers, or, for that matter, even the heptane isomers. Clearly it is essential that a method of systematic nomenclature be devised, so that each different compound may be assigned an unambiguous name." Ex. 2051 (Streitwieser) at 11. Streitwieser goes on to explain that the "method of systematic nomenclature" used to name organic compounds has long-been determined by the International Union of Pure and Applied Chemistry ("IUPAC"). *Id*. at 12. And Streitwieser explains that:

> The IUPAC system of alkane nomenclature is based on the simple fundamental principle of considering all compounds to be derivatives of the longest single carbon chain present in the compound. ***Appendages to this chain are designated by appropriate prefixes.*** This chain is then numbered from one end to the other. The end chosen as number 1 is that which gives the smaller number (a locant) at the first point of difference.

Id. (emphasis added). Thus, under the IUPAC system for naming chemical compounds, it is the *branched* structures that must be labeled with an appropriate prefix—in the case of a straight-chain alkane, there is no need to include a prefix (including the "n-" prefix).

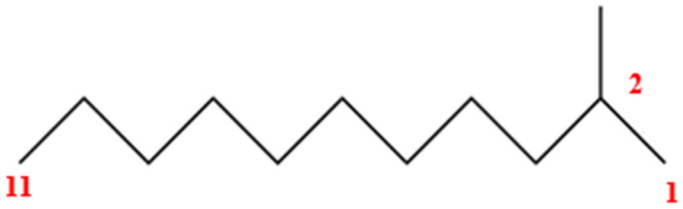
18. In fact, IUPAC has long-published several books with chemical nomenclature rules and recommendations. One of those books is referred to as the Blue Book, which promulgates rules for nomenclature of organic compounds, including alkanes. A POSA would have understood that the IUPAC's Blue Book does not recommend the use of the "n-" prefix when naming straight-chain alkanes or alkyl groups. *See, e.g.*, Ex. 1079 (IUPAC 1993) at 4-6.

19. Dr. Brown opines about dodecane (or a dodecyl moiety) specifically, which he explains can have 355 isomeric structures. Ex. 2073 at ¶ 72. And he discusses a figure in which he depicted "a handful of the 355 isomers that dodecane ($C_{12}H_{26}$) can adopt":



Id. According to Dr Brown, "*n*-dodecane is the linear isomer depicted at the top of this figure, but dodecane can adopt 354 other isomeric forms, only a few of which are depicted above. Other than *n*-dodecane, every other isomer of dodecane is branched in one or more locations." *Id*. But only one structure depicted in Dr. Brown's figure is actually named "dodecane" under the IUPAC rules, which Dr. Brown agreed with during his deposition. *See, e.g.*, Ex. 1077 (Brown Dep. Tr.) at 119:13-121:22.

20. For example, the compound in the middle row on the left of the figure from Dr. Brown's declaration has the following structure:



Ex. 2073 at ¶ 72 (red numbers added by me). Following the IUPAC nomenclature rules, the first step is to determine the longest single carbon chain present in the compound—as shown above, the longest single carbon chain in Dr. Brown's compound is 11 carbons long. And as discussed in Streitwieser and the IUPAC rules, this 11-carbon chain is named based on Greek numbers—here,

the root of Dr. Brown's compound would be named "undecane" (Greek for 11) based on the 11-carbon chain, not "dodecane" (which would indicate a 12-carbon chain). The side-chain (i.e., branched structure) at carbon number 2 would then be added as a prefix, specifying that it is a "methyl" group that branches off of the second carbon. Thus, this compound from Dr. Brown's figure would in fact be named 2-methylundecane.

21. Thus, I disagree with Dr. Brown that a POSA would somehow interpret a compound named "dodecane" (or a compound that includes a "dodecyl" moiety in its name) to somehow refer to *all* of the compounds identified in his figure. The fact that all of the compounds in Dr. Brown's figure have 12 carbon atoms does not somehow mean they are all named "dodecane" as Dr. Brown opines. Rather, if an article or prior art reference were discussing "dodecane" or a compound containing a "dodecyl" moiety (i.e., without the "n-" prefix), a POSA would have understood that, based on the IUPAC rules and their common knowledge it was a reference to a straight chain alkane having 12 carbon atoms. In contrast, a branched alkane, including those depicted in Dr. Brown's figure, would be appended with an appropriate prefix to indicate both *where* the branched side-chain is located and *what* chemical moiety is extending from that position.

22. Indeed, my understanding and interpretation appears to be consistent with that of the '414 patent. I understand the claim language reciting "n-dodecyl-β-D-maltoside" was added to the pending claims of the application that ultimately issued as the '414 patent (i.e., U.S. App. No. 17/332,800) via a preliminary amendment dated May 27, 2021. Ex. 1002, p. 268 ("New" claim 48). In the remarks accompanying the claim amendment, Neurelis stated that "[a]pplicant asserts that no new matter has been added to the application through this amendment and that all claims submitted herewith are fully supported by the specification as filed." *Id*., p. 271. Upon

reviewing the specification filed with the ’800 application, the term “n-dodecyl-β-D-maltoside” is not found anywhere. However, the specification includes multiple references to the term “dodecyl maltoside” (*see, e.g.*, ’414 patent at 31:15-20) and even “dodecyl…β-D-maltoside” (*see, e.g., id*. at 31:9-12 (“Exemplary alkyl glycosides that may be employed include octyl-, nonyl-, decyl-, undecyl-, dodecyl, tridecyl, tetradecyl, pentadecyl, octadecyl α- or β-D-maltoside, -glucoside or sucroside.”)). But nowhere in the specification of the ’414 patent is the name “***n-***dodecyl-β-D-maltoside” referenced. Thus, because Neurelis asserted that the claims are “fully supported by the specification as filed,” it appears that the ’414 patent adopts the same understanding of chemical nomenclature that I have described above, namely that the “***n-***” prefix is not commonly associated with or necessary to designate a straight chain alkane, and that “dodecyl maltoside” ” and “dodecyl beta-D-maltoside” were understood by a POSA to refer to n-dodecyl-β-D-maltoside. *See* Ex. 1062 (Donovan Op. Decl.) at ¶¶ 133-139.

B. Chemical Structures and Nomenclature: n-dodecyl-β-D-maltoside

23. Dr. Brown also opines about the structure of n-dodecyl-β-D-maltoside specifically, breaking it down into its individual chemical moieties. Ex. 2073 at ¶ 81. Dr. Brown reiterates his opinion that “the *n*-dodecyl is a linear chain” and that “[c]onsidering only the dodecyl moiety on its own, there are 354 other chemical compounds (isomers) qualifying as dodecyl-β-D-maltoside.” *Id*. Dr. Brown’s “354 other” isomers of “the dodecyl moiety” apparently comes from Streitwieser, which discloses that there are 355 total isomers of an alkane having 12 carbon atoms. Ex. 2051 at 11. But as I just explained, only *one* of those 355 isomers would actually have an unbranched 12-carbon chain: the straight-chain alkane named simply “dodecane” or “dodecyl” when covalently linked to the saccharide moiety. The remaining 354 isomers would have branched structures where the longest possible chain would be 11-carbons long (e.g., 2-methyl***undecane***) and would be named with appropriate prefixes to designate where and what side chains extend

from the longest carbon chain. *None* of the remaining 354 isomers of a 12-carbon alkane would have "dodecane" or "dodecyl" in their chemical names at all.

C. Chemical Structures and Nomenclature: Saccharides and Glycosides

24. I note that Dr. Brown also opines about the chemical structures and nomenclature rules for saccharides and glycosides. *See, e.g.*, Ex. 2073 at ¶¶ 74-80. Specifically, Dr. Brown opines that certain saccharides were well-known and common, and that they have both alpha and beta anomers. *Id*. Dr. Brown also opines that "[w]hen a saccharide is chemically connected to another chemically distinct moiety, the resulting molecule is often termed a 'glycoside.'" *Id*. at ¶ 78. And Dr. Brown opines that alkyl glycosides "represent[] a broad genus of potential chemical compounds, including accounting for" various "variations" in their chemical structures and bonds. *Id*. at ¶ 79.

25. Dr. Brown apparently believes that these different "variations" of "alkyl glycosides" generally (i.e., the "genus" of alkyl glycosides as opposed to the dodecyl-β-D-maltoside species at issue in this IPR) results in a significant number of potential alkyl glycosides that a POSA would have been aware of or considered. *See, e.g.*, *id*. at ¶ 81. In my opinion, Dr. Brown's discussion of these additional chemical nomenclature and structural issues is irrelevant at least because Meezan expressly discloses the use of dodecyl-β-D-maltoside specifically, as discussed below and in my opening declaration. *See, e.g.*, Ex. 1062 (Donovan Op. Decl.) at ¶¶ 133-139. In other words, Dr. Brown's discussion about the beta and alpha anomers, the potential for D or L stereochemistry, as well as other generalizations about the broad genus of

alkyl maltosides, has no bearing on the issues in this IPR because Meezan specifically identified dodecyl-***β-D-maltoside***.[2]

VI. The '558 Provisional Application Does Not Disclose Alkyl Maltosides, Dodecyl Maltoside, or n-dodecyl-β-D-maltoside

26. As explained in my opening declaration, it is my opinion that the claims of the '414 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 ¶¶ 41-53. In addition, and as I explained in my opening declaration, it is my opinion that the '558 provisional application to which the '414 patent claims priority does not mention or disclose alkyl glycosides, dodecyl maltosides, or n-dodecyl-β-D-maltoside. *Id*.

27. I have reviewed Dr. Brown's declaration and understand he opines that the claimed "n-dodecyl-β-D-maltoside" is supported by the '558 provisional application, and thus he and Neurelis contend that the claims of the '414 patent are entitled to a priority date of March 28, 2008 (the filing date of the '558 provisional application). I disagree with Dr. Brown and Neurelis, and maintain my opinion that the '558 provisional application does not disclose or otherwise support "n-dodecyl-β-D-maltoside," as required by all claims of the '414 patent.

28. Dr. Brown opines that the claimed "n-dodecyl-β-D-maltoside" element is supported and disclosed both in the non-provisional application (filed in 2009) and the '558 provisional application (filed in 2008). *See, e.g.*, Ex. 2073 at ¶¶ 141-142, 178-185. With respect to

[2] While it is my opinion that Dr. Brown's discussion of these additional chemical nomenclature and structural issues is superfluous and irrelevant, and while I do not discuss or address the technical aspects of these issues, that does not mean I agree with Dr. Brown's opinions about any of these background and state of the art issues.

the ’558 provisional application, Dr. Brown offers little explanation for his opinions other than quoting the following excerpts from the ’558 provisional application:

> “The composition of one of claims 1-16, further comprising at least one additional ingredient selected from the group consisting of . . . enhancers….”
>
> “The method of claim 18, wherein the composition comprises at least one additional ingredient selected from the group consisting of . . . enhancers….”
>
> “In some embodiments, the drug delivery system of the invention by advantageously comprise an absorption enhancer. The term ‘enhancer’, means any material which acts to increase absorption across the mucosa and/or increase bioavailability … in some embodiments, enhancing agents that are appropriate include chelating agents (EGTA, EDTA, alginates), surface active agents (especially non-ionic materials), acyl glycerols, fatty acids and salts, tyloxapol, and biological detergents listed in the SIGMA catalog, 1988, page 316-321 (which is incorporated by reference).”

See Ex. 2073 at ¶ 142 (quoting Ex. 1008 (’558 Provisional Application) at claim 17, claim 35, ¶¶ [150], [152]).

29. It is clear from the passage above that “n-dodecyl-β-D-maltoside” (or alkyl glycosides or dodecyl maltosides) is mentioned nowhere in this passage from the ’558 provisional. Instead Dr. Brown opines that the SIGMA catalog’s reference to n-dodecyl-β-D-maltoside is what provides support for the claims of the ’414 patent. *Id.*; *see also*, Ex. 2073 at ¶¶ 141-142, 178-185. For example, Dr. Brown opines that because Sigma was a “well-known” and “large” company that supplied chemicals, it was “a standard in the industry” that a POSA would have considered reliable. Ex. 2073 at ¶ 179. And Dr. Brown opines that the ’558 provisional application’s references to “enhancers” would somehow direct a POSA to the SIGMA catalog, and specifically within the SIGMA catalog to biological detergents and to non-ionic surfactants within that category where they would single out n-dodecyl-β-D-maltoside. *Id*. at ¶¶ 178-185.

30. For the reasons discussed in my opening declaration, I disagree with Dr. Brown. *See, e.g.*, Ex. 1062 at ¶¶ 41-53.

VII. The Claims of the ’414 Patent Would Have Been Obvious to a POSA

A. Dr. Brown’s Obviousness Opinions Merely Reiterate the Same Obviousness Arguments Raised by Neurelis in the ’876 Patent IPR

31. I have reviewed Dr. Brown’s declaration and understand he opines that the claims of the ’414 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.

32. Dr. Brown opines about whether the claims of the ’414 patent may contain water, including residual water associated with excipients like ethanol. *See, e.g.*, Ex. 2073 at ¶¶ 193-195, 210-216. Specifically, Dr. Brown points to a declaration I submitted in the district court proceeding involving the ’414 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 ¶¶ 193-195. 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.

33. As made clear in my original declaration, the obviousness analysis I provided applies the understanding that “consisting of” requires that the claimed solution to “contain[] only” the claimed benzodiazepine drug, one or more natural or synthetic tocopherols or tocotrienols, ethanol, benzyl alcohol, and n-dodecyl-β-D-maltoside. Ex. 1062 (Donovan Op. Decl.) at ¶ 121. 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.

B. Meezan Disclosed and Would Have Motivated a POSA to use n-dodecyl-β-D-maltoside with a Reasonable Expectation of Success

34. Dr. Brown opines that neither Gwozdz nor Meezan disclosed or would have motivated a POSA to use n-dodecyl-β-D-maltoside. *See, e.g.*, Ex. 2073 at ¶¶ 203-209, 255-286. For the reasons discussed in my opening declaration and below, I disagree with Dr. Brown.

35. 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. 2073 at ¶ 233. 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 at ¶¶ 94-99, 103-109.

36. Additionally, the passage from Gwozdz, that I relied on states that other "pharmaceutically acceptable additives" may be 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 ¶ 97 (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 Gwozdz Provisional. Ex. 1064 (Gwozdz Provisional) at 10:10-17. 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 ¶ 97.

37. 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").

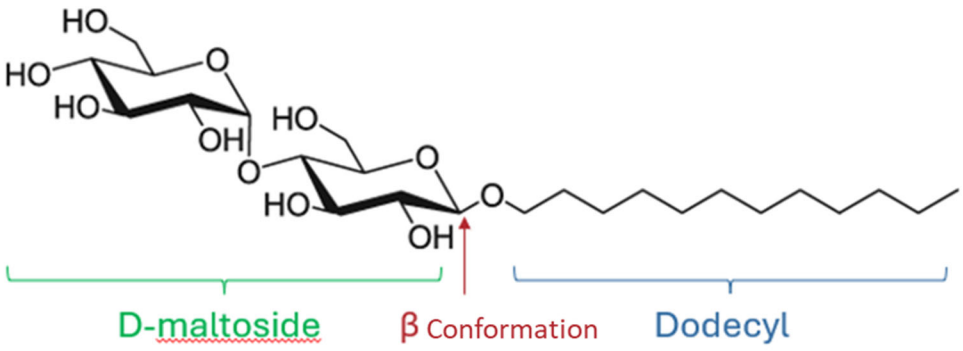
38. And, Dr. Brown's 2007 textbook dedicated a subsection of these formulation approaches to discussing the use of ***absorption enhancers***. *Id*. at 27. Thus, in my opinion,

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.

39. Further, Dr. Brown opines that "[e]ven if a skilled artisan would have considered Meezan, there would have been no reason to modify Gwozdz-PCT to add alkyl glycosides, let alone dodecyl maltoside, let alone *n*-dodecyl-β-D-maltoside (which is not even disclosed in Meezan)." Ex. 2073 (Brown Decl.) at ¶ 255. 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-β-D-maltoside" as a preferred penetration enhancer, where a POSA would have understood that to be a reference to "n-dodecyl-β-D-maltoside." *See, e.g.*, Ex. 1062 (Donovan Op. Decl.) at ¶¶ 90-93, 133-139.

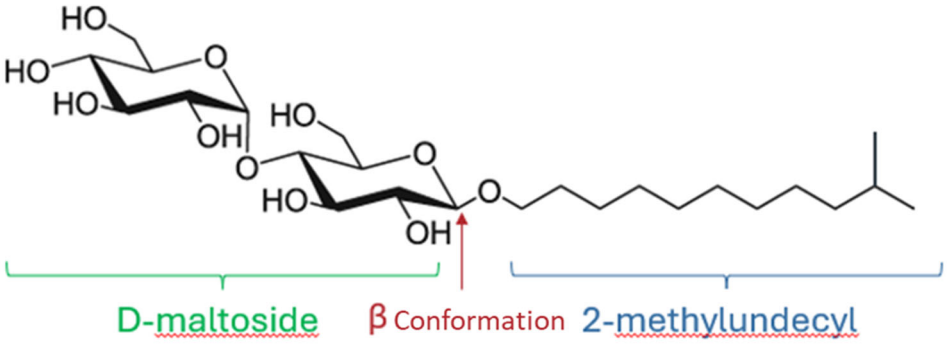
40. I note that Dr. Brown reiterates many of his opinions that the term "dodecyl" could somehow be interpreted by a POSA to refer to the 355 isomers of a 12-carbon alkane. *See, e.g.*, Ex. 2073 at ¶¶ 203-209, 276. As explained above, I disagree with Dr. Brown's opinions about the chemical nomenclature issues generally. *Supra* Section V. Specifically, as explained above, it is my opinion that the "n-" prefix is neither necessary nor used to identify or name straight-chain alkanes. *Id*. And as explained above, Dr. Brown's reference to the 355 isomers of a 12-carbon alkane is irrelevant at least because only one of those isomers could be named "dodecyl," while the 354 other isomers would have a carbon chain that is no longer than 11 carbons long (which would be named "undecyl"). *Id*. Rather, the "branched" alkanes would contain appropriate prefixes that specify (1) the longest carbon chain, (2) where the branched chains extend from the longest carbon chain, and (3) what chemical moiety is extending from each branched position. *Id*.

41. Applying the correct nomenclature rules, a POSA would understand that Meezan's express disclosure of "dodecyl-β-D-maltoside" refers to the following structure (prepared and annotated by me):



See, e.g., Ex. 1010 (Meezan) at ¶¶ [0056], [0092], [0156]-[0159].

42. In contrast, Dr. Brown's reference to branched isomers of dodecane would have entirely different names. For example, as explained above, one of the 12-carbon alkanes that Dr. Brown opines would be named "dodecyl" is in fact named "2-methylundecane," as Dr. Brown himself acknowledged during his deposition. Ex. 1077 (Brown Dep. Tr.) at 119:13-121:22. If that isomer were attached to a β-D-maltoside moiety, it would have the following structure and moieties (prepared and annotated by me):



Thus, I disagree with Dr. Brown that a POSA could somehow interpret Meezan's disclosure of "dodecyl-β-D-maltoside" to refer to a β-D-maltoside moiety having a branched 12-carbon alkyl group.

43. Similarly, as explained above, Dr. Brown opines repeatedly about beta and alpha anomers, the potential for D or L stereochemistry, as well as other generalizations about the broad genus of alkyl maltosides. *See, e.g.*, Ex. 2073 (Brown Decl.) at ¶¶ 133-139, 256-263, 277-280. But as explained above, it is my opinion that Dr. Brown's opinions on these other structural and nomenclature issues have no bearing on the issues in this IPR because Meezan specifically identified dodecyl-***β-D-maltoside***. *See, e.g.*, Ex. 1010 (Meezan) at ¶¶ [0056], [0092], [0156]-[0159]. Thus, it is my opinion that the choice of alkyl group (i.e., dodecyl), anomeric structure (i.e., beta), and stereochemistry (i.e., D) are expressly disclosed by Meezan, and would have encouraged a POSA to use "dodecyl-β-D-maltoside," which a POSA would have understood to refer to "n-dodecyl-β-D-maltoside."

44. In addition, during his deposition, Dr. Brown repeatedly stated that he did not consider standard chemical nomenclature rules, like the IUPAC rules, to form his opinions despite recognizing that those chemical nomenclature rules "will give you the full name of everything in terms of the structure so there is no confusion." *See, e.g.*, Ex. 1077 (Brown Dep. Tr.) at 119:13-121:22. At the same time, Dr. Brown testified that "in pharmaceutical development, you would need to be very specific about the exact structure of what you were using." *Id*. at 91:4-18. In my opinion, Dr. Brown's testimony and opinions on this issue are inconsistent: on the one hand, he opines that it's critical in the pharmaceutical arts to be as precise as possible when discussing chemical names and nomenclature, which he agrees would come from the IUPAC and standard

chemical nomenclature rules, but on the other hand he acknowledges that he did not consider those rules at all.

45. Indeed, Dr. Brown argues that a POSA would understand these nomenclature issues based on "the context of the patents" (i.e., the specification of the '414 patent). *Id*. at 95:6-97:11. But the specification of the '414 patent *never* uses the "n-" prefix when discussing dodecyl-beta-D-maltoside. Rather, the '414 patent uses the "dodecyl maltoside" shorthand when referring to dodecyl-beta-D-maltoside. *See, e.g.*, Ex. 1001 ('414 patent) at 31:15-20 ("Specific excipients that may be employed in a nasal composition according to the invention include alkylsaccharide is ***dodecyl maltoside***, tetradecyl maltoside, sucrose dodecanoate, sucrose monostearate, sucrose distearate, and/or combinations of two or more thereof"); 32:21-22 ("In some embodiments, the alkyl glycoside is ***dodecyl maltoside***…"); 53:32-36 ("All of the solutions and suspensions described in Examples 3 and 4 are formulated as described in Examples 3 and 4, with the addition of a suitable amount of an alkyl glycoside, as described herein, such as ***dodecyl maltoside***…"). Thus, it is not clear to me how the "context of the patents" supports his position regarding "n-dodecyl-β-D-maltoside," and, in fact, the '414 patent appears to support my position laid out in my original declaration that "dodecyl maltoside" and "dodecyl beta-D-maltoside" in Meezan were understood by a POSA to refer to n-dodecyl-β-D-maltoside. *See* Ex. 1062 (Donovan Op. Decl.) at ¶¶133-138.

46. Further, Dr. Brown opines that "Meezan teaches to use 'highly branched' alkyl glycosides rather than linear alkyl glycosides like n-dodecyl-beta-D-maltoside." *See, e.g.*, Ex. 2073 at ¶ 255; *see also, e.g.*, *id*. at ¶¶ 189, 258-259, 262, 271, 273, 276, 281-283; *see also* Ex. 1077 (Brown Dep. Tr.) at 174:8-17. 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).

47. 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*.

48. Relatedly, as noted in my opening declaration, a POSA would have understood the shortened name "dodecyl maltoside" to refer to n-dodecyl-β-D-maltoside. *See, e.g.*, Ex. 1062 at ¶¶ 133-139. The above corrected Meezan specification underscores that point. Indeed, Meezan discloses that "DDM" and "dodecyl maltoside" are shorthand for "n-dodecyl-β-D-maltoside." For example, Meezan discloses an example in which "0.5% dodecyl-β-D-maltoside" was included in an ocular formulation and test results were reported in "Table I." Ex. 1010 (Meezan) at ¶ [0156]. But in Table I, Meezan simply lists "dodecyl maltoside" despite making it clear that Table I was discussing "dodecyl-β-D-maltoside." *Id*. at ¶ [0158], Table I.

49. Finally, I was also informed that Edward Maggio submitted a declaration during the prosecution of an application related to Meezan. I understand that while Dr. Maggio was not directly addressing the Meezan reference I rely on for my opinions, he was characterizing and discussing the same specification (albeit, from a later-filed application that was identical to Meezan). Further, as explained in my opening declaration, I understand Edward Maggio is listed as an inventor on both Meezan and the '414 patent. Thus, in my opinion, Dr. Maggio's view of these chemical nomenclature issues is highly relevant.

50. In his declaration, Dr. Maggio stated:

> 5. The present invention is based on the discovery that the alkyl glycoside, dodecyl-β-D-maltoside (also referred to as n-dodecyl-β-D-maltoside), increases absorption of therapeutic agents to the cerebral spinal fluid (CSF) of the central nervous system (CNS) of a subject upon nasal administration.

Ex. 1076 at 2. In my opinion, Dr. Maggio clearly stated that the Meezan specification's reference to "dodecyl-β-D-maltoside" was a reference to "n-dodecyl-β-D-maltoside." *Id*.

("dodecyl-β-D-maltoside (***also referred to as*** n-dodecyl-β-D-maltoside") (emphasis added). Dr. Maggio's position and view supports my own, namely that a POSA would have understood that the recitation of "dodecyl-β-D-maltoside" is a reference to "n-dodecyl-β-D-maltoside."

51. Additionally, I understand Dr. Brown opines that Meezan disclosed that TDM, not DDM (i.e., dodecyl-β-D-maltoside), was the "most preferred" and best performing alkyl maltoside, and therefore a POSA would have been motivated to use TDM rather than dodecyl-β-D-maltoside. *See, e.g.*, Ex. 2073 at ¶¶ 264-271. 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.

52. In any case, as explained in my opening declaration, Meezan expressly disclosed dodecyl maltoside (i.e., dodecyl-β-D-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 dodecyl-β-D-maltoside was a preferred and effective penetration enhancer. The fact that TDM *may* have been more effective than dodecyl-β-D-maltoside does not mean that dodecyl-β-D-maltoside 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, ¶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 '414 patent would include concentrations of dodecyl-β-D-maltoside found to be effective in Meezan.

53. Thus, I reiterate my opinion, that a POSA would have been motivated by Meezan to use dodecyl-β-D-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.

C. Antimicrobial Properties of Ethanol and Benzyl Alcohol Would Not Be Materially Impacted by Nonionic Surfactants in a Nasal Spray Formulation

54. 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.

55. 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.

56. 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.

57. 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.

VIII. Conclusion and Reservation of Rights

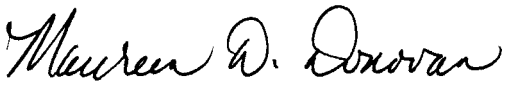
58. For the reasons set forth above and in my opening declaration, it is my opinion that all claims (i.e., claims 1-18) of the ’414 patent are unpatentable as obvious.

59. 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:



Dr. Maureen Donovan

APPENDIX A: MATERIALS CONSIDERED

Exhibit No.	Description
1001	U.S. Patent No. 11,241,414, Administration Of Benzodiazepine Compositions, filed May 27, 2021 ("'414 Patent")
1002	File History for 11,241,414, Ser. No. 17/332,800 ("'414 FH")
1003	U.S. Patent No. 11,793,786, Administration of Benzodiazepine Compositions, filed April 12, 2021 ("'786 Patent")
1004	File History for 11,793,786 Patent, Ser. No. 17/228,514 ("'786 FH")
1005	Non-Provisional Patent Application Serial No. 15/955,397, filed April 17, 2018 ("'397 Application")
1006	File History for Non-Provisional Patent Application Serial No. 15/955,397, filed April 17, 2018 ("'397 FH")
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")
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")

Exhibit No.	Description
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 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")

Exhibit No.	Description
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