IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

NEURELIS, INC., *Plaintiff*, v. PADAGIS LLC, PADAGIS US LLC, AND PADAGIS ISRAEL PHARMACEUTICALS LTD., *Defendants*.	C.A. No. 24-562 (MN) (LEAD CASE)
NEURELIS, INC., *Plaintiff*, v. PADAGIS LLC, PADAGIS US LLC, AND PADAGIS ISRAEL PHARMACEUTICALS LTD., LUPIN INC., LUPIN LTD., AND LUPIN PHARMACEUTICALS, INC., *Defendants*.	C.A. No. 25-821 (MN)
NEURELIS, INC., *Plaintiff*, v. PADAGIS LLC, PADAGIS US LLC, AND PADAGIS ISRAEL PHARMACEUTICALS LTD., *Defendants*.	C.A. No. 25-1228 (MN)
NEURELIS, INC., *Plaintiff*, v. LUPIN INC., LUPIN LTD., AND LUPIN PHARMACEUTICALS, INC. *Defendants*.	C.A. No. 25-1443 (MN)

NEURELIS, INC., *Plaintiff*, v. AMNEAL PHARMACEUTICALS LLC AND AMNEAL PHARMACEUTICALS, INC., *Defendants*.	C.A. No. 26-261 (MN)

DEFENDANTS' PRELIMINARY INVALIDITY CONTENTIONS FOR U.S. PATENT NOS. 8,895,546; 11,241,414; 11,793,786; 12,268,664; 12,324,852; 12,337,061 AND 12,521,400

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Defendants Padagis LLC, Padagis US LLC, and Padagis Israel Pharmaceuticals Ltd. (collectively, "Padagis"), defendants Lupin Inc., Lupin Pharmaceuticals, Inc., and Lupin Limited (collectively, "Lupin"),[1] and defendants Amneal Pharmaceuticals LLC and Amneal Pharmaceuticals, Inc. (together with Padagis and Lupin, "Defendants")[2] hereby provide the following Preliminary Invalidity Contentions to Neurelis, Inc. ("Plaintiff" or "Neurelis") regarding U.S. Patent No. 12,521,400 ("the '400 patent"). Additionally, defendant Amneal hereby provides the following Preliminary Invalidity Contentions to Neurelis regarding U.S. Patent Nos. 11,241,414 ("the '414 patent"), 11,793,786 ("the '786 patent"), 12,268,664 ("the '664 patent"), 12,324,852 ("the '852 patent"), and 12,337,061 ("the '061 patent"). With respect to Amneal and these Preliminary Invalidity Contentions, the '414, '786, '664, '852, '061, and '400 patents are the "Asserted Patents." With respect to Padagis and Lupin and these Preliminary Invalidity Contentions, the '400 patent is the only "Asserted Patent" since the other above-identified patents have already been addressed in earlier-served preliminary invalidity contentions.[3] Neurelis has asserted U.S. Patent No. 8,895,546 ("the '546 patent") against Padagis, but has not asserted the '546 patent against Lupin or Amneal. Accordingly, any reference herein to "Asserted Patents"

[1] With respect to the Lupin defendants, Lupin served Preliminary Invalidity Contentions on behalf of Lupin Inc., Lupin Ltd., and Lupin Pharmaceuticals, Inc., in consolidated C.A. No. 25-821 (MN) and on behalf of Lupin Inc. and Lupin Pharmaceuticals, Inc., in consolidated C.A. No. 25-1443 (MN).

[2] Due to the consolidated action and joint nature of these Preliminary Invalidity Contentions with respect to the '400 patent, and for ease of reading, the term "Defendants" is used to indicate Padagis, Lupin, and Ameal throughout this document. However, these preliminary invalidity contentions are on behalf of Amneal only with respect to the '414, '786, '664, '852, and '061 patents.

[3] In addition, Amneal adopts the preliminary invalidity contentions with respect to the '414 patent and '786 patent previously served by Padagis on December 20, 2024 as well as the preliminary invalidity contentions served by Padagis and Lupin with respect to the '414, '786, '664, '852, and '061 patents on February 6, 2026, and fully incorporates those positions as to Amneal as if set forth herein.

corresponds to the ’414, ’786, ’664, ’852, ’061, and ’400 patents for Amneal, and only the ’400 patent for Padagis and Lupin.

I. INTRODUCTION

Padagis and Lupin previously served preliminary invalidity contentions with respect to U.S. Patent Nos. U.S. 8,895,546 (“the ’546 patent”), the ’414, the ’786, the ’664, the ’852, and the ’061 patents and maintains those contentions as set forth therein. Padagis previously served preliminary invalidity contentions with respect to the ’546 patent, the ’414 patent, and the ’786 patent on December 20, 2024. Further, Padagis filed petitions for *inter partes* review (“IPR”) of the ’546, ’414, and ’786 patents on January 17, 2025. *See* IPR2025-00464, Paper 2 (Jan. 17, 2025) (’546 patent IPR); IPR2025-00465, Paper 2 (Jan. 17, 2025) (’414 patent IPR); IPR2025-00466, Paper 2 (Jan. 17, 2025) (’786 patent IPR). As part of Padagis’s IPR petitions on the ’546, ’414, and ’786 patents, Padagis stipulated “that if the Board institutes [the IPRs] then Petitioner will not pursue in a parallel district court proceeding the same grounds as in this Petition or any grounds that could have reasonably been raised in this Petition. *See Sotera Wireless, Inc. v. Masimo Corp.*, IPR2020-01019, Paper 12 at 17 (PTAB Dec. 1, 2020) (precedential).” Consistent with the *Sotera* stipulation included with Padagis’s IPR petitions on the ’546, ’414, and ’786 patents, Padagis no longer asserts in this district court litigation that the ’546, ’414, and ’786 patents are invalid for the same grounds raised, or any grounds that reasonably could have been raised, in Padagis’s IPR petitions. Accordingly, Padagis does not join any of the obviousness positions set forth by Lupin or Amneal in Section V below with respect to the ’414 and ’786 patents.

Subject to the limitations and reservations above and set forth in the preliminary invalidity contentions previously served by Padagis and Lupin, Defendants contend that the Asserted Patents are invalid for the reasons set forth in these Preliminary Invalidity Contentions. Defendants make these disclosures based on their current knowledge, recognizing that investigations are continuing

and discovery is just beginning. Moreover, facts, documents, and things now known may be imperfectly understood and, accordingly, such facts, documents and things may not be included in the following Preliminary Invalidity Contentions. Defendants reserve the right to amend these contentions and supplement this production to the full extent consistent with the Court's Rules and Orders and in view of any information discovered during litigation. Further, these contentions are provided without prejudice to the rights of Defendants to introduce at trial expert opinions relating to currently known facts and subsequently discovered facts, and subsequently-discovered evidence of currently known facts; and to produce and introduce at trial all evidence, whenever discovered, relating to the proof of currently-known and subsequently-discovered facts.

Defendants incorporate, in full, all prior art references cited in the prosecution histories or post-grant proceedings of the Asserted Patents or any patent claiming priority to any of the Asserted Patents or to which any of the Asserted Patents claim priority, the prosecution histories themselves, as well as all references and arguments made by the Examiners during prosecution.

Discovery in this case is in its early stages, claim terms of the Asserted Patents have not yet been identified for construction by the parties or construed by the Court in this case, and Defendants' investigation is ongoing. Defendants therefore reserve the right to further supplement or alter the positions taken and information disclosed in these Preliminary Invalidity Contentions including, without limitation, the prior art and grounds of invalidity set forth herein, to take into account information or defenses that may come to light as a result of these continuing efforts. Defendants further expressly reserve the right to amend or supplement these contentions in view of any evidence regarding secondary considerations, inventorship, or ownership that Neurelis may be permitted to raise.

Neurelis has not yet served its initial infringement contentions or identified which claims from the Asserted Patents are being asserted against Defendants. Accordingly, Defendants contend that all claims of the Asserted Patents are invalid for the reasons discussed below. Defendants expressly reserve the right to amend, supplement, or modify these contentions after Neurelis serves its infringement contentions and identifies which claims from the Asserted Patents it contends are infringed by Padagis, Lupin, or Amneal.

Defendants' preliminary invalidity positions in these contentions may be in the alternative and do not constitute any concession or admission for purposes of invalidity, enforceability, claim construction, and/or infringement. *See, e.g.*, *Vanmoor v. Wal-Mart Stores, Inc.*, 201 F.3d 1363, 1366 (Fed. Cir. 2000). For example, Defendants' Section 112 arguments may be in the alternative to its obviousness arguments and should not be viewed, in any way, to be concessions about the prior art or knowledge of one of ordinary skill in the art. Likewise, the suggested obviousness combinations are in the alternative to any contentions based on anticipation. The obviousness contentions set forth herein should not be construed to suggest that any reference is not anticipatory by itself.

The information set forth below is provided without waiving: (1) the right to object to the use of any statement or evidence for any purpose, in this action or any other action, on the grounds of privilege, relevance, materiality, or any other appropriate grounds; (2) the right to object to any request involving or relating to the subject matter of the statements herein; or (3) the right to revise, correct, supplement, or clarify any of the statements provided. The contentions of each dependent claim incorporate the contentions of each claim from which the dependent claim depends. This includes all prior art and non-prior art defenses, including all defenses available under 35 U.S.C. §§ 101, 102, 103, and 112.

Defendants object to the disclosure of information that is protected by the attorney-client privilege, attorney work-product immunity, the common interest privilege, the joint defense doctrine or any other applicable privilege or immunity. To the extent Defendants inadvertently disclose information that may be protected from discovery under the attorney-client privilege, the attorney work-product immunity, the common interest privilege, the joint defense doctrine or any other applicable privilege or immunity, such inadvertent disclosure does not constitute a waiver of any such privilege or immunity.

In these Preliminary Invalidity Contentions, Defendants takes no position, one way or the other, as to whether any particular claim phrase or term should be construed as bearing on the scope of any claim of the Asserted Patents by, for example, acting as a limitation or creating an exclusion. These Preliminary Invalidity Contentions are based, at least in part, on Defendants' present understanding of the plain and ordinary meaning of the claims of the Asserted Patents. Defendants take no position regarding the plain and ordinary meaning of any claim terms in these Preliminary Invalidity Contentions. Any statement herein describing or tending to describe any claim element is provided solely for the purpose of understanding the relevant prior art or other basis for invalidity.

These Preliminary Invalidity Contentions may be made in the alternative and are not necessarily intended to be consistent with each other. Furthermore, Defendants' inclusion of prior art that would render a claim anticipated or obvious based on a particular scope of the claim, is not, and should in no way be seen as, an adoption or admission as to the scope of the claim or a claim term's plain and ordinary meaning. Defendants reserve all rights to further supplement or modify the positions and information in these Preliminary Invalidity Contentions, including without limitation, the prior art and grounds of invalidity set forth herein.

It should be recognized that a person of ordinary skill in the art at the time of the purported invention ("POSA") would generally read a prior art reference as a whole and in the context of other publications, literature, and general knowledge in the field. To understand and interpret any specific statement or disclosure in a prior art reference, a POSA would rely upon other information including other publications and general scientific or engineering knowledge. Defendants therefore reserve the right to rely upon other unidentified portions of the prior art references and on other publications and expert testimony to provide context and to aid understanding and interpretation of any identified portions. Defendants also reserve the right to rely upon other portions of the prior art references, other publications, and the testimony of experts to establish that the alleged inventions were inherently disclosed in the prior art, and/or would have been obvious to a POSA, including on the basis of modifying or combining certain cited references. Defendants also reserve the right to rely upon any prior art or admissions relating to prior art in the prosecution histories of any of the Asserted Patents and any patent claiming priority to any of the Asserted Patents or to which any of the Asserted Patents claim priority. In addition, Defendants reserve the right to rely on all prior art produced by Padagis, Lupin, Neurelis, Amneal, or any other party in any other proceeding including re-examinations, oppositions, and *inter partes* review involving any of the Asserted Patents.

II. ASSERTED PATENTS AND CLAIMS

A. The '546 Patent

Based on Plaintiff's initial infringement contentions with respect to the '546 patent, Padagis understands Plaintiff initially asserted claims 1-22 of the '546 patent. However, on January 2, 2026, Neurelis statutorily disclaimed all claims of the '546 patent except claims 17 and 22.

Thus, Padagis understands that only claims 17 and 22 of the ’546 patent remain, and thus are the lone claims of the ’546 patent asserted against Padagis.[4]

The ’546 patent was filed on June 13, 2012, as Application No. 13/495,942 and issued on November 25, 2014. The ’546 patent claims priority as a continuation-in-part of Application No. 12/431,439, filed on March 27, 2009, which claims priority to Provisional Application No. 61/497,017, filed June 14,2011, and Provisional Application No. 61/570,110, filed on December 13, 2011.

Based on presently available information, and in view of the early stage of this case, Padagis states that the claims of the ’546 patent are entitled to a priority date of no earlier than the March 27, 2009 filing date of the ’439 Application. Padagis expressly reserves the right to assert that the claims of the ’546 patent are limited to an effective filing date later than March 27, 2009.

1. The Asserted Claims of the ’546 Patent

Claim 17 of the ’546 patent depends from independent claim 1, and claim 22 depends from claims 16, 15, and 1, all which are listed below (asserted claims 17 and 22 shown in bold text):

1. A pharmaceutical solution for nasal administration consisting of:

> (a) a benzodiazepine drug;(b) one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w);
> (c) ethanol and benzyl alcohol in a combined amount from about 10% to about 70% (w/w); and
> (d) an alkyl glycoside.

15. The pharmaceutical solution of claim 1, wherein the alkyl glycoside is present in pharmaceutical solution in a concentration of at least about 0.01% (w/w).

16. The pharmaceutical solution of claim 15, wherein the alkyl glycoside is present in the pharmaceutical solution in an amount of 0.01% to 1% (w/w).

[4] Neurelis has not asserted the ’546 patent against Lupin or Amneal.

17. The solution of claim 1, consisting of diazepam, vitamin E, ethanol, benzyl alcohol and dodecyl maltoside.

22. The solution of claim 16, wherein the alkyl glycoside is dodecyl maltoside.

'546 patent, claims 1, 15-17, 22.

2. The Specification of the '546 Patent

The '546 patent shares a common specification with the '664 patent. Thus, the specification of the '546 patent contains the same disclosures described below with respect to the '664 patent. *Infra* Section II.D.2.

3. The Prosecution History of the '546 Patent

The '546 Patent was subject to an abbreviated prosecution, consisting of only a restriction requirement, and a single non-final rejection. Specifically, after the issuance of a restriction requirement (Neurelis-00015462-469), the Examiner issued a non-final rejection, finding the claims obvious over U.S. Patent No. 6,193,985 to Sonne et al. ("Sonne") in view of U.S. Patent Publication No. 2006/0046962 to Meezan ("Meezan"). Neurelis-00015558-566.

In response, Neurelis amended independent claim 1 to recite the presence of "ethanol and benzyl alcohol in a combined amount from about 10% to about 70% (w/w)." Neurelis-00015575-589. Neurelis also argued that "[t]he pending claims also require both ethanol and benzyl alcohol in a combined amount of from 10% to 70% (w/w). Neither Sonne nor Meezan teaches or suggests using both ethanol and benzyl alcohol in such amounts. Thus, the combination of references fails to teach or suggest the claimed invention." *Id.* at Neurelis-00015586. The Examiner subsequently withdrew the obviousness rejection and the '546 patent was allowed to issue. Neurelis-00016609-616.

B. The ’414 Patent

The ’414 patent was filed on May 27, 2021, as Application No. 17/332,800 and issued on February 8, 2022. The ’414 patent claims priority as a continuation of Application No. 17,228,514, filed on April 12, 2021, which is a continuation of Application No. 15/995,397, filed on April 17, 2018, which is a continuation of Application No. 12/413,439, filed on March 27, 2009, which claims priority to Provisional Application No. 61/040,558, filed on March 28, 2008.

Based on presently available information, and in view of the early stage of this case, Defendants state that the claims of the ’414 patent are entitled to a priority date of no earlier than the March 27, 2009 filing date of the ’439 Application. Defendants expressly reserve the right to assert that one or more of the claims may only be entitled to an effective filing date later than March 27, 2009.

1. The Claims of the ’414 Patent

The claims of the ’414 patent read as follows (independent claims shown in bold text):

1. A pharmaceutical solution for nasal administration consisting of:

diazepam or a pharmaceutically acceptable salt thereof;

one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from 30% to 95% (w/w);

ethanol and benzyl alcohol in a combined amount from 10% to 70% (w/w); and

n-dodecyl beta-D-maltoside.

2. The pharmaceutical solution of claim 1, wherein the diazepam or pharmaceutically acceptable salt thereof is present in the pharmaceutical solution in a concentration from 1 to 20% (w/v).

3. The pharmaceutical solution of claim 1, wherein the diazepam or pharmaceutically acceptable salt thereof is present in the pharmaceutical solution in a concentration from 10 mg/mL to 250 mg/mL.

4. The pharmaceutical solution of claim 3, wherein the diazepam or pharmaceutically acceptable salt thereof is present in the pharmaceutical solution in a concentration from 20 mg/mL to 50 mg/mL.

5. The pharmaceutical solution of claim 1, wherein the one or more natural or synthetic tocopherols or tocotrienols are selected from the group consisting of: α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, α-tocotrienol, β-tocotrienol, γ-tocotrienol, δ-tocotrienol, tocophersolan, and any combinations thereof.

6. The pharmaceutical solution of claim 1, wherein the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, is in an amount from 45% to 85% (w/w).

7. The pharmaceutical solution of claim 6, wherein the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, is in an amount from 60% to 75% (w/w).

8. The pharmaceutical solution of claim 1, wherein the ethanol and benzyl alcohol is in a combined amount from 15% to 55% (w/w).

9. The pharmaceutical solution of claim 8, wherein the ethanol and benzyl alcohol is in a combined amount from 25% to 40% (w/w).

10. The pharmaceutical solution of claim 1, wherein the solution consists of diazepam, vitamin E, ethanol, benzyl alcohol, and n-dodecyl beta-D-maltoside.

11. A pharmaceutical solution for nasal administration consisting of:

diazepam or a pharmaceutically acceptable salt thereof;

one or more natural or synthetic α-tocopherols, or any combinations thereof, in an amount from 30% to 95% (w/w);

ethanol and benzyl alcohol in a combined amount from 10% to 70% (w/w); and

n-dodecyl beta-D-maltoside.

12. The pharmaceutical solution of claim 11, wherein the diazepam or pharmaceutically acceptable salt thereof is present in the pharmaceutical solution in a concentration from 1 to 20% (w/v).

13. The pharmaceutical solution of claim 11, wherein the diazepam or pharmaceutically acceptable salt thereof is present in the pharmaceutical solution in a concentration from 10 mg/mL to 250 mg/mL.

14. The pharmaceutical solution of claim 13, wherein the diazepam or pharmaceutically acceptable salt thereof is present in the pharmaceutical solution in a concentration from 20 mg/mL to 50 mg/mL.

15. The pharmaceutical solution of claim 11, wherein the one or more natural or synthetic α-tocopherols, or any combinations thereof is in an amount from 45% to 85% (w/w).

16. The pharmaceutical solution of claim 15, wherein the one or more natural or synthetic α-tocopherols, or any combinations thereof is in an amount from 60% to 75% (w/w).

17. The pharmaceutical solution of claim 11, wherein the ethanol and benzyl alcohol is in a combined amount from 15% to 55% (w/w).

18. The pharmaceutical solution of claim 17, wherein the ethanol and benzyl alcohol is in a combined amount from 25% to 40% (w/w).

'414 patent at claims 1-18.

2. The Specification of the '414 Patent

The '414 patent shares a common specification with the '664 patent. Thus, the specification of the '414 patent contains the same disclosures described below with respect to the '664 patent. *Infra* Section II.D.2.

3. The Prosecution History of the '414 Patent

The '414 patent was subject to minimal prosecution. During prosecution, Neurelis submitted a Track 1 request to expedite prosecution of the '414 patent, which was granted by the Examiner. Neurelis-00000205-206.

No substantive office actions were issued by the Examiner prior to the notice of allowance provided by the Examiner on December 13, 2021. Neurelis-00000374-382. In the reasons for allowance provided in the notice of allowance, the Examiner stated that the claimed "alkyl glycoside," and specifically n-dodecyl β-maltoside, finds support in the priority applications by virtue of its citation to the Sigma Catalog referenced in the priority application (which appears to be a reference to the '558 Provisional noted above). Neurelis-00000379-380. Based on this alleged

support in the ’558 Provisional, the Examiner stated that “[t]he instant claims receive a priority date of March 28, 2008. As such, Gwozdz (WO 2009120933) does not qualify as prior art.” *Id.* However, for a number of reasons, the Examiner’s priority date determination was incorrect, including at least because the Sigma Catalog (non-patent literature) cannot provide support for essential matter recited in the claims, and, even if the Sigma Catalog could provide support for this essential matter, the ’414 patent claims do not have adequate support in the ’558 Provisional. Consequently, the earliest possible priority date for ’414 patent claims is the filing of the ’439 Application on March 27, 2009.

C. The ’786 Patent

The ’786 patent was filed on April 12, 2021, as Application No. 17,228,514 and issued on October 24, 2023. The ’786 patent claims priority as a continuation of Application No. 15/995,397, filed on April 17, 2018, which is a continuation of Application No. 12/413,439, filed on March 27, 2009, which claims priority to Provisional Application No. 61/040,558, filed on March 28, 2008.

Based on presently available information, and in view of the early stage of this case, Defendants state that the claims of the ’786 patent are entitled to a priority date of no earlier than the March 27, 2009 filing date of the ’439 Application, which contains the first support for alkyl glycosides. Defendants expressly reserve the right to assert that one or more of the claims may only be entitled to an effective filing date later than March 27, 2009.

1. The Claims of the ’786 Patent

The claims of the ’786 patent read as follows (independent claims shown in bold text):

1. A pharmaceutical solution for nasal administration consisting of:

> **a therapeutically effective amount of diazepam or a pharmaceutically acceptable salt thereof;**
>
> **one or more natural or synthetic tocopherols or tocotrienols selected from the group consisting of α-tocopherol, β-tocopherol, γ-tocopherol,**

δ-tocopherol, α-tocotrienol, β-tocotrienol, γ-tocotrienol, δ-tocotrienol, tocophersolan, any isomers thereof, any esters thereof, and any combinations thereof, in an amount from 30% to 95% (w/w);

one or more alcohols in an amount from 10% to 70% (w/w), wherein the one or more alcohols comprises benzyl alcohol; and

n-dodecyl beta-D-maltoside.

2. The pharmaceutical solution of claim 1, wherein the therapeutically effective amount of diazepam or pharmaceutically acceptable salt thereof is present in the pharmaceutical solution in a concentration from 1 to 20% (w/v).

3. The pharmaceutical solution of claim 1, wherein the therapeutically effective amount of diazepam or pharmaceutically acceptable salt thereof is present in the pharmaceutical solution in a concentration from 10 mg/mL to 250 mg/mL.

4. The pharmaceutical solution of claim 3, wherein the therapeutically effective amount of diazepam or pharmaceutically acceptable salt thereof is present in the pharmaceutical solution in a concentration from 20 mg/mL to 50 mg/mL.

5. The pharmaceutical solution of claim 1, wherein the one or more natural or synthetic tocopherols or tocotrienols is in an amount from 45% to 85% (w/w).

6. The pharmaceutical solution of claim 5, wherein the one or more natural or synthetic tocopherols or tocotrienols is in an amount from 60% to 75% (w/w).

7. The pharmaceutical solution of claim 1, wherein the one or more alcohols is benzyl alcohol and a second alcohol selected from ethanol, propyl alcohol, butyl alcohol, pentanol, any isomers thereof, and any combinations thereof.

8. The pharmaceutical solution of claim 1, wherein the one or more alcohols are in an amount from 15% to 55% (w/w).

9. The pharmaceutical solution of claim 8, wherein the one or more alcohols are in an amount from 25% to 40% (w/w).

10. The pharmaceutical solution of claim 1, wherein the solution consists of diazepam, vitamin E, benzyl alcohol, and n-dodecyl beta-D-maltoside.

11. A pharmaceutical solution for nasal administration consisting of:

a therapeutically effective amount of diazepam or a pharmaceutically acceptable salt thereof;

one or more natural or synthetic α-tocopherols selected from the group consisting of tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, tocophersolan, any isomers thereof, any esters thereof, and any combinations thereof, in an amount from 30% to 95% (w/w);

one or more alcohols in an amount from 10% to 70% (w/w), wherein the one or more alcohols comprises benzyl alcohol; and

n-dodecyl beta-D-maltoside.

12. The pharmaceutical solution of claim 11, wherein the therapeutically effective amount of diazepam or pharmaceutically acceptable salt thereof is present in the pharmaceutical solution in a concentration from 1 to 20% (w/v).

13. The pharmaceutical solution of claim 11, wherein the therapeutically effective amount of diazepam or pharmaceutically acceptable salt thereof is present in the pharmaceutical solution in a concentration from 10 mg/mL to 250 mg/mL.

14. The pharmaceutical solution of claim 13, wherein the therapeutically effective amount of diazepam or pharmaceutically acceptable salt thereof is present in the pharmaceutical solution in a concentration from 20 mg/mL to 50 mg/mL.

15. The pharmaceutical solution of claim 11, wherein the one or more natural or synthetic tocopherols is in an amount from 45% to 85% (w/w).

16. The pharmaceutical solution of claim 15, wherein the one or more natural or synthetic tocopherols is in an amount from 60% to 75% (w/w).

17. The pharmaceutical solution of claim 11, wherein the one or more alcohols is benzyl alcohol and a second alcohol selected from ethanol, propyl alcohol, butyl alcohol, pentanol, any isomers thereof, and any combinations thereof.

18. The pharmaceutical solution of claim 11, wherein the one or more alcohols are in an amount from 15% to 55% (w/w).

19. The pharmaceutical solution of claim 18, wherein the one or more alcohols are in an amount from 25% to 40% (w/w).

20. The pharmaceutical solution of claim 1, wherein the therapeutically effective amount of diazepam or pharmaceutically acceptable salt thereof present in the pharmaceutical solution is from about 5 to about 20 mg.

21. The pharmaceutical solution of claim 11, wherein the therapeutically effective amount of diazepam or pharmaceutically acceptable salt thereof present in the pharmaceutical solution is from about 1 mg to about 20 mg.

22. The pharmaceutical solution of claim 1, wherein the n-dodecyl beta-D-maltoside is present in the pharmaceutical solution in an amount from about 0.01% (w/v) to about 1% (w/v).

23. The pharmaceutical solution of claim 11, wherein the n-dodecyl beta-D-maltoside is present in the pharmaceutical solution in an amount from about 0.01% (w/v) to about 1% (w/v).

24. The pharmaceutical solution of claim 1, wherein the n-dodecyl beta-D-maltoside is present in the pharmaceutical solution in an amount from about 0.125% (w/v) to about 0.5% (w/v).

25. The pharmaceutical solution of claim 11, wherein the n-dodecyl beta-D-maltoside is present in the pharmaceutical solution in an amount from about 0.125% (w/v) to about 0.5% (w/v).

26. The pharmaceutical solution of claim 1, wherein the α-tocopherol is Vitamin E USP.

27. The pharmaceutical solution of claim 11, wherein the α-tocopherol is Vitamin E USP.

'786 patent at claims 1-27.

2. The Specification of the '786 Patent

The '786 patent shares a common specification with the '664 patent. Thus, the specification of the '786 patent contains the same disclosures described below with respect to the '664 patent. *Infra* Section II.D.2.

3. The Prosecution History of the '786 Patent

During prosecution of the '786 patent, the Examiner issued a non-final rejection on March 16, 2023, finding pending claims 48-67 indefinite for reciting tocopherols and tocotrienols and "any isomers thereof, any esters thereof, any analogs or derivatives thereof." Neurelis-00013126-134. The Examiner also rejected claims 48-67 as obvious over Sonne (U.S. 6,193,985) in view of Meezan (U.S. Pub. No. 2006/0046962). *Id.*

In response, Neurelis amended the claims to recite "one or more natural or synthetic tocopherols or tocotrienols selected from the group consisting of αtocopherol,…" in an effort to

overcome the indefiniteness rejection. Neurelis-00013215-227. Regarding the obviousness rejection, Neurelis asserted that, among other things, the prior art failed to provide a reasonable expectation that the pharmaceutical solutions cited by the Examiner could be used for nasal administration; that the teachings of Sonne and Meezan were repetitive, and not properly combinable; and that the prior art references failed to teach all of the claim limitations. *Id*. The Examiner withdrew the rejections and subsequently issued a notice of allowance on July 24, 2023. Neurelis-00013231-237.

D. The ’664 Patent

The ’664 patent was filed on July 24, 2024 as Application No. 18/782,666 (“the ’666 Application”) and issued on April 8, 2025. The ’664 patent claims priority to several earlier-filed U.S. patent applications, including as a continuation of Application No. 12/431,439 (“the ’439 Application”), filed on March 27, 2009. The ’439 application claims priority to Provisional Application No. 61/040,558, filed March 28, 2008.

Based on presently available information, and in view of the early stage of this case, Defendants state that the claims of the ’664 patent are entitled to a priority date of no earlier than the March 27, 2009 filing date of the ’439 Application. Defendants expressly reserve the right to assert that the claims of the ’664 patent are limited to an effective filing date later than March 27, 2009.

1. The Claims of the ’664 Patent

The ’664 patent issued with 18 claims, of which only claim 1 is an independent claim (in bold text below). The claims of the ’664 patent read as follows:

1. A pharmaceutical composition for intranasal administration comprising:

> **about 1 to about 20 mg of diazepam dissolved in about 45% to about 85% (w/w) of one or more natural or synthetic tocopherols or tocotrienols selected from the group consisting of: α-tocopherol, β-**

tocopherol, γ-tocopherol, δ-tocopherol, α-tocotrienol, β-tocotrienol, γ-tocotrienol, δ-tocotrienol, tocophersolan, any esters thereof and any combinations thereof, and about 25% to about 40% (w/w) of one or more alcohols selected from the group consisting of ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, and any combinations thereof, and about 0.01% to about 1% (w/v) of dodecyl β-D-maltoside, wherein the pharmaceutical composition is a solution and contains less than 1% water, wherein the pharmaceutical composition is in a pharmaceutically-acceptable spray formulation.

2. The pharmaceutical composition of claim 1, wherein the one or more natural or synthetic tocopherols or tocotrienols is α-tocopherol.

3. The pharmaceutical composition of claim 1, wherein the therapeutically effective amount of the diazepam is present in the pharmaceutical solution at a concentration of about 10 mg/mL to about 250 mg/mL.

4. The pharmaceutical composition of claim 1, wherein the diazepam is present in the pharmaceutical solution at a concentration of about 20 mg/mL to about 50 mg/mL.

5. The pharmaceutical composition of claim 1, wherein the diazepam is about 2 mg to about 10 mg.

6. The pharmaceutical composition of claim 1, wherein the pharmaceutical solution comprises one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof in an amount from about 60% to about 75% (w/w).

7. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition further comprises at least one additional ingredient selected from the group consisting of stabilizers, coloring agents, pH adjusters, buffering agents, preservatives, wetting agents, flavoring agents and combinations thereof.

8. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition is about 25 μL to about 250 μL.

9. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition is about 50 μL to about 150 μL.

10. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition is about 100 μL.

11. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition contains less than 0.5% water.

12. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition contains less than 0.25% water.

13. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition contains less than 0.1% water.

14. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition contains no water.

15. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition contains no more than 0.01% of a diazepam impurity.

16. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition contains no more than 0.01% of a diazepam impurity at 25° C. and 60% relative humidity, 30° C. and 65% relative humidity and 40° C. and 75% relative humidity.

17. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition maintains a similar average spray content at 25° C. and 60% relative humidity, 30° C. and 65% relative humidity and 40° C. and 75% relative humidity each measured at one month, three months and six months.

18. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition maintains a similar average spray content uniformity at 25° C. and 60% relative humidity and 40° C. and 75% relative humidity.

'664 patent, claims 1-18.

2. The Specification of the '664 Patent

The '664 patent is related to and shares a common specification with the '546, '414, and '786 patents. Like the '546, '414, and '786 patents, the '664 patent "relates to pharmaceutical compositions comprising one or more benzodiazepine drugs for nasal administration, methods for producing and for using such compositions." '664 patent at Abstract.

The background section of the specification explains that "the benzodiazepine family consists of drugs such as diazepam, lorazepam, and medazepam." *Id*. at 1:25-29. According to the specification, "[c]urrent formulations of benzodiazepine drugs can be administered orally, rectally, or parenterally. The ability to utilize these and other types of formulations has been significantly limited due, in many cases, to solubility challenges." *Id*. at 1:52-56.

The summary section of the specification goes on to describe "pharmaceutical composition[s] for nasal administration" containing a benzodiazepine drug and various types and amounts of excipients. *Id*. at 2:16-5:46. For example, the specification states that the compositions can contain "a benzodiazepine drug; one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); and one or more alcohols or glycols, or any combinations thereof, in an amount from about 5% to about 70% (w/w), preferably about 10% to about 70% (w/w) in a pharmaceutically-acceptable formulation for administration to one or more nasal mucosal membranes of the patient." *Id*. at 2:18-27. According to the summary section, the compositions may contain a number of different benzodiazepine drugs (*id*. at 2:40-49), "natural or synthetic tocopherols or tocotrienols" (*id*. at 2:57-3:3), and alcohols or glycols (*id*. at 3:4-16). The compositions may also contain "at least one additional ingredient selected from the group consisting of: active pharmaceutical ingredients; enhancers; excipients; and agents used to adjust the pH, buffer the composition, prevent degradation, and improve appearance, odor, or taste." *Id*. at 3:47-51.

The detailed description section of the specification also describes "pharmaceutical compositions of one or more benzodiazepine drugs" containing various types and amounts of excipients. *Id*. at 5:56-14:33. The specification states that the intranasal compositions "can provide for improved bioavailability of benzodiazepine drugs, delivery of higher concentrations of benzodiazepine drugs via the nasal route, faster attainment of therapeutic levels of benzodiazepine in the blood plasma, avoidance of the liver portal vein and concomitant avoidance of first pass effects and/or faster presentation of benzodiazepine drug to the brain." *Id*. at 15:58-16:3. "By use of the present carrier system, which in some embodiments, provides an improved ability to dissolve benzodiazepine drugs, the present invention allows benzodiazepine drugs to be

administered to one or more mucosal membranes, including to nasal mucosal membranes." *Id*. at 16:7-12. "Nasal administration of the composition can result in faster presentation of the one or more benzodiazepine drugs to the brain due to the close proximity of the membranes and the brain." *Id*. at 16:21-24.

The specification explains that:

> Diazepam is a benzodiazepine drug having sedative, tranquilizing and muscle relaxing properties. It is classified as an anxiolytic and skeletal muscle relaxant. It possesses anxiolytic, anticonvulsant, sedative, skeletal muscle relaxant and amnesic properties. The dosage of diazepam may vary by indication, however it is expected that a therapeutic dose will be in the range of about 1 to about 20, preferably about 2 to about 10 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Diazepam may be manufactured using the process disclosed in one of U.S. Pat. Nos. 3,371,085; 3,109,843; 3,136,815 or 3,102,116, each of which is incorporated herein by reference in its entirety.

Id. at 18:22-34.

The detailed description section also discloses that a "Carrier System" containing "Vitamin E and one or more lower alkyl alcohols or one or more lower alkyl glycols" may be used. *Id*. at 29:57; 30:35-39. "Vitamin E can provide an effective carrier for benzodiazepine drugs. In some embodiments, benzodiazepines are soluble, or partially soluble, in Vitamin E." *Id*. at 30:22-25. "Furthermore, use of Vitamin E can have the added benefit of either avoiding irritation of sensitive mucosal membranes and/or soothing irritated mucosal membranes." *Id*. at 30:27-29. Because Vitamin E is "hydrophobic" and was known to form emulsions, the carrier system described by the specification may contain "one or more lower alkyl alcohols or one or more lower alkyl glycols." *Id*. at 30:35-39.

The detailed description separately discloses that the compositions may include additional excipients, such as a "penetration enhancer." *Id*. at 30:48-52. According to the specification, "[t]he term 'penetration enhancer', means any material which acts to increase absorption across the

mucosa and/or increases bioavailability." *Id*. at 31:35-37. The penetration enhancer may be an "alkyl glycoside." *Id*. at 30:48-52. "Alkyl glycosides that are particularly considered useful in embodiments of the invention include those marketed under the name Intravail®." *Id*. at 31:13-15.

The specification of the '664 patent also discloses various examples. *Id*. at 42:1-54:6. Examples 1-3 relate to "solutions" prepared using certain amounts of diazepam, α-tocopherol or Vitamin E, and ethanol. *Id*. at 42:1-43:30. Example 4 relates to diazepam "suspensions" containing diazepam and various excipients. *Id*. at 43:33-44:26. Example 5 discloses stability test results on the solutions and suspensions described in Examples 3 and 4. *Id*. at 44:31-52:30.

Examples 6-10 are prophetic examples without any corresponding working examples in the specification. *Id*. at 52:31-53:61. Example 6 states that "the solutions and suspensions described in Examples 3 and 4" may be formulated "with the addition of a suitable amount of an alkyl glycoside, as described herein, such as dodecyl maltoside, tetradecyl maltoside, sucrose dodecanoate, sucrose monostearate, sucrose distearate, and/or combinations of two or more thereof, or marketed as Intravail® by Aegis Therapeutics, San Diego, CA." *Id*. at 52:33-40. Finally, examples 7-10 relate to prophetic studies that could be performed on "[t]he solutions and suspensions of Examples 3, 4 and 6" to investigate pharmacokinetic, blood brain barrier-permeability, efficacy, and other related properties. *Id*. at 52:44-53:61.

3. The Prosecution History of the '664 Patent

The '664 patent was filed as the '666 Application on July 24, 2024. The '666 Application was filed with 18 claims, including one independent claim which read as follows:

> 1. A pharmaceutical composition for intranasal administration comprising:
>
> about 1 to about 20 mg of diazepam dissolved in about 45% to about 85% (w/w) of one or more natural or synthetic tocopherols or tocotrienols selected from the group consisting of: atocopherol, ß-tocopherol, y-tocopherol, 8-tocopherol, a-tocotrienol, ß- tocotrienol, y- tocotrienol, 8- tocotrienol, tocophersolan, any isomers thereof, any esters thereof and any combinations thereof, and about 25% to about 40%

> (w/w) of one or more alcohols selected from the group consisting of ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, isomers thereof and any combinations thereof, and about 0.01% to about 1% (w/v) of dodecyl ß-D-maltoside, wherein the pharmaceutical composition is a solution and contains less than 1% water.

Neurelis-02030651. Dependent claims 2-18 all depended from independent claim 1 and are identical to the dependent claims recited in the '664 patent. *Id*.; *see also supra* Section II.D.1.

On October 31, 2024, the examiner issued a non-final rejection. The examiner rejected the claims as obvious over (1) PCT Patent App. No. WO2009/121039 (Cartt); (2) U.S. Pat. No. 6,193,985 (Sonne) in view of U.S. Pat. App. Pub. No. 2006/0046962 (Meezan); and (3) Sonne in view of Meezan and the Pharmacopeial Forum (Vol. 30, No. 1, Jan.-Feb. 2004, 96-97). Neurelis-02030793-814. The examiner also rejected all claims for obviousness-type double patenting over various issued patents and related, pending patent applications. *Id*.

Following a December 3, 2024 interview with the examiner, Neurelis responded to the rejections. Neurelis-02031041-1063. Neurelis first argued that "the Office has erred in asserting a 2011 effective filing date for this application" and that "[t]he effective filing date of this application is March 28, 2008 (provisional filing date) or March 27, 2009 (non-provisional filing date)." *Id*. at Neurelis-02031045-046. Thus, with respect to the examiner's obviousness rejection based on Cartt, Neurelis argued that "Cartt is not available as prior art" because "[t]he effective filing date of the instant application is the same as the filing date of Cartt (i.e., March 27, 2009)." *Id*.

Neurelis also disagreed with the examiner's remaining obviousness rejections. Specifically, the examiner argued that Sonne taught "the use of a tocopherol or a derivative thereof as a solvent and/or emulsifier for substantially insoluble and sparingly soluble biologically active agents," such as diazepam, along with a co-solvent like ethanol and glycols. Neurelis-02030793-814. The examiner acknowledged that "Sonne does not teach a surfactant or a surfactant that is an

alkyl glycoside," but argued that Meezan taught the use of alkyl glycosides for intranasal formulations. *Id*. Finally, the examiner argued that "[t]he Pharmacopeial Forum teaches a diazepam composition may not contain more than 0.01% of the diazepam related impurity identified as compound A." *Id*.

In response, Neurelis argued that the examiner failed to show that the following claim elements were disclosed by Sonne, Meezan, and the Pharmacopeial Forum: (1) "pharmaceutical composition is a solution"; (2) "about 25% to about 40% (w/w) of one or more alcohols"; and (3) "contains less than 1% water." Neurelis-02031041-1063. Neurelis also argued that Sonne's disclosure of emulsions, "admonish[ment]" of alcohols, and use of aqueous or water-based ingredients teaches away from the claimed intranasal solutions. *Id*. at Neurelis-02031049. And Neurelis argued that, "[w]hile Meezan does teach the use of dodecyl β-D-maltoside ('DDM') as a stabilizer amongst others, as noted by the Office, Meezan provides no guidance for specifically using DDM with a benzodiazepine, let alone diazepam." *Id*. at Neurelis-02031050.

Further, Neurelis argued that "[e]xperimentation revealed that the claimed combination as a solution is surprisingly stable and meets impurity specifications." *Id*. at Neurelis-02031055-57. Specifically:

> [I]t was surprising to discover that the claimed solution was capable of achieving stability while meeting the viscosity and impurity requirements for an intranasal spray. Specifically, in Example 5 of the present application, Applicant demonstrated that solutions of diazepam are both chemically and physically stable and meet all impurity specifications under both standard and accelerated stability conditions, whereas suspensions of diazepam were not.

Id. Neurelis also argued that:

> Moreover, the claimed amount of DDM was sufficient to enhance absorption of the benzodiazepine drug while not significantly irritating the nasal mucosa. As noted in Example 6, 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." While the raw data is not shown in Example 6, the

> suitable amount needed is shown in paragraph [0136], which is a range of about 0.01% (w/v) to about 1% (w/v). See paragraph [0136] of the originally filed specification. This amount was sufficient "to enhance absorption of the benzodiazepine drug, while at the same time not significantly irritating the nasal mucosa." *Id.* Thus, the DDM amounts are critical since DDM amounts outside this range do not achieve this balance of absorption without irritation.

Id.

Finally, Neurelis amended independent claim 1 "to further recite that 'the pharmaceutical composition is in a pharmaceutically-acceptable spray formulation'" and to remove the phrase "the isomers thereof" from the claim. *See, e.g.*, Neurelis-02031042.

On February 7, 2025, the examiner issued a notice of allowance and withdrew the obviousness and double patenting rejections (which were addressed via a terminal disclaimer and other non-substantive actions). Neurelis-02031506-513. The examiner stated that "Applicant's arguments regarding priority … are persuasive" and withdrew the obviousness rejection related to Cartt. *Id*. With respect to the remaining obviousness rejections, the examiner stated that they were withdrawn "in view of the amendment to claim 1" and because of "applicant's argument (*see* page 8 of the Remarks dated 01/09/2025) that the prior art of Sonne teaches away from intranasal spray solutions." *Id*. The '664 patent subsequently issued on April 8, 2025.[i5]

E. The '852 Patent

The '852 patent was filed on June 2, 2021 as Application No. 17/336,389 ("the '389 Application") and issued on June 10, 2025. The '852 patent claims priority to several earlier-filed U.S. patent applications, including as a continuation of Application No. 15/470,498, filed on

[5] Neurelis subsequently filed a request for a certificate of correction on December 15, 2025, which requests to add the following paragraph to the specification: "The subject matter disclosed was developed and the claimed invention was made by or on behalf of the following parties to a joint research agreement: Particle Sciences, Inc. and Questcor Pharmaceuticals, Inc. (as predecessor-in-interest to Hale BioPharma Ventures, LLC)." Request for Cert. of Correction dated Dec. 15, 2025. The USPTO's response to Neurelis's request was not publicly available as of the date these contentions were served.

March 27, 2017, which is a continuation of Application No. 14/527,613, filed on October 29, 2014, which is a continuation of Application No. 13/495,942 (the "'942 Application"), filed on June 13, 2012. The '942 Application claims priority to Provisional Application No. 61/570,110, filed on December 13, 2011 and Provisional Application No. 61/497,017, filed on June 14, 2011.

Based on presently available information, and in view of the early stage of this case, Defendants state that the claims of the '852 patent are entitled to a priority date of no earlier than the June 13, 2012 filing date of the '942 Application. Defendants expressly reserve the right to assert that the claims of the '852 patent are limited to an effective filing date later than June 13, 2012. *Infra* Section VI.K.

1. The Claims of the '852 Patent

The '852 patent issued with 31 claims, which read as follows (independent claims shown in bold text):

> **1. A method of treating bouts of intermittent and stereotypic episodes of increased seizure activity in an epilepsy patient that is distinguishable from other seizures suffered by the patient comprising:**
>
> > **administering a single spray of 100 µL to one nasal mucosal membrane of the patient of a pharmaceutical solution consisting of:**
> >
> > **56.47 mg of vitamin E USP +/−5%;**
> > **10 mg of diazepam;**
> > **0.25 mg of dodecyl maltoside;**
> > **10.50 mg of benzyl alcohol +/−5%, and a sufficient quantity of ethanol;**
>
> **wherein administering the single spray of the pharmaceutical solution to the patient achieves 92.5% to 107.5% of the bioavailability of an equivalent dose of diazepam administered intravenously and is safe and effective in treating the bouts of intermittent and stereotypic episodes of increased seizure activity in the patient; and**
>
> **wherein administering the single spray of the pharmaceutical solution to the one nasal mucosal membrane of the patient results in a treatment selected from the group consisting of a reduction in the severity of the seizure, a reduction in the probability that the patient will experience a repeat seizure, an increase in the interval between a current seizure and a next seizure in the**

patient, a reduction in the frequency of seizure in the patient and combinations thereof.

2. The method of claim 1, wherein the treatment achieves 96% of the bioavailability of an equivalent dose of diazepam administered intravenously.

3. The method of claim 1, where the treatment achieves a Tmax of about 1.5 hours.

4. The method of claim 1, wherein the pharmaceutical solution is substantially free of water.

5. The method of claim 1, wherein the single spray of 100 µL is administered to one nasal mucosal membrane of the patient as a single metered spray.

6. A method of treating bouts of intermittent and stereotypic episodes of increased seizure activity in an epilepsy patient that is distinguishable from other seizures suffered by the patient comprising:

> **administering a single spray of 100 µL of a stable pharmaceutical solution to one nasal mucosal membrane of the patient and administering a second single spray of 100 µL of the pharmaceutical solution to a second nasal mucosal membrane of the patient, the 100 µL of the pharmaceutical solution consisting of:**
>
> **56.47 mg of vitamin E USP +/−5%;**
> **7.5 mg of diazepam;**
> **0.25 mg of dodecyl maltoside;**
> **10.50 mg of benzyl alcohol +/−5%, and a sufficient quantity of ethanol;**

wherein administering the single spray and the second single spray of the pharmaceutical solution to the patient achieves 92.5% to 107.5% of the bioavailability of an equivalent dose of diazepam administered intravenously and is safe and effective in treating the bouts of intermittent and stereotypic episodes of increased seizure activity in the patient; and

wherein administering the single spray and the second single spray of the pharmaceutical solution to the patient results in a treatment selected from the group consisting of a reduction in the severity of the seizure, a reduction in the probability that the patient will experience a repeat seizure, an increase in the interval between a current seizure and a next seizure in the patient, a reduction in the frequency of seizure in the patient and combinations thereof.

7. The method of claim 6, wherein the treatment achieves 96% of the bioavailability of an equivalent dose of diazepam administered intravenously.

8. The method of claim 6, where the treatment achieves a Tmax of about 1.5 hours.

9. The method of claim 6, wherein the pharmaceutical solution is substantially free of water.

10. A method of treating bouts of intermittent and stereotypic episodes of increased seizure activity in an epilepsy patient that is distinguishable from other seizures suffered by the patient comprising:

> **administering as a single spray of 100 µL to one nasal mucosal membrane of the patient of a pharmaceutical solution consisting of:**
>
> **56.47 mg of vitamin E USP +/−5%;**
> **5 mg of diazepam;**
> **0.25 mg of dodecyl maltoside;**
> **10.50 mg of benzyl alcohol +/−5%, and a sufficient quantity of ethanol;**

wherein administering the single spray of the pharmaceutical solution to the patient achieves 92.5% to 107.5% of the bioavailability of an equivalent dose of diazepam administered intravenously and is safe and effective in treating the bouts of intermittent and stereotypic episodes of increased seizure activity in the patient; and

wherein administering the single spray of the pharmaceutical solution to the patient achieves results in a treatment selected from the group consisting of a reduction in the severity of the seizure, a reduction in the probability that the patient will experience a repeat seizure, an increase in the interval between a current seizure and a next seizure in the patient, a reduction in the frequency of seizure in the patient and combinations thereof.

11. The method of claim 10, wherein the treatment achieves 96% of the bioavailability of an equivalent dose of diazepam administered intravenously.

12. The method of claim 10, where the treatment achieves a Tmax of about 1.5 hours.

13. The method of claim 10, wherein the pharmaceutical solution is substantially free of water.

14. A method of treating bouts of intermittent and stereotypic episodes of increased seizure activity in an epilepsy patient that is distinguishable from other seizures suffered by the patient comprising:

> **administering a single spray of 100 µL of a stable pharmaceutical solution to one nasal mucosal membrane of the patient and administering a second single spray of 100 µL of the pharmaceutical**

solution to a second nasal mucosal membrane of the patient, the 100 μL of the pharmaceutical solution consisting of:

56.47 mg of vitamin E USP +/−5%;
10 mg of diazepam;
0.25 mg of dodecyl maltoside;
10.50 mg of benzyl alcohol +/−5%, and a sufficient quantity of ethanol;

wherein administering the single spray and the second single spray of the pharmaceutical solution to the patient achieves 92.5% to 107.5% of the bioavailability of an equivalent dose of diazepam administered intravenously and is safe and effective in treating the bouts of intermittent and stereotypic episodes of increased seizure activity in the patient;

wherein administering the single spray and the second single spray of the pharmaceutical solution to the patient results in a treatment selected from the group consisting of a reduction in the severity of the seizure, a reduction in the probability that the patient will experience a repeat seizure, an increase in the interval between a current seizure and a next seizure in the patient, a reduction in the frequency of seizure in the patient and combinations thereof.

15. The method of claim 14, wherein the treatment achieves 96% of the bioavailability of an equivalent dose of diazepam administered intravenously.

16. The method of claim 14, where the treatment achieves a Tmax of about 1.5 hours.

17. The method of claim 14, wherein the pharmaceutical solution is substantially free of water.

18. The method of claim 1, wherein administering the single spray of the pharmaceutical solution to the patient achieves 96% to 97% of the bioavailability of an equivalent dose of diazepam administered intravenously.

19. The method of claim 14, wherein administering the single spray and the second single spray of the pharmaceutical solution to the patient achieves 96% to 97% of the bioavailability of an equivalent dose of diazepam administered intravenously.

20. The method of claim 1, wherein administering the single spray of the pharmaceutical solution to the one nasal mucosal membrane of the patient results in treatment in less than about 5 minutes and treatment over about 24 hours.

21. The method of claim 6, wherein administering the single spray and the second single spray of the pharmaceutical solution to the patient results in treatment in less than about 5 minutes and treatment over about 24 hours.

22. The method of claim 10, wherein administering the single spray of the pharmaceutical solution to the patient results in treatment in less than about 5 minutes and treatment over about 24 hours.

23. The method of claim 14, wherein administering the single spray and the second single spray of the pharmaceutical solution to the patient results in treatment in less than about 5 minutes and treatment over about 24 hours.

24. The method of claim 1, wherein administering the single spray of the pharmaceutical solution to the one nasal mucosal membrane of the patient exhibits a half-life ($t_{1/2}$) of about 49.2 hours.

25. The method of claim 6, wherein administering the single spray and the second single spray of the pharmaceutical solution to the patient exhibits a half-life ($t_{1/2)}$ of about 49.2 hours.

26. The method of claim 10, wherein administering the single spray of the pharmaceutical solution to the patient exhibits a half-life ($t_{1/2}$) of about 49.2 hours.

27. The method of claim 14, wherein administering the single spray and the second single spray of the pharmaceutical solution to the patient exhibits a half-life ($t_{1/2}$) of about 49.2 hours.

28. The method of claim 1, wherein dodecyl maltoside is n-dodecyl-β-D-maltoside.

29. The method of claim 6, wherein dodecyl maltoside is n-dodecyl-β-D-maltoside.

30. The method of claim 10, wherein dodecyl maltoside is n-dodecyl-β-D-maltoside.

31. The method of claim 14, wherein dodecyl maltoside is n-dodecyl-β-D-maltoside.

'852 patent, claims 1-31.

2. The Specification of the '852 Patent

Despite having a later effective filing date and specification than the '664 patent, the '852 patent's specification shares many similarities with the '664 patent's specification. Like the '664 patent, the '852 patent "relates to pharmaceutical compositions comprising one or more benzodiazepine drugs for nasal administration, methods for producing and for using such compositions." '852 patent at Abstract.

Further, like the ’664 patent, the background section of the ’852 patent explains that “the benzodiazepine family consists of drugs such as diazepam, lorazepam, and medazepam,” *id*. at 1:26-30, and that “[c]urrent formulations of benzodiazepine drugs can be administered orally, rectally, or parenterally. The ability to utilize these and other types of formulations has been significantly limited due, in many cases, to solubility challenges,” *id*. at 1:50-54.

The Summary section of the ’852 patent discloses that “there are provided (non-aqueous) pharmaceutical solutions for nasal administration consisting of: (a) a benzodiazepine drug; (b) one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); (c) one or more alcohols or glycols, or any combinations thereof, in an amount from about 10% to about 70% (w/w); and (d) an alkyl glycoside, in a pharmaceutically-acceptable solution for administration to one or more nasal mucosal membranes of a patient.” *Id*. at 2:21-30. According to the summary section, the compositions may contain a number of different benzodiazepine drugs (*id*. at 2:36-43), “natural or synthetic tocopherols or tocotrienols” (*id*. at 2:48-54), and alcohols or glycols (*id*. at 2:54-61).

The Summary section of the ’852 patent also describes “a method of treating a patient with a disorder which may be treatable with a benzodiazepine drug, comprising: administering to one or more nasal mucosal membranes of a patient” the benzodiazepine intranasal solutions. *Id*. at 3:23-38. As part of the method of treating a patient, “the benzodiazepine is administered in a therapeutically effective amount from about 1 mg to about 20 mg” and “in a dosage volume from about 10 μL to about 200 μL.” *Id*. at 4:25-29.

The Detailed Description section of the specification likewise describes “pharmaceutical compositions of one or more benzodiazepine drugs and methods of using such pharmaceutical compositions.” *Id*. at 9:11-13. The specification reiterates that the compositions may contain a

benzodiazepine drug, natural or synthetic tocopherols or tocotrienols, alcohols or glycols, an alkyl glycoside, and other excipients. *Id*. at 9:15-11:43. And the specification discloses that "the composition comprises a benzodiazepine drug that is fully dissolved in a solvent comprising a natural or synthetic tocopherol or tocotrienol and an alcohol or glycol, wherein the solution is at least substantially free of water. (In some embodiments, 'substantially free of water' indicates that the solution contains less than about 1%, less than about 0.5%, less than about 0.25% or less than about 0.1% water.)." *Id*. at 11:47-54.

The Detailed Description section also states that:

> It should be recognized by those of skill in the art that additional benzodiazepine compounds that have heretofore been considered to have marginal or little therapeutic benefit, either because of low bioavailability, poor pharmacokinetic properties or poor pharmacodynamic properties, may find use through the present invention, which can provide for improved bioavailability of benzodiazepine drugs, delivery of higher concentrations of benzodiazepine drugs via the nasal route, faster attainment of therapeutic levels of benzodiazepine in the blood plasma, avoidance of the liver portal vein and concomitant avoidance of first pass effects and/or faster presentation of benzodiazepine drug to the brain.

Id. at 19:3-18. The specification also states that:

> Nasal administration of the composition can result in faster presentation of the one or more benzodiazepine drugs to the brain due to the close proximity of the membranes and the brain. A seizing patient, for example, suffers from rigid muscles and uncontrollable movement. This can make oral and/or intravenous administration difficult or inconvenient. However, the nasal passageways remain open and easily accessible, and therefore is a useful route of administration for of the present invention.

Id. at 19:41-51.

Further, like the '664 patent, the '852 patent's specification explains that:

> Diazepam is a benzodiazepine drug having sedative, tranquilizing and muscle relaxing properties. It is classified as an anxiolytic and skeletal muscle relaxant. It possesses anxiolytic, anticonvulsant, sedative, skeletal muscle relaxant and amnesic properties. The dosage of diazepam may vary by indication, however it is expected that a therapeutic dose will be in the range of about 1 to about 20, preferably about 2 to about 10 mg per dose, from 1 to 8, preferably from 2 to 8, and

> in some preferred embodiments about 4 to about 6 times per day. Diazepam may be manufactured using the process disclosed in one of U.S. Pat. Nos. 3,371,085; 3,109,843; 3,136,815 or 3,102,116, each of which is incorporated herein by reference in its entirety.

Id. at 21:50-62. The ’852 patent also states that:

> [D]iazepam is used alone or in combination with another anticonvulsant drug to treat seizure, protect against seizure, reduce or ameliorate the intensity of seizure, reduce or ameliorate the frequency of seizure, and/or prevent occurrence or re-occurrence of seizure. Diazepam may be administered by the patient or other person (such as a healthcare professional) while the patient is in a non-seizing state to protect against seizure. Even where protection against seizure is not absolute, administration of diazepam may reduce or ameliorate the intensity of seizure and/or reduce or ameliorate the frequency of seizure. In some embodiments, administration of diazepam may prevent occurrence of seizure. In some embodiments, especially where the patient is prone to experiencing serial seizures or status epilepticus, administration of diazepam may aid in interrupting the seizure cycle and may thus prevent the re-occurrence of seizure. In addition to the benzodiazepines (such as diazepam), other anti-convulsant drugs may be combined with diazepam to provide a synergistic anticonvulsant effect.

Id. at 1-21.

Further, the specification of the ’852 patent contains the same examples disclosed in the specification of the ’664 patent (*supra* Section II.D.2; ’852 patent at 46:60-60:50) as well as additional examples (’852 patent at 60:51-63:60). In Example 11, “[a] pharmaceutical composition comprising diazepam was prepared as a composition formulated as a solution to be delivered via a nasal delivery device.” *Id*. at 60:53-55. A “solution” described in Example 11 contained the following ingredients:

TABLE 11-1

Ingredient	Concentration (% (w/v))
Diazepam	10.00% (w/v)
α-tocopherol*	56.47% (w/v)
Ethanol (dehydrated)	q.s. ((~18.07) % (w/v))
Intravail A3**	0.25% (w/v)
Benzyl alcohol	10.50% (w/v)

*Vitamin E,
**Dodecyl maltoside

Id. at 60:57-61:8. Example 11 also disclosed a "suspension" formulation, which contained the following ingredients:

Component	Function	Concentration (mg/mL)
Diazepam	Active	100.0
Methyl Paraben	Preservative	2.0
Propyl Paraben	Preservative	0.5
Intravail A3	Absorption aid	2.5
Vitamin E TPGS	Dispersant	10.0
Propylene Glycol	Dispersant	100.0
Povidone	Suspending agent	5.0
Water	Carrier	q.s. to 1.0 mL

Id. at 61:52-65.

Example 11 also reported stability and clinical test results for the solution and suspension formulations. *Id*. at 60:51-63:60. With respect to the clinical testing, the specification states that:

> A three-period, three-treatment, six-sequence, randomized cross-over study was conducted in healthy volunteers. For each dose, each volunteer was domiciled for at least 12 hours prior to each dose and until after a 24 hour pharmacokinetic sample was collected. Single doses of 100 μL of the pharmaceutical compositions described in Tables 11-1 and 11-2 were administered to each volunteer as one spray to the left nostril of 100 μL per spray. Pharmacokinetic samples were collected at 22 time points over 10 days. (PK time points: 2.5, 5, 10, 15, 20, 30 and 45 minutes, 1, 1.5, 2, 4, 12, 24, 36, 48, 72, 96, 144, 192 and 240 hours after each dose.) No serious adverse events were noted. PK data were compared with those obtained with 5 mg of diazepam administered intravenously. The PK data are summarized in Table 11-3 and FIGS. 1-3.

> The solution of Table 11-1 and the suspension of Table 11-2 were found to be well-tolerated with only mild adverse events reported. The solution of Table 11-1 was further found to have similar bioavailability to intravenous administration of diazepam (96% to 97% of i.v.) The intranasal formulation of Table 11-1 exhibited a Tmax of 1.5 hours, a Cmax of approximately 272 ng/mL. These results are comparable to those reported in the literature for commercially available diazepam gel (Diastat®).

Id. at 62:39-62.

Table 11-3 reports the following "summary of pharmacokinetic data obtained for the solution and a suspension form of diazepam":

TABLE 11-3

Summary of Pharmacokinetic Parameters for Intranasal (10 mg) and IV (5 mg) Diazepam

	Diazepam Nasal Spray (10 mg/100 µL)				Diazepam Injection	
	NRL-1.A Suspension		NRL-1B Solution		5 mg/mL IV	
Parameter [a]	n	Mean (SD) [b]	n	Mean (SD) [b]	n	Mean (SD) [b]
C_{max} (ng/mL)	24	221 (78.6)	24	272 (100)	24	555 (316)
T_{max} (h) [b]	24	1.00 (0.6, 2.0)	24	1.50 (0.8, 4.0)	24	0.03 (0.03, 0.50)
AUC_{0-t} (h × ng/mL)	24	5229 (1463)	24	7340 (1882)	24	3832 (1150)
$AUC_{0-\infty}$ (h × ng/mL)	20	5381 (1409)	20	7338 (2072)	24	4104 (1318)
λz (h^{-1})	20	0.0142 (0.0053)	20	0.0155 (0.0046)	24	0.0142 (0.0055)
t½ (h)	20	56.2 (23.0)	20	49.2 (16.9)	24	56.2 (21.0)

[a] Mean values are presented as arithmetic means.
[b] Median (min, max) reported for T_{max}

Id. at 63:30-50.

3. The Prosecution History of the '852 Patent

The '852 patent was filed on June 2, 2021 as the '389 Application with 65 claims covering pharmaceutical formulations and methods of treating patients. Neurelis-02031682-688. On April 15, 2022, before the examiner issued any rejections, Neurelis cancelled all of the original claims and filed new claims directed to methods "of treating a patient with epilepsy" by administering diazepam formulations to the patient. Neurelis-02042529-531.

On July 20, 2023, the examiner rejected the claims as indefinite, obvious, and for obviousness-type double patenting. Neurelis-02049647-657. The examiner's indefiniteness

rejection was based on the claims' recitation of "vitamin E" as an ingredient in the claimed formulation. *Id*. According to the examiner, because the specification defined vitamin E to refer to tocopherol or tocotrienols with "one or more atoms or functional groups" being replaced, "[w]ithout specifying how many atoms or functional groups can be replaced, the instant claims permit the inclusion of molecules which are not structurally related to tocopherol or tocotrienols." *Id*. The examiner stated that "[a]s such, the metes and bounds of the instant claims are unclear." *Id*.

Further, the examiner's obviousness rejection was based on Cartt (i.e., U.S. Patent App. Pub. No. 2009/0258865). *Id*. The examiner argued that Cartt taught the claimed diazepam intranasal formulations as well as methods of treating patients for epilepsy. *Id*.

On October 25, 2023, Neurelis responded to the examiner's rejections. Neurelis-02049980-50015. Neurelis canceled certain pending claims, amended other pending claims, and submitted new claims directed to methods of treating patients for epilepsy. *Id*. Pursuant to an examiner interview, Neurelis agreed to limit the claims "to recite that the vitamin E is selected from α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, α-tocotrienol, β-tocotrienol, γ-tocotrienol, δ-tocotrienol, isomers thereof, esters thereof and combinations thereof to overcome" the indefiniteness rejection. *Id*. And Neurelis amended the claims to recite "[a] method of treating bouts of intermittent and stereotypic episodes of increased seizure activity in an epilepsy patient that is distinguishable from other seizures suffered by the patient" instead of a method of treating "a patient with epilepsy." *Id*.

Further, Neurelis presented a number of arguments in response to the examiner's obviousness and double patenting rejections. With respect to the examiner's obviousness rejection based on Cartt, Neurelis argued that Cartt "fails to provide any teaching, suggestion, or motivation

to arrive at the instant claims and importantly fails to recognize or point the skilled artisan to the importance of several key features introduced in 2012 and claimed herein which when combined allow for the safe and effective use of the Valtoco FDA Approved Products and Valtoco Product Candidates." *Id*. Specifically, Neurelis pointed to the following features:

> (i) inclusion of at least 10% and up to about 40% of benzyl alcohol in the pharmaceutical solutions permitting solubility of higher doses of diazepam of 10 mg/100 µL for the Valtoco FDA Approved Products and 20 mg/100 µL for the Valtoco Product Candidates. This also allows consistency of ingredients referenced to the 10 mg dose in the Valtoco FDA Approved Products (e.g., 100 mg/ml);
>
> (ii) inclusion of about 0.25% (w/v) or about 0.5% (w/v) dodecyl maltoside ("DDM") in the pharmaceutical solutions to permit adequate penetration of diazepam through the nasal mucosa and achieving the surprising 96% absolute bioavailability and pharmacokinetics;
>
> (iii) the development of stable and safe pharmaceutical solutions useful for nasal delivery of diazepam in a spray of appropriate viscosity, volume and physical characteristics to achieve desired efficacy while being minimally irritating to the nasal passage;
>
> (iv) achieving a pharmacokinetic profile biocomparable to rectally administered Diastat rectal gel (diazepam) with nearly all absorption of diazepam being through the nose (as opposed to "leaking" - running back out of the nose or being swallowed and orally absorbed); and
>
> (v) the recognition that the claimed pharmaceutical solutions administered in a 100 µL spray are both fast acting (successful treatment within a median time of about less than 5 minutes) and long lasting (about 87% of patients tested during clinical trials do not utilize an additional dose within 24 hours of their initial dose).

Id.

Further, according to Neurelis, "it is surprising and unexpected that the claimed invention of a single 100 µL spray administration in one nostril (claims 67 and 74) or each nostril (claim 90) consistently and reliably achieves the necessary: (i) stability; (ii) viscosity; (iii) safety; (iv) efficacy with both rapid onset of action and prolonged effect in epilepsy patients experiencing ARS." *Id*. Specifically, Neurelis argued that it was surprising and unexpected to find that the use of benzyl

alcohol and DDM resulted in suitable intranasal formulations. *Id*. And Neurelis presented numerous other arguments related to the stability, efficacy, pharmacokinetics, and bioavailability of the claimed diazepam formulations. *Id*.

Neurelis also argued that various secondary considerations of non-obviousness should overcome any prima facie case of obviousness with respect to the pending claims. *Id*. For example, Neurelis argued that there was a long-felt but unmet need "for rescue-treatment of ARS with a benzodiazepine generally, and with diazepam, specifically." *Id*. In addition, Neurelis argued that "[o]thers have attempted to make intranasal formulations of diazepam but have failed to move beyond an academic exercise to create an easy to use, effective rescue treatment for ARS." *Id*. And Neurelis argued that the Valtoco product received "industry praise." *Id*.

In support of these arguments, Neurelis submitted a declaration from Stuart Madden, who is not a listed inventor of the Asserted Patents but asserts that he was "closely involved in the development and commercialization of Valtoco®, and higher-concentration, single spray product candidates of Valtoco, which are encompassed by the pending claims of the '389 Application." Neurelis-02049865-881. In his declaration, Dr. Madden reiterated many of the same points described in the specification of the '852 patent about the prior art's recognition that a nasal formulation of diazepam would be desirable and that a POSA would have understood the need to dissolve an effective amount of diazepam in a small volume to achieve an intranasal diazepam formulation. *Id*. at Neurelis-02049865-869. Dr. Madden also discussed the Valtoco product, and explained that it is an intranasal diazepam formulation suitable for the treatment of acute repetitive seizures ("ARS"). *Id*. at Neurelis-02049865-866.

Further, Dr. Madden asserted that the FDA approved Valtoco products contain the amounts of Vitamin E, diazepam, benzyl alcohol and ethanol, and DDM claimed in the '852 patent. *Id*. at

Neurelis-02049872-874. According to Dr. Madden, Neurelis's early attempts "to solubilize in a solvent system containing a mixture of Vitamin E and ethanol" were done because "diazepam was known to be soluble in Vitamin E and ethanol was used to help decrease the viscosity so that the formulation would be suitable for a nasal spray." *Id*. Dr. Madden asserted that those Vitamin E-ethanol solvent systems were only capable of dissolving diazepam at a concentration of about 80 mg/mL, which was below the "maximum target concentration of 100 mg/mL." *Id*. Dr. Madden asserted that subsequent experiments found that "about 10.5 mg (equivalent to about 10%) of benzyl alcohol with Vitamin E and ethanol was needed to achieve the maximum target concentration of 100 mg/ml of diazepam." *Id*.

Dr. Madden next asserted that:

> The cited art does not appreciate that there is a target concentration necessary to achieve a viable intranasal formulation solely from a solubility perspective. Nor does the cited art teach, suggest, or otherwise guide a skilled artisan to the inclusion of benzyl alcohol to solve the diazepam solubility issue in the solvent system; rather, the cited art teaches that any alcohol in any amount could be utilized and fails to distinguish benzyl alcohol and benzyl alcohol in a concentration of at least 10%, and up to about 40%, achieves the effective dose in about 100 µL of the solution.

Id. at Neurelis-02049874. And Dr. Madden asserted that, because "[a]lcohols are known to irritate the nasal cavity," it was "surprising that Applicant selected an alcohol for use in its intranasal formulations." *Id*. Thus, Dr. Madden asserted that "[s]uch concerns would have guided a skilled artisan away from the selection of benzyl alcohol in amounts of 10% or greater, (including about 40%) in an intranasal formulation for the treatment of ARS in epilepsy patients." *Id*.

In addition, Dr. Madden argued that it was surprising and unexpected that the claimed amounts of DDM achieved the resulting bioavailability. *Id*. at Neurelis-02049876-881. Dr. Madden asserted that amounts of DDM below 0.25% and above 0.5% did not achieve the claimed bioavailability. *Id*. Dr. Madden argued that Neurelis's "achievement of an absolute bioavailability

of about 96% with the Valtoco FDA Approved Products is clinically important and unexpected. Prior formulations achieved anywhere from about 40-78% bioavailability. The fact that this bioavailability occurs without oral absorption is also unique." *Id*.

On December 7, 2023, the examiner issued a final rejection for several reasons. Neurelis-02052445-463.

First, the examiner took issue with Neurelis's attempt "to incorporate subject matter into this application by reference to the Diastat® product label is ineffective because the subject matter is considered 'essential material', given it is the condition being treated in the claimed method." *Id*.

Second, the examiner argued that the claim phrase "[a] method of treating bouts of intermittent and stereotypic episodes of increased seizure activity in an epilepsy patient that is distinguishable from other seizures suffered by the patient," as recited in the amended claims, was new matter. *Id*. Because the examiner was "unable to locate support for" that claim phrase in the specification—specifically, support for *both* intermittent *and* stereotypic episodes—the claims were rejected. *Id*.

Third, the examiner disagreed with Neurelis's obviousness arguments and again rejected the claims as obvious in view of Cartt. *Id*. For example, the examiner took issue with Neurelis's argument that the claimed formulations narrowly covered the Valtoco product. *Id*. "Applicant are [sic] arguing limitations which are not present in the instant claims in part because the 'about' modifier is defined so broadly in the instant specification. The instant claims do not define the term 'about' but permit at least a ±20% variation [069]." *Id*. Because Cartt disclosed formulations encompassed by the claims, as modified by the term "about," the examiner maintained the obviousness rejection. *Id*. Further, the examiner was not persuaded by Neurelis's secondary

considerations arguments at least because they were insufficient to overcome the prima facie case of obviousness based on Cartt. *Id*.

In response to the examiner's final rejection, Neurelis again amended the claims and argued that the examiner's rejections should be withdrawn. Neurelis-02052485-2508. The claim amendments narrowed the scope of the claimed formulations (i.e., removed the term "about" and recited specific amounts of each ingredient) and narrowed or added limitations related to the method of treatment aspects of the claims. *Id*.

Further, Neurelis disagreed with the examiner's essential material (i.e., the incorporation by reference of the Diastat information) and new matter (i.e., the lack of support for *both* intermittent *and* stereotypic episodes) rejections. *Id*. Specifically, Neurelis argued that Diastat was well-known by POSAs, and thus any references to Diastat would not constitute new matter or essential material. *Id*. Neurelis also pointed to paragraphs 238 and 239 to argue that the specification supported the treatment of both intermittent *and* stereotypic episodes. *Id*.

With respect to the examiner's obviousness rejections, Neurelis argued that the examiner's reliance on the term "about" was moot because "the components of the pharmaceutical solution of the claimed methods no longer recite the term 'about'; on the other hand, Cartt 2009's formulation amounts recite 'about' a particular range. Thus, the claimed amounts no longer necessarily lie within the ranges of the prior art because Cartt 2009's ranges fluctuate." *Id*. And Neurelis reiterated that even if the examiner maintained the prima facie obviousness arguments, the previously submitted secondary considerations of nonobviousness should save the claims (as amended) from being considered obvious. *Id*.

The examiner subsequently issued another non-final rejection, arguing that the specification lacked support for the amended claims: "Examiner is unable to locate support in the

instant specification for a method consisting of applying a single spray of 100µL of solution consisting of 56.47 mg of vitamin E USP, 7.50 mg or 5 mg of diazepam; 0.25 mg of dodecyl maltoside; and 10.50 mg of benzyl alcohol; and a sufficient quantity of ethanol which results in 96-97% bioavailability." Neurelis-02052548-2567. And the examiner again maintained the obviousness rejection based on Cartt. *Id*.

Neurelis then amended the claims to address the examiner's "new matter" rejection (broadening the claims to "recite 92.5% to 107.5% bioavailability" instead of 96-97% bioavailability). Neurelis-02052609-644. And Neurelis maintained its positions with respect to obviousness. *Id*.

On March 13, 2025, the examiner issued an additional non-final rejection. Neurelis-02053111-119. Specifically, the examiner rejected the claims as obvious over "Gwozdz (WO 2009/120933), in view of Diastat (Physician's Desk Reference, 2000, excerpts), Meezan '962 (US 2006/0046962), and Cartt '784 (US 2008/0279784)." *Id*.

Neurelis subsequently agreed to amend the claims to remove (and add) certain limitations and argued that the amended claims were not obvious over the prior art. Neurelis-02053154-176 . Neurelis argued that the prior art did not disclose certain claim limitations, namely the treatment of "intermittent, stereotypic episodes of frequent seizures activity (i.e., acute repetitive seizures) ('ARS'), which is distinguished from serial seizures or status epilepticus." *Id*. And Neurelis again argued that certain secondary considerations of nonobviousness, supported by a second declaration from Stuart Madden that was similar to his first declaration, should render the claims non-obvious. Neurelis-02053142-153.

On April 24, 2025, the examiner issued a notice of allowance without providing any reasons for allowance. Neurelis-02053181-186. The ’852 patent subsequently issued on June 10, 2025.

F. The ’061 Patent

The ’061 patent was filed on April 15, 2022 as Application No. 17/721,595 (“the ’595 Application”) and issued on June 24, 2025. The ’061 patent claims priority to several earlier-filed U.S. patent applications, including as a continuation of Application No. 17/336,389 (i.e., the ’852 patent), which claims priority to the ’942 Application, filed on June 13, 2012, and other non-provisional and provisional applications, as described above. *Supra* Section II.E.

Based on presently available information, and in view of the early stage of this case, Defendants state that the claims of the ’061 patent are entitled to a priority date of no earlier than the June 13, 2012 filing date of the ’942 Application. Defendants expressly reserve the right to assert that the claims of the ’061 patent are limited to an effective filing date later than June 13, 2012.

1. The Claims of the ’061 Patent

The ’061 patent issued with 62 claims, which read as follows[6] (independent claims shown in bold text):

> **1. A method of treating bouts of intermittent and stereotypic episodes of increased seizure activity in an epilepsy patient that is distinguishable from other seizures suffered by the patient consisting of:**
>
> > **administering a single spray of 100 µL of a stable pharmaceutical solution to a nostril of the patient, the pharmaceutical solution containing:**
> >
> > **56.47 mg of vitamin E USP;**
> > **10 mg of diazepam;**

[6] The claims of the ’061 patent listed here include the changes made by Neurelis in a post-issuance certificate of correction approved by the USPTO on July 22, 2025.

0.25 mg of dodecyl maltoside;
10.50 mg of benzyl alcohol; and
a sufficient quantity of ethanol;

wherein administering the single spray of the pharmaceutical solution achieves 96% to 97% of the bioavailability of an equivalent dose of diazepam administered intravenously;

wherein administering the single spray of the pharmaceutical solution is safe and effective in treating the bouts of intermittent and stereotypic episodes of increased seizure activity in the patient; and

wherein administering the single spray of the pharmaceutical solution results in a treatment selected from the group consisting of a reduction in the severity of the seizure, a reduction in the probability that the patient will experience a repeat seizure, an increase in the interval between a current seizure and a next seizure in the patient, a reduction in the frequency of seizure in the patient and combinations thereof.

2. The method of claim 1, wherein the pharmaceutical solution is stable at 25° C. and 60% relative humidity for at least 3 months.

3. The method of claim 1, wherein administering the single spray of the pharmaceutical solution results in treatment in less than about 5 minutes.

4. The method of claim 3, wherein administering the single spray of the pharmaceutical solution results in treatment over about 24 hours.

5. A method of treating bouts of intermittent and stereotypic episodes of increased seizure activity in an epilepsy patient that is distinguishable from other seizures suffered by the patient consisting of:

administering a single spray of 100 μL of a stable pharmaceutical solution to a nostril of the patient and administering a second single spray of 100 μL of the pharmaceutical solution to a second nostril of the patient, each of the 100 μL of the pharmaceutical solution containing:

56.47 mg of vitamin E USP;
10 mg of diazepam;
0.25 mg of dodecyl maltoside;
10.50 mg of benzyl alcohol; and
a sufficient quantity of ethanol;

wherein administering the single spray and administering the second single spray of the pharmaceutical solution achieves 96% to 97% of the

bioavailability of an equivalent dose of diazepam administered intravenously;

wherein administering the single spray and administering the second single spray of the pharmaceutical solution is safe and effective in treating the bouts of intermittent and stereotypic episodes of increased seizure activity in the patient; and

wherein administering the single spray and administering the second single spray of the pharmaceutical solution results in a treatment selected from the group consisting of a reduction in the severity of the seizure, a reduction in the probability that the patient will experience a repeat seizure, an increase in the interval between a current seizure and a next seizure in the patient, a reduction in the frequency of seizure in the patient and combinations thereof.

6. The method of claim 5, wherein the pharmaceutical solution is stable at 25° C. and 60% relative humidity for at least 3 months.

7. The method of claim 5, wherein administering the single spray and administering the second single spray of the pharmaceutical solution results in treatment in less than about 5 minutes.

8. The method of claim 7, wherein administering the single spray and administering the second single spray of the pharmaceutical solution results in treatment over about 24 hours.

9. The method of claim 1, wherein the single spray of 100 μL is administered to a nostril of the patient as a single metered spray.

10. The method of claim 5, wherein the single spray of 100 μL and the second single spray of 100 μL are each administered to a nostril of the patient as a single metered spray.

11. The method of claim 1, wherein the ethanol is dehydrated ethanol.

12. The method of claim 5, wherein the ethanol is dehydrated ethanol.

13. The method of claim 1, wherein the dodecyl maltoside is n-dodecyl-β-D-maltoside.

14. The method of claim 5, wherein the dodecyl maltoside is n-dodecyl-β-D-maltoside.

15. The method of claim 1, wherein the pharmaceutical solution exhibits an approximate area under a blood plasma concentration curve measuring total drug exposure across time ($AUC_{0-\infty}$) of 7338 hours*ng/ml.

16. The method of claim 5, wherein the pharmaceutical solution exhibits an approximate area under a blood plasma concentration curve measuring total drug exposure across time ($AUC_{0-\infty}$) of 7338 hours*ng/mL.

17. The method of claim 1, wherein the pharmaceutical solution exhibits an approximate C_{max} of 272 ng/mL.

18. The method of claim 5, wherein the pharmaceutical solution exhibits an approximate C_{max} of 272 ng/mL.

19. The method of claim 1, wherein the pharmaceutical solution exhibits an approximate T_{max} of 1.5 hours.

20. The method of claim 5, wherein the pharmaceutical solution exhibits an approximate T_{max} of 1.5 hours.

21. A method of treating bouts of intermittent and stereotypic episodes of increased seizure activity in an epilepsy patient that is distinguishable from other seizures suffered by the patient comprising:

> **administering a single spray of 100 µL +/−5% of a stable pharmaceutical solution to a nostril of the patient, the pharmaceutical solution containing:**
>
> **56.47 mg of vitamin E USP +/−5%;**
> **10 mg of diazepam;**
> **0.25 mg of dodecyl maltoside +/−5%;**
> **10.50 mg of benzyl alcohol +/−5%; and**
> **a sufficient quantity of ethanol;**
>
> **wherein administering the single spray of the pharmaceutical solution achieves 92.5% to 107.5% of the bioavailability of an equivalent dose of diazepam administered intravenously;**
>
> **wherein administering the single spray of the pharmaceutical solution is safe and effective in treating the bouts of intermittent and stereotypic episodes of increased seizure activity in the patient; and**
>
> **wherein administering the single spray of the pharmaceutical solution results in a treatment selected from the group consisting of a reduction in the severity of the seizure, a reduction in the probability that the patient will experience a repeat seizure, an increase in the interval**

between a current seizure and a next seizure in the patient, a reduction in the frequency of seizure in the patient and combinations thereof.

22. The method of claim 21, wherein the pharmaceutical solution is stable at 25° C. and 60% relative humidity for at least 3 months.

23. The method of claim 21, wherein administering the single spray of the pharmaceutical solution results in treatment in less than about 5 minutes.

24. The method of claim 21, wherein administering the single spray of the pharmaceutical solution results in treatment over about 24 hours.

25. The method of claim 21, wherein the single spray of 100 μL is administered to a nostril of the patient as a single metered spray.

26. The method of claim 21, wherein the ethanol is dehydrated ethanol.

27. The method of claim 21, wherein the dodecyl maltoside is n-dodecyl-β-D-maltoside.

28. The method of claim 21, wherein the pharmaceutical solution exhibits an approximate area under a blood plasma concentration curve measuring total drug exposure across time ($AUC_{0-\infty}$) of 7338 hours*ng/mL.

29. The method of claim 21, wherein the pharmaceutical solution exhibits an approximate C_{max} of 272 ng/mL.

30. The method of claim 21, wherein the pharmaceutical solution exhibits an approximate T_{max} of 1.5 hours.

31. The method of claim 21, wherein the pharmaceutical solution exhibits a half-life of about 49.2 hours.

32. The method of claim 21, wherein the absolute bioavailability is 96% to 97%.

33. A method of treating bouts of intermittent and stereotypic episodes of increased seizure activity in an epilepsy patient that is distinguishable from other seizures suffered by the patient comprising:

administering a single spray of 100 μL +/−5% of a stable pharmaceutical solution to a nostril of the patient and administering a second single spray of 100 μL +/−5% of the pharmaceutical solution to a second nostril of the patient, each of the 100 μL +/−5% of the pharmaceutical solution containing:

56.47 mg of vitamin E USP +/−5%;

10 mg of diazepam;
0.25 mg of dodecyl maltoside +/−5%;
10.50 mg of benzyl alcohol +/−5%; and
a sufficient quantity of ethanol;

wherein administering the single spray and administering the second single spray of the pharmaceutical solution achieves 92.5% to 107.5% of the bioavailability of an equivalent dose of diazepam administered intravenously;

wherein administering the single spray and administering the second single spray of the pharmaceutical solution is safe and effective in treating the bouts of intermittent and stereotypic episodes of increased seizure activity in the patient; and

wherein administering the single spray and administering the second single spray of the pharmaceutical solution results in a treatment selected from the group consisting of a reduction in the severity of the seizure, a reduction in the probability that the patient will experience a repeat seizure, an increase in the interval between a current seizure and a next seizure in the patient, a reduction in the frequency of seizure in the patient and combinations thereof.

34. The method of claim 33, wherein the pharmaceutical solution is stable at 25° C. and 60% relative humidity for at least 3 months.

35. The method of claim 33, wherein administering the single spray and the second single spray of the pharmaceutical solution results in treatment in less than about 5 minutes.

36. The method of claim 33, wherein administering the single spray and the second single spray of the pharmaceutical solution results in treatment over about 24 hours.

37. The method of claim 33, wherein the single spray of 100 μL +/−5% and the second single spray of 100 μL +/−5% are each administered to a nostril of the patient as a single metered spray.

38. The method of claim 33, wherein the ethanol is dehydrated ethanol.

39. The method of claim 33, wherein the dodecyl maltoside is n-dodecyl-β-D-maltoside.

40. The method of claim 33, wherein the pharmaceutical solution exhibits an approximate T_{max} of 1.5 hours.

41. The method of claim 33, wherein the pharmaceutical solution exhibits a half-life of about 49.2 hours.

42. The method of claim 33, wherein the absolute bioavailability is 96% to 97%.

43. A method of treating bouts of intermittent and stereotypic episodes of increased seizure activity in an epilepsy patient that is distinguishable from other seizures suffered by the patient comprising:

administering a single spray of 100 µL +/−5% of a stable pharmaceutical solution to a nostril of the patient and administering a second single spray of 100 µL +/−5% of the pharmaceutical solution to a second nostril of the patient, each of the 100 µL +/−5% of the pharmaceutical solution containing:

56.47 mg of vitamin E USP +/−5%;
7.5 mg of diazepam;
0.25 mg of dodecyl maltoside +/−5%;
10.50 mg of benzyl alcohol +/−5%; and
a sufficient quantity of ethanol;

wherein administering the single spray and administering the second single spray of the pharmaceutical solution achieves 92.5% to 107.5% of the bioavailability of an equivalent dose of diazepam administered intravenously;

wherein administering the single spray and administering the second single spray of the pharmaceutical solution is safe and effective in treating the bouts of intermittent and stereotypic episodes of increased seizure activity in the patient; and

wherein administering the single spray and administering the second single spray of the pharmaceutical solution results in a treatment selected from the group consisting of a reduction in the severity of the seizure, a reduction in the probability that the patient will experience a repeat seizure, an increase in the interval between a current seizure and a next seizure in the patient, a reduction in the frequency of seizure in the patient and combinations thereof.

44. The method of claim 43, wherein the pharmaceutical solution is stable at 25° C. and 60% relative humidity for at least 3 months.

45. The method of claim 43, wherein administering the single spray and the second single spray of the pharmaceutical solution results in treatment in less than about 5 minutes.

46. The method of claim 43, wherein administering the single spray and the second single spray of the pharmaceutical solution results in treatment over about 24 hours.
47. The method of claim 43, wherein the single spray of 100 μL +/−5% and the second single spray of 100 μL +/−5% are each administered to a nostril of the patient as a single metered spray.

48. The method of claim 43, wherein the ethanol is dehydrated ethanol.

49. The method of claim 43, wherein the dodecyl maltoside is n-dodecyl-β-D-maltoside.

50. The method of claim 43, wherein the pharmaceutical solution exhibits an approximate T_{max} of 1.5 hours.

51. The method of claim 43, wherein the pharmaceutical solution exhibits a half-life of about 49.2 hours.

52. The method of claim 43, wherein the absolute bioavailability is 96% to 97%.

53. A method of treating bouts of intermittent and stereotypic episodes of increased seizure activity in an epilepsy patient that is distinguishable from other seizures suffered by the patient comprising:

administering a single spray of 100 μL +/−5% of a stable pharmaceutical solution to a nostril of the patient, the pharmaceutical solution containing:

56.47 mg of vitamin E USP +/−5%;
5 mg of diazepam;
0.25 mg of dodecyl maltoside +/−5%;
10.50 mg of benzyl alcohol +/−5%; and
a sufficient quantity of ethanol;

wherein administering the single spray of the pharmaceutical solution achieves 92.5% to 107.5% of the bioavailability of an equivalent dose of diazepam administered intravenously;

wherein administering the single spray of the pharmaceutical solution is safe and effective in treating the bouts of intermittent and stereotypic episodes of increased seizure activity in the patient; and

wherein administering the single spray of the pharmaceutical solution results in a treatment selected from the group consisting of a reduction in the severity of the seizure, a reduction in the probability that the patient will experience a repeat seizure, an increase in the interval

between a current seizure and a next seizure in the patient, a reduction in the frequency of seizure in the patient and combinations thereof.

54. The method of claim 53, wherein the pharmaceutical solution is stable at 25° C. and 60% relative humidity for at least 3 months.

55. The method of claim 53, wherein administering the single spray of the pharmaceutical solution results in treatment in less than about 5 minutes.

56. The method of claim 53, wherein administering the single spray of the pharmaceutical solution results in treatment over about 24 hours.

57. The method of claim 53, wherein the single spray of 100 μL is administered to a nostril of the patient as a single metered spray.

58. The method of claim 53, wherein the ethanol is dehydrated ethanol.

59. The method of claim 53, wherein the dodecyl maltoside is n-dodecyl-β-D-maltoside.

60. The method of claim 53, wherein the pharmaceutical solution exhibits an approximate T_{max} of 1.5 hours.

61. The method of claim 53, wherein the pharmaceutical solution exhibits a half-life of about 49.2 hours.

62. The method of claim 53, wherein the absolute bioavailability is 96% to 97%.

'061 patent, claims 1-62.

2. The Specification of the '061 Patent

The '061 patent shares a common specification with the '852 patent. Thus, the specification of the '061 patent contains the same disclosures described above with respect to the '852 patent. *Supra* Section II.E.2.

3. The Prosecution History of the '061 Patent

The '061 patent was filed as the '595 Application on April 15, 2022 with 23 claims directed to methods of treating epilepsy by administering a "pharmaceutical solution" containing specific amounts of diazepam and certain excipients. Neurelis-02053368-370.

Similar to the ’852 patent, the examiner rejected the pending claims as obvious (over a second Cartt reference, WO2008137960), and for obviousness-type double patenting over several related patents and pending patent applications. Neurelis-02053507-517. Neurelis responded to the examiner’s rejections, presenting similar arguments as those made during the prosecution of the ’852 patent. Neurelis-02053602-623. Namely, Neurelis argued that Cartt (WO2008137960) was directed to suspensions, not solutions, of diazepam for the treatment of “intermittent and stereotypic increased seizure activity in the patient that is distinguishable from other seizures suffered by the patient,” and thus did not render the pending claims obvious. *Id*. And Neurelis argued that Cartt did not disclose various dosing and other treatment-related claim elements. *Id*.

The examiner issued a final rejection (Neurelis-02053635-650), and Neurelis agreed to amend the claims to recite a method of treating “breakthrough seizures” specifically (Neurelis-02053661-681) to overcome the rejections.

On July 19, 2023, the examiner issued an additional non-final rejection that was similar to the July 20, 2023 non-final rejection issued during prosecution of the ’852 patent (i.e., rejecting the claims as indefinite, obvious, and for obviousness-type double patenting). Neurelis-02053731-743; *see also supra* Section II.E.3. Neurelis responded to the examiner’s rejection with a similar response as the response filed during prosecution of the ’852 patent, along with a declaration from Stuart Madden. Neurelis-02054086-4100.

The examiner issued a final rejection, again arguing that the specification did not support the claimed method of treatment (and constituted new matter), and that the pending claims were obvious over Cartt (U.S. Patent App. Pub. No. 2009/0258865) for the same reasons discussed above. Neurelis-02058116-133; *see also supra* Section II.E.3. Neurelis again responded by proposing to remove the term “about” from the claims, and argued that the specification otherwise

supported the claims, which, Neurelis argued, were not obvious over Cartt. Neurelis-02058156-175. After several rounds of rejections and responses, the examiner issued a final rejection on March 28, 2024, and Neurelis filed a notice of appeal on August 28, 2024. Neurelis-02058349-389.

By the time Neurelis filed its appeal, the pending claims had been amended to recite (independent claim 1 being representative of the pending claims):

> 1. A method of treating bouts of intermittent and stereotypic episodes of increased seizure activity in an epilepsy patient that is distinguishable from other seizures suffered by the patient consisting of:
>
> administering a single spray of 100 μL of a stable pharmaceutical solution to a nostril of the patient, the pharmaceutical solution consisting of:
>
> 56.47 mg of vitamin E USP;
> 10 mg of diazepam;
> 0.25 mg of dodecyl maltoside;
> 10.50 mg of benzyl alcohol; and
> a sufficient quantity of ethanol;
>
> wherein administering the single spray of the pharmaceutical solution achieves 96% to 97% of the bioavailability of an equivalent dose of diazepam administered intravenously;
>
> wherein administering the single spray of the pharmaceutical solution is safe and effective in treating the bouts of intermittent and stereotypic episodes of increased seizure activity in the patient; and
>
> wherein administering the single spray of the pharmaceutical solution results in a treatment selected from the group consisting of a reduction in the severity of the seizure, a reduction in the probability that the patient will experience a repeat seizure, an increase in the interval between a current seizure and a next seizure in the patient, a reduction in the frequency of seizure in the patient and combinations thereof.

Neurelis-02058390. In its opening brief, Neurelis reiterated many of the same arguments it made earlier in the prosecution of the ’061 patent as well as during the prosecution of the ’852 patent. Neurelis-02058349-389

The examiner filed an answering brief, withdrawing the obviousness rejection based on Cartt (U.S. App. No. 2009/0258865) in light of Neurelis's opening brief. Neurelis-02058907-912. Neurelis then filed an additional amendment to address the remaining obviousness-type double patenting rejections, which relied on the '546 patent in view of Cartt. Neurelis-02058922-944. Neurelis argued that the claims of the '061 patent are patentably distinct from the claims of the '546 patent primarily because of the treatment, bioavailability, and pharmacokinetic properties recited in the claims of the '061 patent. *Id*. According to Neurelis, "[t]he specific modality for treating ARS differs from serial seizure patients" as disclosed in Cartt. Thus, "one of ordinary skill in the art would not look to a reference such as Cartt or the claims of the '546 Patent because '[none] of the references make any mention of treating ARS and, therefore, do not appreciate the dose and excipient concentrations necessary to treat that specific indication. Furthermore, formulating the solution with the combination of excipients at the precise amounts recited in the claims to achieve sufficient solubility and bioavailability to treat ARS at a given dosage can only be determined through extensive experimentation...none of the references provide any guidance for developing a solution that is used to treat ARS as recited in the claims.'" *Id*. (Quoting Madden Declaration). Finally, Neurelis argued that the secondary considerations positions described above are also sufficient to overcome the ODP rejection. *Id*.

The examiner subsequently issued a notice of allowance without providing any reasons for allowance. Neurelis-02058953-958. The '061 patent then issued on June 24, 2025.

G. The '400 Patent

The '400 patent was filed on July 24, 2024 as Application No. 18/782,646 ("the '646 Application") and issued on January 13, 2026. The '400 patent claims priority to several earlier-filed U.S. patent applications, including as a continuation of Application No. 12/431,439 ("the

’439 Application”), filed on March 27, 2009. The ’439 application claims priority to Provisional Application No. 61/040,558 (“the ’558 Provisional”), filed March 28, 2008.

Based on presently available information, and in view of the early stage of this case, Defendants state that the claims of the ’400 patent are entitled to a priority date of no earlier than the March 28, 2008 filing date of the ’558 Provisional, but expressly reserve the right to assert that one or more of the claims may only be entitled to an effective filing date later than March 28, 2008.

1. The Claims of the ’400 Patent

The ’400 patent issued with 21 claims, of which only claims 1, 12, and 20 are independent claims (in bold text below). The claims of the ’400 patent read as follows:

1. A pharmaceutical composition for intranasal administration comprising:

> **about 1 to about 20 mg of diazepam dissolved in about 45% to about 85% (w/w) of one or more natural or synthetic tocopherols or tocotrienols selected from the group consisting of α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, α-tocotrienol, β-tocotrienol, γ-tocotrienol, δ-tocotrienol, tocophersolan, any esters thereof and any combinations thereof, and about 25% to about 40% (w/w) of one or more alcohols selected from the group consisting of ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, and any combinations thereof, wherein the pharmaceutical composition is a solution of 50 µL to 150 µL, and wherein the pharmaceutical composition is in a pharmaceutically-acceptable spray formulation for intranasal administration.**

2. The pharmaceutical composition of claim 1, wherein the natural or synthetic tocopherols or tocotrienols are selected from the group consisting of: α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, tocophersolan, any esters thereof and any combinations thereof.

3. The pharmaceutical composition of claim 1, wherein the natural or synthetic tocopherols or tocotrienols is α-tocopherol.

4. The pharmaceutical composition of claim 1, wherein the one or more alcohols is selected from the group consisting of ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, isomers thereof and any combinations thereof.

5. The pharmaceutical composition of claim 1, wherein the diazepam is present in the pharmaceutical solution at a concentration of about 10 mg/mL to about 250 mg/mL.

6. The pharmaceutical composition of claim 1, wherein the pharmaceutical solution comprises one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof in an amount from about 60% to about 75% (w/w).

7. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition further comprises at least one additional ingredient selected from the group consisting of stabilizers, coloring agents, pH adjusters, buffering agents, preservatives, wetting agents, flavoring agents and combinations thereof.

8. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition further comprises an absorption enhancer.

9. The pharmaceutical composition of claim 8, wherein the absorption enhancer is present in the pharmaceutical composition at a concentration of up to 20% (w/v).

10. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition is about 100 μL.

11. The pharmaceutical composition of claim 1, wherein the therapeutically effective amount of the diazepam is about 2 mg to about 10 mg.

12. A pharmaceutical composition for intranasal administration comprising:

> **about 1 to about 20 mg of diazepam dissolved in about 45% to about 85% (w/w) of α-tocopherol, and about 25% to about 40% (w/w) of one or more alcohols selected from the group consisting of ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, isomers thereof and any combinations thereof, wherein the pharmaceutical composition is a solution of 50 μL to 150 μL, and wherein the pharmaceutical composition is in a pharmaceutically-acceptable spray formulation for intranasal administration.**

13. The pharmaceutical composition of claim 12, wherein the diazepam is present in the pharmaceutical solution at a concentration of about 10 mg/mL to about 250 mg/mL.

14. The pharmaceutical composition of claim 12, wherein the diazepam is about 2 mg to about 10 mg.

15. The pharmaceutical composition of claim 12, wherein the pharmaceutical solution comprises α-tocopherol in an amount from about 60% to about 75% (w/w).

16. The pharmaceutical composition of claim 12, wherein the pharmaceutical composition further comprises at least one additional ingredient selected from the

group consisting of stabilizers, coloring agents, pH adjusters, buffering agents, preservatives, wetting agents, flavoring agents and combinations thereof.

17. The pharmaceutical composition of claim 12, wherein the pharmaceutical composition further comprises an absorption enhancer.

18. The pharmaceutical composition of claim 17, wherein the absorption enhancer is present in the pharmaceutical composition at a concentration of up to 20% (w/v).

19. The pharmaceutical composition of claim 12, wherein the pharmaceutical composition is about 100 μL.

20. A pharmaceutical composition for intranasal administration comprising:

about 1 to about 20 mg of diazepam dissolved in about 45% to about 85% (w/w) of α-tocopherol and about 25% to about 40% (w/w) of one or more alcohols selected from the group consisting of ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, and any combinations thereof, wherein the pharmaceutical composition is a solution of about 100 μL, and wherein the pharmaceutical composition is in a pharmaceutically-acceptable spray formulation for intranasal administration.

21. The pharmaceutical composition of claim 20, wherein the pharmaceutical composition further comprises an absorption enhancer.

'400 patent, claims 1-21.

2. The Specification of the '400 Patent

The '400 patent shares a common specification with the '786 patent. Thus, the specification of the '400 patent contains the same disclosures described above with respect to the '786 patent. *Supra* Section II.C.2.

3. The Prosecution History of the '400 Patent

The '400 patent, filed as U.S. Application No. 18/782,646 ("the '646 application") was originally filed with a total of 30 claims. U.S. Patent No. 12,521,400, Prosecution History, App. No. 18/782,646 ("'400 FH") application filed July 24, 2024, at 68-71. During prosecution, the Examiner issued a non-final rejection on December 10, 2024, finding pending claims 1-13, 17-26, and 30 obvious over Sonne (U.S. 6,193,985) in view of Li et al. (International Journal of

Pharmaceutics 199(2000):65-76). ’400 FH, Office Action dated Dec. 10, 2024, at 4. The Examiner further asserted that claims 14-16 and 27-29 were obvious over Sonne in view of Li, in view of Meezan et al. (US 2006/0046962). *Id*. at 11.

In the response dated March 10, 2025, Neurelis amended the claims to recite “about 1 to about 20 mg of diazepam,” “about 15% to about 55%” of the one or more alcohols, and narrowing the composition to recite a solution volume “of 50 μL to 150 μL, and wherein the pharmaceutical composition is in a pharmaceutically-acceptable spray formulation for intranasal administration.” ’400 FH, Response dated March 10, 2025, at 2. Regarding the obviousness rejection of claims 1-13, 17-26, and 30 over Sonne in view of Li, Neurelis asserted that (1) Sonne’s intranasal spray formulations are emulsions and teach away from intranasal spray solutions; (2) Sonne teaches away from alcohol solutions for intranasal sprays; and (3) Li does not cure the deficiencies of Sonne’s formulation and, since Li’s formulation requires an ethanol alcohol, the prior art combination would negate the principle of operation of Sonne. *Id*. at 8-12.

Further, regarding the obviousness rejection of claims 14-16 and 27-29 over Sonne in view of Li, in view of Meezan, Neurelis asserted that the Office failed to explain why a POSA would limit the amount of absorption enhancer at “up to 20% w/v;” that Meezan’s alkyl glycosides were a redundant advantage based on Sonne allegedly solving the problem of delivering substantially insoluble active agents in a clinically effective way; and that Meezan does not solve the fundamental emulsion and alcohol issues of Sonne and Li. *Id*. at 13-14.

Subsequently, the Examiner issued a final rejection on May 14, 2025, maintaining the obviousness rejections over Sonne in view of Li, and Sonne in view of Li in view of Meezan. ’400 FH, Final Office-Action dated May 14, 2025, at 4-14. In response, Neurelis further amended the claims to recite “about 45% to about 85% (w/w)” of the one or more natural or synthetic

tocopherols or tocotrienols, and "about 25% to about 40% (w/w) of one or more alcohols selected from the group consisting of ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, and any combinations thereof." '400 FH, Request for Continued Examination dated September 23, 2025, at 2. In the remarks accompanying the claim amendments, and supported by the declaration of Dr. Sveinbjorn Gizurarson, Ph.D., Neurelis argued that: (1) Sonne neither teaches nor suggests any intranasal spray solution dosage forms with alcohol; (2) the mucosal irritation caused by the presence of alcohols teaches away from the claimed nasal spray formulations; and (3) the claimed solutions allegedly provides surprisingly low nasal irritation despite higher alcohol concentrations compared to competing formulations. *Id*. at 8-15. The Examiner subsequently withdrew the rejections and issued a notice of allowance on October 17, 2025. '400 FH, Notice of Allowance dated October 17, 2025.

III. LEGAL FRAMEWORK

A. Obviousness

A claim is invalid for obviousness if "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person of ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a). For example, the refinement of ranges does not typically impart patentability of a claimed invention over the prior art. *See, e.g., Merck & Co. Inc. v. Biocraft Labs Inc.*, 874 F.2d 804 (Fed. Cir. 1989); *In re Geisler*, 116 F.3d 1465 (Fed. Cir. 1997). Absent a demonstration of criticality, variation in a concentration, temperature, or other such feature does not indicate nonobviousness over prior art disclosing a different value for the same parameter. *See In re Woodruff*, 919 F.2d 1575 (Fed. Cir. 1990). In particular, a claim is obvious if it teaches a range that, while not overlapping with the prior art, is close enough that a POSA would expect

them to have the same properties. *See Titanium Metals Corp. of Am. v. Banner*, 778 F.2d 775 (Fed. Cir. 1985).

A claimed modification of a prior art product is "obvious to try" where there are a "finite number of identified, predictable solutions," and if such modification is successful, "it is likely the product not of innovation but of ordinary and common sense." *KSR, Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 421 (2007). Accordingly, if the prior art explicitly teaches an array of features, and the prior art components "provide only their known properties, to produce results shown or predicted in the prior art," then such combinations would have been obvious. *See Sanofi-Aventis Deutschland GmbH v. Glenmark Pharm., Inc. USA*, 748 F.3d 1354, 1360–61 (Fed. Cir. 2014). Moreover, whether a particular feature or embodiment is identified as "preferred" in a prior art reference does not limit the scope of the overall reference as disclosure against a later claim. *See Id.*

A claim may also be shown to be obvious in view of the prior art. Although the ultimate determination of obviousness under § 103 is a question of law, the evaluation is based on several underlying factual factors, often referred to as "the Graham factors," including: "(1) the scope and content of the prior art; (2) the level of ordinary skill in the pertinent art; (3) the differences between the claimed invention and the prior art; and (4) evidence of secondary factors, such as commercial success, long-felt need, and the failure of others." *Innovention Toys, LLC v. MGA Entm't, Inc.*, 637 F.3d 1314 (Fed. Cir. 2011) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966)). However, even secondary considerations of nonobviousness may be inadequate to overcome a strong prima facie case of obviousness. *Leapfrog Enters., Inc. v. Fisher-Price, Inc.*, 485 F.3d 1157, 1162 (Fed. Cir. 2007).

The Supreme Court's decision in *KSR* further indicates that the *Graham* factors are to be evaluated flexibly and in view of common sense. Specifically, *KSR* indicates that pressure to solve a known problem, the presence of a limited number of predictable solutions, and anticipated success are all relevant factors in determining whether an invention is obvious. The inquiry may be referred to as the "common sense" standard, and is described below:

> When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103. . . . Rigid preventative rules that deny fact finders recourse to common sense, however, are neither necessary under our case law nor consistent with it.

KSR, 550 U.S. at 418-19.

The common-sense standard provides that the motivation to combine references may be present in the nature of the problem to be solved or known by one of skill in the art. In establishing any of the contentions set forth herein, Defendants may rely on common sense and/or the knowledge of a POSA at the time of the alleged inventions.

Further, the Federal Circuit has long recognized that "inherency may supply a missing claim limitation in an obviousness analysis." *PAR Pharm., Inc. v. TWI Pharms., Inc.*, 773 F.3d 1186, 1194–95 (Fed. Cir. 2014); *see also In re Napier*, 55 F.3d 610, 613 (Fed. Cir. 1995) ("The inherent teaching of a prior art reference, a question of fact, arises both in the context of anticipation and obviousness."); *Hospira, Inc. v. Fresenius Kabi USA, LLC*, 946 F.3d 1322, 1329 (Fed. Cir. 2020) ("Extrinsic evidence can be used to demonstrate what is 'necessarily present' in a prior art embodiment even if the extrinsic evidence is not itself prior art"). For example, the Federal Circuit has held that pharmacokinetic properties of a drug can be inherently obvious, even if they are not expressly disclosed in the prior art. *Persion Pharms. LLC v. Alvogen Malta*

Operations Ltd., 945 F.3d 1184, 1191 (Fed. Cir. 2019). Thus, where claimed properties or features are not expressly disclosed in the prior art, they may still be inherently obvious.

B. Obviousness Type Double Patenting

Non-statutory double patenting is a judicially-created doctrine, which prohibits an inventor from obtaining a second patent for claims that are not patentably distinct from the claims of the first patent." *In re Lonardo*, 119 F.3d 960, 965 (Fed. Cir. 1997); *Gilead Scis., Inc. v. Natco Pharma Ltd*., 753 F.3d 1208, 1214-15 (Fed. Cir. 2014). It "prevent[s] the extension of the term of a patent, even where an express statutory basis for the rejection is missing, by prohibiting the issuance of the claims in a second patent not patentably distinct from the claims of the first patent." *Otsuka Pharm. Co.* v. *Sandoz, Inc.*, 678 F.3d 1280, 1297 (Fed. Cir. 2012) (quoting *In re Longi*, 759 F.2d 887, 892 (Fed. Cir. 1985); *see Geneva Pharm., Inc. v. GlaxoSmithKline PLC*, 349 F.3d 1373, 1377-78 (Fed. Cir. 2003). A later patent claim is not patentably distinct from an earlier patent claim if the later claim is obvious over, or anticipated by, the earlier claim. *In re Longi, 759 F.2d at 896* (affirming a holding of obviousness-type double patenting because the claims at issue were obvious over claims in four prior art patents); *Sun Pharm. Indus., Ltd. v. Eli Lilly & Co.*, 611 F.3d 1381, 1385 (Fed. Cir. 2010) ("'A later claim that is not patentably distinct from,' i.e., 'is obvious over[] or anticipated by,' an earlier claim is invalid for obviousness-type double patenting") (quoting *Eli Lilly v. Barr Labs*., 251 F.3d 955, 968 (Fed. Cir. 2001)). The doctrine of obviousness-type double patenting is available as a defense when the patents are commonly owned or share common inventors and is primarily intended "to prevent unjustified timewise extension of the right to exclude granted by a patent no matter how the extension is brought about." *In re Hubbell*, 709 F.3d 1140, 1145, 1447-48 (Fed. Cir. 2013) (quoting *In re Van Ornum*, 686 F.2d 937, 943 (C.C.P.A. 1982)).

The obviousness-type double patenting analysis involves two steps: "First, the court 'construes the claim[s] in the [reference] patent and the claim[s] in the [] patent [at issue] and determines the differences.' Second, the court 'determines whether those differences render the claims patentably distinct.'" *Abbvie Inc. v. Mathilda & Terence Kennedy Inst. of Rheumatology Tr.*, 764 F.3d 1366, 1374 (Fed. Cir. 2014). Thus, a later claim that is not patentably distinct from, i.e., is obvious over or anticipated by, an earlier claim is invalid for obviousness-type double patenting. *See Sun Pharm.*, 611 F.3d at 1385.

C. Section 112

Under 35 U.S.C. § 112, the specification must "contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same." 35 U.S.C. § 112.

1. Written Description

Under 35 U.S.C. § 112(a), "[t]he specification shall contain a written description of the invention." The inventor must describe the invention so that the public will know what it is and that he or she has truly made the claimed invention. *See Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 736 (2002) ("The [ ] requirements must be satisfied before issuance of the patent, for exclusive patent rights are given in exchange for disclosing the invention to the public. What is claimed by the patent application must be the same as what is disclosed in the specification. . . ." (internal citations omitted)).

The Federal Circuit has made it clear that the description must allow one of ordinary skill in the art to recognize that the inventor had possession of the claimed subject matter at the time of filing. *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc). "[I]t is the specification itself that must demonstrate possession." *Id.* at 1352. Assessing possession as

shown in in the disclosure requires "an objective inquiry into the four corners of the specification." *Id.* at 1351. Ultimately, "the specification must describe an invention understandable to [a person of ordinary skill in the art] and show that the inventor actually invented the invention claimed." *Id.* For the purposes of written description, the invention is "whatever is now claimed." *See, e.g., PowerOasis, Inv. v. T-Mobile USA, Inc.*, 522 F.3d 1299, 1311 (Fed. Cir. 2008). A "mere wish or plan" for obtaining the claimed invention is not adequate written description. *Regents of the Univ. of Cal. v. Eli Lilly Co.*, 119 F.3d 1559, 1566 (Fed. Cir. 1997).

The written description "must do more than merely disclose that which would render the claimed invention obvious." *ICU Med., Inc. v. Alaris Med. Sys., Inc.*, 558 F.3d 1368, 1377 (Fed. Cir. 2009). Each claim limitation must be described in the specification. *Id.*. The level of detail required to satisfy the written description requirement depends on the scope of the claims and predictability of the relevant technology. *See Centocor Ortho Biotech, Inc. v. Abbott Labs.*, 636 F.3d 1341, 1344 (Fed. Cir. 2011). In an unpredictable art, a higher level of detail is required to show that the inventors possessed what was claimed. *See, e.g., Burroughs Wellcome Co. v. Barr Labs., Inc.*, 40 F.3d 1223, 1229 (Fed. Cir. 1994).

Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimation of general ideas that may or may not be workable. *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1366 (Fed. Cir. 1997); *see also Centocor*, 636 F.3d at 1350-53 (claim to provisional application filing date rejected for lack of disclosure of the claimed subject matter). Thus, "the lack of any disclosure of examples may be considered when determining whether the claimed invention is adequately described." *Boston Sci. Corp. v. Johnson & Johnson*, 647 F.3d 1353, 1364 (Fed. Cir. 2011). Moreover, a patentee may not rely on information "well-known in

the art" to supply the lacking written description in an unpredictable art. *See, e.g., Univ. of Rochester*, 358 F.3d at 927.

In addition, the written description must "sufficiently demonstrate[] that the inventors possessed the full scope of the claimed invention." *Juno Therapeutics, Inc. v. Kite Pharma, Inc.*, 10 F.4th 1330, 1336 (Fed. Cir. 2021). "For generic claims," the Federal Circuit has "set forth a number of factors for evaluating the adequacy of the disclosure, including 'the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, [and] the predictability of the aspect at issue.'" *Juno*, 10 F.4th at 1335. And "[f]or genus claims using functional language … the written description 'must demonstrate that the applicant has made a generic invention that achieves the claimed result and do so by showing that the applicant has invented species sufficient to support a claim to the functionally-defined genus.'" *Id.* at 1335.

2. Enablement

A patent's specification must describe the invention and "the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains ... to make and use the same." 35 U.S.C. § 112(a). Claims are not enabled when, at the effective filing date of the patent, a POSA could not practice their full scope without undue experimentation. *See Wyeth & Cordis Corp. v. Abbott Labs*., 720 F.3d 1380, 1384 (Fed. Cir. 2013). In addition, the scope of enablement must be commensurate with the full scope of the claim. *Id.* at 1384–85; *see also AK Steel Corp. v. Sollac and Ugine*, 344 F.3d 1234, 1244 (Fed. Cir. 2003).

"The purpose of the enablement requirement is to ensure that the public is told how to carry out the invention, i.e., to make and use it." *Amgen Inc. v. Sanofi, Aventisub LLC*, 987 F.3d 1080, 1084 (Fed. Cir. 2021). The "disclosure must be at least commensurate with the scope of the claims." *Id.* As the Supreme Court explained, "the specification must enable the full scope of the

invention as defined by its claims. The more one claims, the more one must enable." *Id.* at 610. Further, "the enablement inquiry for claims that include functional requirements can be particularly focused on the breadth of those requirements, especially where predictability and guidance fall short." *Id.* at 1086.

The Federal Circuit has provided several factors that may be utilized in determining whether a disclosure would require undue experimentation: (1) the quantity of experimentation necessary; (2) the amount of direction or guidance disclosed in the patent; (3) the presence or absence of working examples in the patent; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability of the art; and (8) the breadth of the claims. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

3. Indefiniteness

"[A] patent is invalid for indefiniteness if its claims, read in light of the specification delineating the patent, and the prosecution history, fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention." *Nautilus, Inc. v. Biosig Instruments, Inc.,* 134 S. Ct. 2120, 2124 (2014). "[A] patent must be precise enough to afford clear notice of what is claimed, thereby apprising the public of what is still open to them." *Id.* at 2129 (quotations and citations omitted). The analysis to determine if a claim is invalid for indefiniteness examines the claims, specification, and prosecution history "to ascertain if they convey to one of skill in the art with reasonable certainty the scope of the invention claimed." *Teva Pharm. USA, Inc. v. Sandoz, Inc.*, 789 F.3d 1335, 1341 (Fed. Cir. 2015).

Further, claims are indefinite where there are multiple methods of defining or measuring a claimed parameter that yield materially different results without guidance in the patent or prosecution history as to which method should be used. *See, e.g.*, *Dow Chem. Co. v. Nova Chems. Corp.*, 803 F.3d 620, 634 (Fed. Cir. 2015); *Teva Pharms. USA, Inc. v. Sandoz, Inc.*, 789 F.3d 1335,

1345 (Fed. Cir. 2015); *Pac. Coast. Bldg. Pods., Inc. v. CertainTeed Gypsum, Inc.*, 816 F. App'x 454, 460 (Fed. Cir. 2020).

IV. LEVEL OF ORDINARY SKILL IN THE ART

1. The '400, '664, '414, and '786 Patents

Because the '400 patent is related to, and claims similar intranasal diazepam formulations as, the '546, '414, '786, and '664 patents, Defendants contend that the POSA with respect to the '400 patent would be the same as the POSA with respect to the '546, '414, '786, and '664 patents. Specifically, 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 five years of experience, or a Master's, Ph.D. or Pharm.D. degree with several years of experience. 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. A POSA is considered to be aware of all relevant prior art, including the prior art described below, and would have had the capability to draw inferences from the references, including combining the references and then drawing additional inferences from the combined teachings.

2. The '852 and '061 Patents

The '852 and '061 patents claim methods of treating "bouts of intermittent and stereotypic episodes of increased seizure activity in an epilepsy patient that is distinguishable from other seizures suffered by the patient" by administering specific amounts and doses of diazepam in specific pharmaceutical formulations to achieve specific treatment endpoints, pharmacokinetic properties, and other related properties. *See generally* all claims of the '852 and '061 patents. Accordingly, the claims of the '852 and '061 patents encompass subject matter related to

pharmaceutical formulations and/or chemistry, medical treatment issues, and pharmacokinetic issues.

A POSA with respect to the ’852 and ’061 patents would have been an individual or member of a multi-disciplinary team with the skills, education, and expertise to formulate and administer an intranasal benzodiazepine formulation for patient treatment. Such an individual or team would have included 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 five years of experience, or a Master’s, Ph.D. or Pharm.D. degree with several years of experience. Such an individual or team also 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, including, among other things, knowledge of solubility, stability, pharmacokinetics, pharmacodynamics, and other pharmaceutical characteristics. Finally, such an individual or team would have included an individual with a medical degree and experience treating patients that suffer from seizures, such as a medical doctor that practices as a neurologist or epileptologist. Further, a POSA is considered to be aware of all relevant prior art, including the prior art described below, and would have had the capability to draw inferences from the references, including combining the references and then drawing additional inferences from the combined teachings.

V. INVALIDITY OF THE ’664, ’414, ’786, AND ’400 PATENTS

A. The Priority Date of the ’664, ’414, and ’786 Patents

As explained above, the earliest possible priority date of the ’664, ’414, and ’786 patents is March 27, 2009. *Supra* Section II.A-D. While these patents purport to claim priority to an earlier-filed provisional application, the PTAB previously determined that the earlier-filed provisional

application does not provide support for formulations containing alkyl glycosides (i.e., DDM) in an IPR involving a patent related to the '664, '414, and '786 patents. *See, e.g.*, IPR2019-00451, Paper 44 at 23 (Aug. 6, 2020). The PTAB came to a similar conclusion in its institution decisions in IPRs filed by Padagis on the '546, '414, and '786 patents. *See, e.g.*, IPR2025-00464, Paper 13 at 13-14 (Sep. 16, 2025). Accordingly, Neurelis is collaterally estopped from asserting an earlier priority date, and the claims of the '664, '414, and '786 patents are entitled to a priority date of no earlier than March 27, 2009.

Based on presently available information, and in view of the early stage of this case, Defendants have provided the analysis herein based on a priority date for the '400 patent of no earlier than the March 28, 2008 filing date of the '558 Provisional, but expressly reserve the right to assert that one or more of the claims may only be entitled to an effective filing date later than March 28, 2008.

B. Background of Technology

1. Treatment of Epilepsy

Acute isolated seizure, repetitive or recurrent seizures and status epilepticus are all deemed medical emergencies. Wermeling at 352. Mortality and "worse neurologic outcome" (as referred to in the literature) are directly associated with the duration of seizure activity, underscoring the importance of fast treatment of acute seizures. *Id.* The literature prior to 2009 included a number of consensus statements regarding the pharmacologic treatment protocols for seizures when patients are in pre-hospital, institutional and home-bound settings, all of which identified benzodiazepines (including lorazepam, diazepam, midazolam and clonazepam) as first line medications. *Id.* The rapidity by which a medication can be delivered to the systemic circulation and then to the brain plays a significant role in reducing the time needed to treat seizures and the opportunity to reduce the associated damage to the central nervous system. *Id.*

Patients with life-threatening or unstable conditions presenting to pre-hospital or hospital emergency facilities will typically have an intravenous (IV) line established, if possible, for rapid administration of medications. *See also* EMS at 54. However, alternative routes of administration are employed in the field, as clinically indicated, including intramuscular injection and transmucosal approaches such as rectal, nasal, buccal and endotracheal administration. As noted, patients experiencing epileptic seizures have a medical emergency and require prompt medical care. *See*, e.g., Lowenstein I; Lowenstein II; Wang; and Stavem. Numerous guidelines and references have recognized the need for prompt treatment, and have recommended various transmucosal routes of benzodiazepine delivery when IV access has not yet been established. *See* e.g., Logroscino; Feen; Pang; Smith; and Ericksson.

Formulations for the intranasal administration of antiepileptic medications, including benzodiazepines, have been studied with various preparations. For example, intranasal midazolam has been extensively studied in children and adults for sedation in preparation for procedures, in delivery of anesthesia, and in epilepsy patients, and has been recommended as a potential drug delivery technique in patients requiring prompt intervention. *See e.g.,* Wolfe; Meierkord; and Prasad.

Under ideal conditions, most medication is absorbed from the nasal cavity and into the bloodstream within 15-20 minutes, generally avoiding first-pass metabolism in the gut and liver. *See* Constantino. However, a second absorption phase due to subsequent oral absorption can be observed with nasally administered medications having incomplete nasal absorption. Regarding oral absorption, diazepam is known to be well absorbed, with reported oral bioavailability values of 90% or greater. Ritschel at 377; Goodman & Gillman at 1948 (citing 100% ± 14% oral availability); and Valium label at 1 (citing >90% absorption after oral administration).

2. Product Design Considerations

As further discussed in the art (*see, e.g.*, Wermeling) many intranasal delivery products have been developed to serve various purposes or unmet medical needs. A nasal spray is often preferred over injectable dosage forms, for the obvious reason of avoiding the pain associated with injection by needle. Additionally, many intranasal products are also designed for rapid action, including in the treatment of migraine headache (sumatriptan, butorphanol, zolmitriptan, dihydroergotamine) or for pain relief (fentanyl, hydromorphone). *See* Constantino; Rudy.

Wermeling (reporting on the findings of Constantino et al.) discussed several key factors and considerations for the successful development of nasal spray formulations, as shown below:

Table 1. *Chemistry and Formulation Issues Affecting Intranasal Medication Bioavailability and Tolerability*

- Potent medication, <20 mg per dose
- Molecular weight, <1000 Daltons
- Excellent water solubility
- pKa and pH control of aqueous solutions
- Osmolality—isotonic to slightly hypertonic
- Stability in processing and storage
- Compatibility with sprayer components
- Use of special excipients to manage
  - Solubility
  - Stability
  - Permeation

See Wermeling at 354.

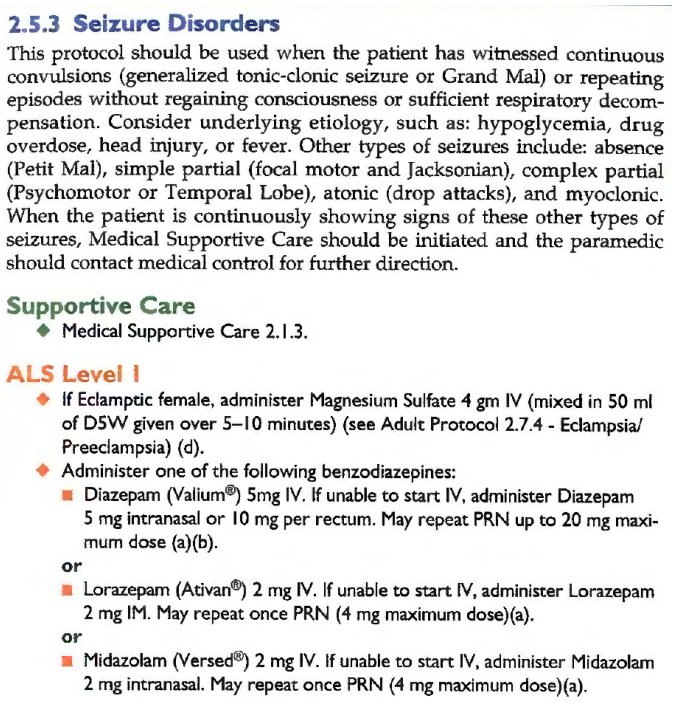
Wermeling further explains "[p]hysical-chemical properties of the candidates must also be considered. Water-solubility is important for formulation considerations. Log P, derived from the octanol/water partition coefficient, is a surrogate for lipophilicity, and a potential [sic] for compounds to diffuse across biologic membranes." Wermeling at 354. It was well-known that benzodiazepines have sufficient lipophilic character to readily cross biologic membranes (*id.*), meaning that benzodiazepines would be considered a logical choice for intranasal administration.

Benzodiazepines also satisfy the potency requirement for potential nasal administration, as therapeutic doses are typically less than 20 mg. *See id.* Doses of drug compound "must have sufficient solubility to be administered in approximately 100 µL to 200 µL (1 spray per naris (nostril)) of solution," with the understanding that the total dose may be delivered in smaller doses delivered to each nostril, etc. *See id.* The nasal cavity can retain 100 to 150 µL without causing immediate run-off out the front of the nose or down the naso-pharynx. *Id.*

Water is often considered a preferred solvent, but many medications, including the benzodiazepines, do not have sufficient water solubility to formulate a nasal product. *Id.* Consequently, when developing formulations for medications having low water solubility, a POSA would look to non-aqueous solvents, and would also consider additional solubilization strategies.

Design of the formulation must account for other factors as well. Viscosity enhancing agents such as methylcellulose can promote retention in the nasal cavity by slowing the ciliary clearance of mucus. Surfactants or polymers can be employed to enhance transmembrane permeation. Additionally, the drug and formulation must be stable in the device during processing and storage, and thus may require stabilizers.

The device utilized for delivery of the formulation is also important. A standard syringe with Luer fitting to accept a mucosal nasal atomizer (Mucosal Atomization DeviceTM ("MAD"); Teleflex) has also been used to draw up and administer injection-based drug solutions into the nasal cavity for opiate overdoses and to treat acute pain. Indeed, this device has been used to deliver midazolam, lorazepam, and diazepam formulations to the nasal cavity of a seizing patient. *See*, e.g., EMS at 0030 (which is copied below again for convenience); *see also* at 0029 and 0037-0039:



2.5.3 Seizure Disorders

This protocol should be used when the patient has witnessed continuous convulsions (generalized tonic-clonic seizure or Grand Mal) or repeating episodes without regaining consciousness or sufficient respiratory decompensation. Consider underlying etiology, such as: hypoglycemia, drug overdose, head injury, or fever. Other types of seizures include: absence (Petit Mal), simple partial (focal motor and Jacksonian), complex partial (Psychomotor or Temporal Lobe), atonic (drop attacks), and myoclonic. When the patient is continuously showing signs of these other types of seizures, Medical Supportive Care should be initiated and the paramedic should contact medical control for further direction.

Supportive Care

- Medical Supportive Care 2.1.3.

ALS Level I

- If Eclamptic female, administer Magnesium Sulfate 4 gm IV (mixed in 50 ml of D5W given over 5–10 minutes) (see Adult Protocol 2.7.4 - Eclampsia/ Preeclampsia) (d).
- Administer one of the following benzodiazepines:
  - Diazepam (Valium®) 5mg IV. If unable to start IV, administer Diazepam 5 mg intranasal or 10 mg per rectum. May repeat PRN up to 20 mg maximum dose (a)(b).

  or
  - Lorazepam (Ativan®) 2 mg IV. If unable to start IV, administer Lorazepam 2 mg IM. May repeat once PRN (4 mg maximum dose)(a).

  or
  - Midazolam (Versed®) 2 mg IV. If unable to start IV, administer Midazolam 2 mg intranasal. May repeat once PRN (4 mg maximum dose)(a).

As illustrated above, the EMS reference discloses that 5 mg doses of diazepam could be administered intranasally in emergent seizure patients requiring treatment with benzodiazepines, by utilizing the MAD device noted above.

Due to the water insoluble nature of benzodiazepines, a common approach to nasal delivery formulation is to employ organic solvents or co-solvents with or without water. While there is a risk of transient irritation from such formulations, the risk-benefit assessment clearly still favors use of such products in treatment of life-threatening circumstances such as seizures.

3. Prior Art Experience with Intranasal Delivery of Benzodiazepines for Treatment of Seizures Prior To 2009

Studies demonstrating nasal delivery of midazolam to treat seizures are prevalent in the literature. O'Regan documented the successful intranasal administration of 0.2 mg/kg of midazolam (administering a midazolam injection solution intranasally). O'Regan at 1044. The results demonstrated successful cessation of seizures in 14 of 19 children with difficult to treat seizures. *Id.* at 1042.

Additionally, others have compared intranasal midazolam to intravenous diazepam for reduction of seizure rates and time to cessation. *See* Mittal; Mahmoudian; and Lahat. All of the articles concluded that intranasal midazolam was equally effective as IV diazepam in treatment of seizures; and intranasal midazolam reduced time to cessation of seizures by eliminating the need to establish IV access.

Bhattacharyya conducted a controlled trial of intranasal midazolam versus rectal diazepam in children. There was a shorter time to seizure cessation in the midazolam group. Intranasal midazolam had a superior tolerability profile with lower incidences of drowsiness, nausea, and respiratory depression.

Intranasal drug delivery has also been readily accepted by patients and consumers as demonstrated by the considerable usage of various over-the-counter and prescription products.

Further, the Florida Regional Common EMS Protocols Field Guide, Jones & Bartlett Publishers (2005), prescribed the use of diazepam IV solution to be used with a MAD nasal spray device for intranasal administration of diazepam to treat seizures. *See* EMS at 54 (illustrated above). As reported in the Physician's Desk Reference (PDR), each mL of Valium (Diazepam) IV "contains 5 mg diazepam compounded with 40% propylene glycol, 10% ethyl alcohol, 5% sodium benzoate and benzoic acid as buffers, and 1.5% benzyl alcohol as preservative." PDR at 2676. Consequently, EMS established that diazepam formulations containing propylene glycol, ethanol (ethyl alcohol), benzyl alcohol, and sodium benzoate/benzoic acid (as buffers) could be administered intranasally for the emergency treatment of seizures.

For at least these reasons, the medical literature is replete with examples of the successful use and development of intranasal formulations containing various benzodiazepine compounds, including diazepam, for the successful treatment of acute seizures.

References that may be relied upon to demonstrate the state of the art as of the priority date of the Asserted Patents include:

Reference	Publication Date	Short Cite
U.S. Patent No. 9,763,876, *Administration Of Benzodiazepine Compositions*	October 29, 2014	'876 patent
Ritschel, *Handbook of Basic Pharmacokinetics*, Chapter 36 (Bioavailability and Bioequivalence), Drug Intelligence Publications, Illinois	1992	Ritschel
Osborne et al., *Skin Penetration Enhancers Cited in the Technical Literature*, Pharmaceutical Technology	November 1997	Osborne
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
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.	May 14, 2009	Ivaturi
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	2003	Rowe
PDR 54th Edition 2000, DIASTAT® (diazepam rectal gel); MIACALCIN® (Calcitonin Nasal Spray); VALIUM® (diazepam injection), Physicians' Desk Reference	2000	PDR
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	2002	Knoester
Florida Regional Common EMS Protocols Field Guide, Jones and Barlett Publishers, MA	2005	EMS
Valium® Tablet Label, Roche	January 2008	Valium Label
Wolfe T, Macfarlane T. *Intranasal midazolam therapy for pediatric status epilepticus.* Am J Emerg Med 2006; 24:43-346	2006	Wolfe

Reference	Publication Date	Short Cite
Holsti M, Sill B, Firth S, et al., *Prehospital intranasal midazolam for the treatment of pediatric seizures.* Ped Emerg Care 2007; 23: 148-153	2007	Holsti
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	2005	Greenblatt
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	1996	O'Regan
Bhattacharyya M, Kalra V, Gulati S. *Intranasal midazolam vs rectal diazepam in acute childhood seizures.* Pediatric Neurology 2006; 34: 355-359	2006	Bhattacharyya
SIGMA Chemical Company Catalog	1988	Sigma Catalog
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
Hardman, et al., Editors, Goodman & Gilman's, The Pharmacological Basis of Therapeutics, 10th Edition	2001	Goodman & Gilman
Loftsson T, Gudmundsdottir H, Sigurjonsdittur JF, et al. Cyclodextrin solubilization of benzodiazepines: formulation of midazolam nasal spray. Int J Pharm 2001; 212:29-40	2001	Loftsson
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	2001	Gudmundsdottir
Dale O., Nilsen T., Loftsson T. *Intranasal midazolam: a comparison of two delivery devices in human volunteers.* J Pharmacy Pharmacol 2006; 58: 1311-1318	2006	Dale
Burstein AH, Modica R, Hatton M, et al. *Pharmacokinetics and pharmacodynamics of midazolam after intranasal administration.* J Clin Pharmacol 1997; 37: 711-718	1997	Burstein
Wermeling, D, Record K, Kelly T, et al*., Pharmacokinetics and pharamcodynamics of a new intranasal midazolam formulation in healthy volunteers.* Anesth Analg 2006; 103: 344-349	2006	Wermeling II

Reference	Publication Date	Short Cite
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Lau SWJ, Slattery JT. Intl J Pharmaceutics. *Absorption of diazepam and lorazepam following intranasal administration.* Int J Pharmaceutics 1989; 54: 171-174	1989	Lau
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C. Identification of Invalidating Prior Art

Defendants identify the following prior art that, alone or in combination with other references, renders obvious the claims of the '664, '414, '786, and '400 patents. Defendants reserve the right to rely upon additional prior art or documents as discovery progresses, to the extent not addressed herein. Defendants reserve the right to rely on all prior art cited or discussed during the prosecution of any of the Asserted Patents and any patent claiming priority to any of the Asserted Patents or to which any of the Asserted Patents claim priority. As such, Defendants incorporate by reference, in full, all prior art references cited in any of the Asserted Patents or in any of the prosecution histories of any of the Asserted Patents and any patent claiming priority to any of the Asserted Patents or to which any of the Asserted Patents claim priority. Defendants further reserve the right to identify and rely on additional art or teachings or disclosures within the art in the event that Defendants' evaluation of the prior art teachings or disclosures is in any way contested.

Defendants reserve the right to rely on these cited or uncited references as well as other teachings or disclosures in the field to demonstrate the state of art and/or the knowledge and level of skills of a POSA at the relevant times. Defendants intend to rely upon each reference in its entirety to the extent relevant and/or appropriate, including references cited in and/or referenced within the references identified below.

Prior art not included in these Preliminary Invalidity Contentions may become relevant depending upon the positions Neurelis asserts (*e.g.*, the infringement or claim construction positions asserted by Neurelis), the claim constructions adopted by the Court, and the priority date(s) determined for any of the Asserted Patents. In addition, Defendants may uncover additional prior art and/or relevant information during discovery. Defendants reserve the right to supplement, modify, or amend these Preliminary Invalidity Contentions with additional prior art, or different

versions of the references listed herein, as discovery continues in light of information provided by Neurelis concerning its infringement allegations, claim constructions, or alleged earliest priority dates of the Asserted Patents, or in light of the Court's claim construction or other rulings and orders.

The following table summarizes the prior art references that Defendants contend renders the claims of the '664, '414, '786, and '400 patents patent obvious:

Prior Art Reference[7]	**Effective Publication Date**	**Short Cite**
WIPO Pub. No. WO 2009/120933 to Gwozdz et al.	March 28, 2008	Gwozdz
U.S. Pub. No. 2006/0046962 to Meezan et al.	March 2, 2006	Meezan
U.S. Pub. No. 2007/0208011 to Cloyd et al.	September 6, 2007	Cloyd
U.S. Pub. No. 2008/0279784 to Cartt et al.	November 13, 2008	Cartt 2008
USP 23/NF 18, Ed., "United States Pharmacopeia. The National Formulary," The United States Pharmacopoeial Convention Inc., Rockville, 1995	1995	USP
Florida Regional Common EMS Protocols Field Guide, Jones and Bartlett Publishers, 2005	2005	Florida EMS Manual
U.S. Patent No. 6,193,985	February 27, 2001	Sonne
Physician's Desk Reference (PDR) 54th Edition 2000, DIASTAT® (diazepam rectal gel); MIACALCIN® (Calcitonin Nasal Spray); VALIUM® (diazepam injection), Physicians' Desk Reference	2000	PDR
Lianli Li et al., *Rapid-Onset Intranasal Deliver of Anticonvulsants: Pharmacokinetic and Pharmacodynamic Evaluation in Rabbits*, 199 INT'L J. OF PHARMACEUTICS 65, 65 (2000)	2000	Li
U.S. Pub. No. US 2008/0070904 to Jamieson et al.	2008	Jamieson
U.S. Pub. No. US 2004/0176359 to Wermeling et al.	2004	Wermeling V

[7] Defendants reserve the right to rely on any Invalidating Prior Art reference in combination with any other Invalidating Prior Art reference consistent with the disclosures provided herein. Specific combinations of Invalidating Prior Art references discussed below are exemplary only.

Prior Art Reference[7]	Effective Publication Date	Short Cite
Pharmacopeial Forum Jan.-Feb. 2004, 30(1):96-97	2004	Pharmacopeial Forum for Diazepam
U.S. Patent No. 6,627,211	2003	Choi
WIPO Pub. No. WO2009/046444 to Costantino	2007	Costantino '444

D. Preliminary Summary of the Prior Art References

1. Gwozdz

WIPO Publication No. WO 2009/120933 to Gwozdz et al. entitled "Pharmaceutical Solutions and Method for Solubilizing Therapeutic Agents" published October 1, 2009. Gwozdz claims priority to U.S. Prov. App. No. 61/040,281 ("the '281 provisional"), filed March 28, 2008. All of the teachings and disclosure provided herein are supported in the specification of the '281 Provisional. Based on the filing date of the '281 Provisional, Gwozdz constitutes prior art against the '664, '414, and '786 patents under § 102(e)(1). The table below includes exemplary citations from Gwozdz and the corresponding disclosure in the '281 Provisional that supports the cited disclosure in Gwozdz.

Gwozdz Citations in this Petition (EX1009)	**'281 Provisional Supporting Disclosure (EX1064)**
4:13-17	p. 4, lines 9-13
4:19-21	p. 4, lines 14-17
4:24-26	p. 4, lines 20-22
4:29-31	p. 4, lines 25-27
5:12-14	p. 5, lines 8-11
5:33-6:2	p. 5, lines 30-34
6:2-11	p. 6, lines 4-9
6:13-15	p. 6, lines 9-13
7:3-11	p. 7, lines 1-9
7:12-19	p. 7, lines 10-17
7:20-28	p. 7, lines 18-26

Gwozdz Citations in this Petition (EX1009)	**'281 Provisional Supporting Disclosure (EX1064)**
7:29-34	p. 7, lines 27-32
8:6-18	p. 8, lines 5-17
10:9-16	p. 10, lines 10-17

Gwozdz is directed to pharmaceutical solutions for solubilizing therapeutic agents in "one or more natural or synthetic tocopherols or tocotrienols, or any combination thereof and one or more alcohols or glycols, or any combination thereof." Gwozdz at 4:13-17. Gwozdz states that the therapeutic agent may include various compounds, including diazepam, stating:

> Exemplary hydrophobic or lipophilic therapeutic agents which can be solubilized in accordance with the present invention include, but are in no way limited to, steroids such as Dexamethasone, 17-beta-Estradiol; benzodiazepenes such as Diazepam, alprazolam, bromazepam, chlordiazepoxidem, clonazepam, estazolam, flunitrazepam, flurazepam, lorazepam, lormetazepam, mexazolam, nitrazepam, oxazepam, temazepam, and triazolam; Rapamycin and analogues; Taxol (paclitaxel) and analogues; Actinomycin D; Prostaglandins (PGEl) ; Vitamin A; Probucol; Batimastat; Statins (HMG-CoA Reductase Inhibitors; Trapidil (and other anti-proliferative Growth Factor Inhibitors); Cytochalasin B; and microtubule binding agents such as epothilones, elutherobin and discodermolide.

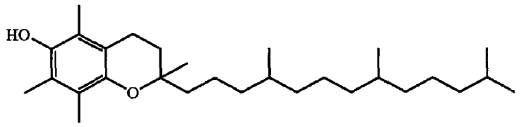
Id. at 8:6-18.

In fact, Gwozdz identified diazepam (a benzodiazepine) as a preferred therapeutic agent for use in the solubilizing solutions described therein, stating that the solubility of diazepam can be increased from less than or equal to 6.67% (in ethanol) to "approaching the 10% level" (when incorporating tocopherol into the solution). *Id*. at 7:12-16.

Regarding the components of the solubilizing solutions, Gwozdz states the following:

> The present invention is directed to the use of ***one or more tocopherols and/or tocotrienols and one or more alcohols*** and/or glycols as pharmaceutically acceptable solvents for solubilizing therapeutic agents, in particular hydrophobic or lipophilic therapeutic agents.
>
> …
>
> Tocopherols and/or tocotrienols for use in accordance with the present invention include a family of natural and synthetic compounds, also known by the generic

names tocols or vitamin E. Alpha-tocopherol is the most abundant and active form of this family of compounds, and it has the following chemical structure:



Other members of this family include beta-, gamma-, and delta-tocopherol, alpha-, beta-, gamma-, and delta-tocotrienols, tocopsoralen, alpha-tocopherol derivatives and/or analogs such as tocopherol acetate, phosphate, succinate, nicotinate and linoleate, as well as isomers thereof and esters thereof. Use of the phrase tocopherol (s) and/or tocotrienol (s) herein is meant to be inclusive of any member of this family alone or in combination. ***In one embodiment of the present invention the tocopherol (s) and/or tocotrienol (s) employed is alpha-tocopherol***.

Examples of alcohol (s) for use in the present invention include, but are not limited to ***ethanol***, propyl alcohol, butyl alcohol, pentanol, ***benzyl alcohol***, and any isomers thereof, ***and any combinations thereof***.

…

In one embodiment of the present invention the alcohol is ethanol (ethyl alcohol) . Preferred is use of an ethanol that is biocompatible in the sense that it is not toxic and does not cause any physiological or pharmacological effects. In this regard, the ethanol is desirably 180 to 200 proof ethanol, i.e., in the range of 90-100% ethanol. Advantageously, diluting a tocopherol or tocotrienol with an alcohol or glycol dramatically reduces the inherent viscosity of the tocopherol or tocotrienol thereby allowing for generation of sprayable formulations.

Id. at 4:29-33, 5:33-7:2 (emphasis added).

Regarding the combination of the tocopherol and alcohols, Gwozdz states:

In accordance with the present invention, solutions of one or more tocopherols and/or tocotrienols and one or more alcohols and/or glycols are used in the solubilization of hydrophobic or lipophilic therapeutic agents thereby providing increased bioavailability of the therapeutic agent. In some embodiments, the tocopherol (s) and/or tocotrienol (s) is in an amount from about 30% to about 99% (w/w) and the alcohol (s) and/or glycol (s) is in an amount about 1% to about 70% (w/w).

As a non-limiting example, the solubility of Diazepam at room temperature is less than or equal to 6.67% in 190 proof ethanol. However, combining tocopherol and ethanol has been found to provide solubility of the Diazepam approaching the 10% level. By way of illustration, at 70% tocopherol : 30% ethanol (200 proof) , Diazepam is soluble to greater than or equal to 8% and at 95% tocopherol : 5% ethanol (200 proof), Diazepam is soluble at greater than or equal to 9%.

> Accordingly, preferred for some embodiments is that alpha-tocopherol and ethanol constitute 60% to 99% and 1% to 40%, respectively, of the pharmaceutical solution. In other embodiments, the alpha-tocopherol and ethanol constitute approximately 70% to 90% and 10% to 30%, respectively, of the pharmaceutical solution. In still other embodiments, the tocopherol and ethanol are used at ratios of approximately 95:5, 90:10, 85:15, 80-20, 75:25, 70:30, 65:35, or 60:40, respectively.

Id. at 7:3-19.

Moreover, Gwozdz states that additional "pharmaceutically acceptable additives" may be incorporated into the solubilizing solution.

Id. at 10:3-16.

Further, Gwozdz explains that the solubilizing solutions are preferably used for the nasal administration of therapeutic agents, stating:

> Pharmaceutical solutions of the instant invention are particularly useful in formulations to be administered to mucosal membranes, i.e. the nasal mucosa or lungs of a subject by any suitable means. For many therapeutic agents, administration via the nasal route provides for faster attainment of therapeutic levels of the therapeutic agent systemically . However, many therapeutic agents are so slightly soluble in water that a therapeutically effective amount cannot be dissolved in a volume of aqueous solvent that is amenable to application to a mucosal membrane. Use of a pharmaceutical solution of the present invention, however, provides for improved ability to dissolve lipophilic and lipophilic therapeutic agents, thus providing a useful delivery system for administration of such agents to one or more mucosal membranes, including the nasal mucosal membranes. Such solutions can be administered via, for example, a metered dose inhaler or nebulizer, or in a mist sprayer.

Id. at 9:19-10:2.

As noted above, Gwozdz states that the pharmaceutical solutions of the instant invention are preferably utilized to deliver drugs to the nasal mucosa via the nasal route, which provides faster achievement of systemic therapeutic agent concentrations. *Id*. Gwozdz explains that the therapeutic agent may be administered to the nasal mucosa utilizing known delivery mechanisms, such as metered dose inhalers, nebulizers, or nasal mist sprayers. *Id*.

2. Meezan

U.S. Patent Application Publication No. 2006/0046962 to Meezan et al. is titled "Absorption Enhancers for Drug Administration," and was published on March 2, 2006. Meezan was published more than one year prior to the earliest possible priority date for the '664, '414, '786, and '400 patents, and constitutes prior art against the under § 102(b).

Meezan is directed to non-irritating compositions designed for improved bioavailability of therapeutic agents. Meezan states:

> The invention relates generally to non-irritating, non-toxic compositions providing enhanced bioavailability and more specifically to alkyl glycoside or saccharide alkyl ester compositions for delivery of therapeutic agents to a subject.

Meezan at ¶ [0002].

Meezan states that the invention is directed to alkyl glycoside or saccharide alkyl ester compositions that provide enhanced bioavailability of therapeutic agents. In particular, Meezan states the following regarding the alkyl glycoside component:

> Alkyl glycosides of the present invention can include, but are not limited to: alkyl glycosides, such as octyl-, nonyl-, decyl-, undecyl-, dodecyl-, tridecyl-, tetradecyl-, pentadecyl-,hexadecyl-, heptadecyl-, and octadecyl-α- or β-D-maltoside, -glucoside or -sucroside….
>
> …
>
> Similarly, some preferred glycosides include maltose, sucrose, and glucose linked by glycosidic linkage to an alkyl chain of 9, 10, 12, 13, 14, 16, 18, 20, 22, or 24 carbon atoms, e.g., nonyl-, decyl-, dodecyl- and tetradecyl sucroside, glucoside, and maltoside, etc. These compositions are nontoxic, since they are degraded to an alcohol and an oligosaccharide, and amphipathic.

Id. at [0056]-[0058].

Moreover, Meezan states that the alkyl glycoside compounds can be utilized with a wide variety of therapeutic agents, in a wide variety of dosage forms, stating:

> [T]he present invention provides compositions, including alkyl glycosides and/or saccharide alkyl esters and a therapeutic agent (e.g. small molecule organic drug

> molecules, low molecular weight peptides such as Exenatide, GLP-1 and the like, proteins, and non-peptide therapeutic polymers such as low molecular weight heparin and inhibitory RNA), methods of administering and using the compositions e.g. via the oral, ocular, nasal, nasolacrimal, inhalation or pulmonary, oral cavity (sublingual or Buccal cell) or cerebral spinal fluid (CSF) delivery route, and methods of ameliorating a disease state in a subject by administration of such compositions.

Id. at ¶ [0004].

Meezan explains that the alkyl glycoside compositions can be used to enhance the bioavailability of "small molecule organic drug molecules," indicating that the compositions can be utilized with a broad array of potential drug compounds. *Id*. Additionally, Meezan states that the compositions may be utilized to administer drug compounds via the nasal delivery route, among others. *Id*.

Regarding the amount of the alkyl glycoside to be used in the compositions, Meezan states:

> 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…For example, alkyl glycosides in the range of about 0.01% to about 6% by weight result in good stabilization of the drug….

Id. at ¶ [0149]. Thus, Meezan explains that alkyl glycosides in concentrations ranging from about 0.01% to about 6% by weight resulted in "good stabilization of the drug." *Id*. Additionally, Meezan again identifies dodecyl maltoside (i.e., "DDM") as one of the preferred alkyl glycosides having a stabilizing effect on the drug compound. *Id*. Further, Example 3 of Meezan discloses that "studies show that alkylmaltosides with the longer alkyl chains (or number of carbon atoms), e.g., dodecyl-, tridecyl, and tetradecyl-β-D-maltosides, are more effective." *Id*. at ¶ [0149].

3. Cartt 2008

U.S. Pub. No. 2008/0279784 to Cartt et al. titled "Nasal Administration of Benzodiazepines" was published on November 13, 2008, and claims priority to U.S. Provisional

Pat. App. No. 60/916,550 filed May 7, 2007. Cartt 2008 constitutes prior art against the '664, '414, '786, and '400 patents under § 102(a) and/or § 102(e)(1).

Cartt 2008 is directed to nasal formulations for the administration of benzodiazepine drug compounds, including diazepam. Cartt 2008 at ¶ [0028]. In particular, Cartt 2008 explains exemplary doses of diazepam to be delivered to patients per dose via nasal administration:

> Diazepam is a benzodiazepine drug having sedative, tranquilizing and muscle relaxing properties. It is classified as an anxiolytic and skeletal muscle relaxant. It possesses anxiolytic, anticonvulsant, sedative, skeletal muscle relaxant and amnesic properties. The dosage of Diazepam may vary by indication, however it is expected that a therapeutic dose will be in the range of about 1 to about 20, preferably about 2 to about 10 mg per dose….

Id. at ¶ [0063].

Cartt 2008 further states the following regarding the typical concentrations of diazepam in the nasal formulations:

> In some embodiments, the benzodiazepine or pharmaceutically acceptable salt thereof is present in a concentration of from about 0.05 mg/mL up to about 600 mg/mL.

Id. at ¶ [0034]. Thus, Cartt 2008 states that the benzodiazepine is formulated in concentrations ranging from about 0.05 mg/mL to about 600 mg/mL. *Id*.

4. USP

USP 23/NF 18, Ed., "United States Pharmacopeia. The National Formulary," The United States Pharmacopoeial Convention Inc., Rockville was published in 1995 and constitutes prior art against the '664, '414, '786, and '400 patents under § 102(b).

USP provides the official monograph for vitamin E, stating:

> Vitamin E is a form of alpha tocopherol (C29H50O2). It includes the following d- or dl-alpha tocopherol (C29H50O2); d- or dl-alpha tocopheryl acetate (C31H52O3); d- or dl-alpha tocopheryl acid succinate (C33H54O5). It contains not less than 96.0 percent and not more than 102.00 percent of C29H50O2, C31H52O3, or C33H54O5, respectively.

USP at 1631.

Thus, USP explains that Vitamin E represents a form of alpha tocopherol that may include d- or dl-alpha tocopherol ($C_{29}H_{50}O_2$); d- or dl-alpha tocopheryl acetate ($C_{31}H_{52}O_3$); d- or dl-alpha tocopheryl acid succinate ($C_{33}H_{54}O_5$).

5. Florida EMS Manual

The Florida EMS Manual was published in 2005 and constitutes prior art against the '664, '414, '786, and '400 patents under § 102(b).

The Florida EMS Manual discloses protocols that should be used to treat patients suffering from seizures. Florida EMS Manual at 54. Florida EMS Manual identifies benzodiazepine drugs as being useful and effective to treat seizures, and says to administer:

> Diazepam (Valium®) 5 mg IV. If unable to start IV, administer Diazepam 5 mg ***intranasal*** or 10 mg per rectum. May repeat PRN up to 20 mg maximum dose (a)(b).

Id. Further, Florida EMS Manual explains that "[i]ntranasal administration of benzodiazepines requires the use of a mucosal atomization device." *Id*. at 55.

6. PDR

Physician's Desk Reference (PDR) was published in 2000 and constitutes prior art against the '664, '414, '786, and '400 patents under § 102(b).

PDR discloses that each mL of Valium (Diazepam) IV "contains 5 mg diazepam compounded with 40% propylene glycol, 10% ethyl alcohol, 5% sodium benzoate and benzoic acid as buffers, and 1.5% benzyl alcohol as preservative." PDR at 2676. PDR also discloses that Diastat (Diazepam) rectal gel "contains 5 mg/ml diazepam, propylene glycol, ethyl alcohol (10%), hydroxypropyl methylcellulose, sodium benzoate, benzyl alcohol (1.5%), benzoic acid and water. *Id*. at 1012.

7. Cloyd

U.S. Pub. No. 2007/0208011 to Cloyd et al. was published on September 6, 2007, and constitutes prior art against the ’664, ’414, and ’786 patents under § 102(b), and the ’400 patent under § 102(a)

Cloyd discloses “supersaturated solutions of benzodiazepines, such as diazepam, glycofurol and water and their use for intranasal (NS) administration to combat various disorders.” Cloyd at Abstract. Cloyd explains that existing routes of administration (i.e., intravenous, oral, rectal) for benzodiazepines, including diazepam, suffered from “shortcomings that diminish their usefulness in treating seizure emergencies.” *Id*. at ¶ [0008]. Thus, Cloyd discloses intranasal solution formulations of benzodiazepines as an alternative administration route. *Id*. at ¶¶ [0012]-[0013].

Cloyd explains that the intranasal solution formulation should contain “at least about 10 mg/ml of the benzodiazepine, and in particular, the composition can provide at least between about 5 mg/ml and about 60 mg/ml of the benzodiazepine, i.e., diazepam.” *Id*. at ¶ [0013]. Cloyd also discloses that “[a] major difficulty presented by the nasal route is the small size of the nasal cavity, such that total dosing volume (which may involve administration through both nostrils) should not generally exceed 150 µl per nostril. Assuming that a DZP dose of 10 mg would be required in adults, a highly concentrated diazepam solution is required.” *Id*. at ¶ [0082].

8. Sonne

U.S. Patent No. 6,193,985 to Mette Rydahl Sonne was published on February 27, 2001, and constitutes prior art against the ’664, ’414, ’786, and ’400 patents under § 102(b).

Sonne discloses “the use of a tocopherol or a derivative thereof as a solvent … for substantially insoluble and sparingly soluble biologically active agents, especially in the manufacture of pharmaceutical compositions.” Sonne at Abstract. According to Sonne, the

tocopherol compositions are "especially" suitable for intranasal administration. *Id*. Sonne explains that tocopherols are excellent solvents for drugs which are substantially insoluble "whilst at the same time having a very low irritative potential for mucosal tissues." *Id.* at 2:55-58

Sonne also discloses that the intranasal tocopherol formulations may be useful for the formulation of benzodiazepines, including diazepam specifically. *Id*. at 2:4-62; *see also id.* at 3:54-59 ("[n]asal, rectal and oral cavity administrations are particularly preferred."). Further, Sonne explains that "administration of drugs with very low water solubility to the nose is difficult, because of the limited volume which is acceptable for the nose (about 100 µl). The first example has a very high concentration of diazepam, and it is possible to administrate diazepam to the nose and to achieve a rapid clinical effect." *Id*. at 7:25-30. To that end, Sonne discloses examples of a "diazepam nosedrop" formulations containing diazepam and various excipients, including Vitamin E and α-Tocopherol. *Id*. at 7:32-8:27, 10:20-11:13. Sonne also explains that "[t]he formulations according to the invention may be optimized with respect to bioadhesion, sprayability and viscosity, as desired" by incorporating "co-solvents" like "alcohols such as ethanol … or benzyl alcohol." *Id*. at 6:47-53.

Further, Sonne discloses that the formulations may developed as tocopherol-based solutions, stating:

> The compositions of the invention may be used directly as solutions of the bioactive agent in the tocopherol solvent. However such solutions are viscous, and the viscosity may be too high for certain applications, for example to achieve a sprayable formulation for nasal application. Viscosity can be reduced by addition of co-solvents such as ethanol, but this is less desired, since solutions of this kind tend to be irritating to certain mucosal tissues.

Id. at 3:60-67. Sonne also discloses that the tocopherol solutions may be emulsified "by mixing the tocopherol-based 'oil phase' containing the dissolved bioactive agent with an appropriate aqueous phase, eg. water, saline or buffer solutions." *Id*. at 4:3-6.

Sonne also teaches that compositions of the disclosed inventions "may contain from 1 to 99.99% (w/w), preferably 20 to 99.99%, most preferably 40 to 99.99% (w/w) of the tocopherol or tocopherol derivative solvent." Sonne at 5:55-58. Sonne also explains that "[t]ocopherols are a range of natural and synthetic compounds, also known by the generic term Vitamin E. α-Tocopherol . . . is the most active and widely distributed in nature, and has been the most widely studied." Sonne at 3:5-10.

9. Li

Li was published in 2000, and constitutes prior art against the '664, '414, '786, and '400 patents under § 102(b).

Li discloses the intranasal administration of diazepam "to assess the feasibility of this approach for the emergency treatment of status epilepticus." Li at Abstract. To prepare the intranasal diazepam formulation, diazepam was "dissolved in 200 μL of vehicle consisting of propylene glycol (PG), ethanol (EtOH), and water in the presence or absence of 1% sodium glycocholate (SGC)." *Id*. The studied solutions included one that contained about 20 mg diazepam with about 30% ethanol in about 1 ml of total vehicle. *Id*. at 67.

Further, Li explains that "the nasal route has received a great deal of attention as a convenient and reliable mode for the systemic administration of drugs." *Id*. at 66. Thus, according to Li, "a great need exists for solvent vehicles, in which the solubility of the drug is high and which, on the other hand, are nonirritating to the nasal mucosa. The solubility problem is even more critical for a very poorly water-soluble drug such as" diazepam. *Id*. Li also explains that "[a]dding a chemical adjuvant or permeation enhancer, including bile salts," like SGC, "can increase the intranasal absorption of drugs." *Id*.

Li concludes that "[t]he peak [diazepam] concentration . . . increased significantly with increasing [ethanol] concentrations in the [intranasal] formulation (20-60%)." *Id*. at 71-72. Li

also concludes that "[t]he nasal administration of [diazepam] . . . formulations in 1% SGC containing EtOH:PG:water cosolvent elicited a very fast PD response, which was less than 1.5 min. In turn, this response time appeared to be essentially identical to that seen from an IV injection of a benzodiazepine." *Id*. at 74.

10. Jamieson

U.S. Patent Application Publication No. 2008/0070904 to Jamieson et al. (hereinafter "Jamieson") is titled "Pharmaceutical Compositions of Benzodiazepines and Method of Use thereof," and was published on March 20, 2008, and constitutes prior art under at least § 102(a).

Jamieson discloses inventions that "include[] benzodiazepine compositions formulated for intranasal administration, comprising a binary solvent system comprising a first solvent in which the benzodiazepine is soluble, the first solvent capable of penetrating nasal mucosal tissue, and a second solvent in which the benzodiazepine in [sic] less soluble." Jamieson at Abstract. The compositions disclosed therein were recognized as those that may treat a variety of disorders, including specifically seizures. *Id*. at Abstract, [Claim 1], [Claim 13], [Claim 34].

Jamieson discloses compositions that include a therapeutically effective amount of a benzodiazepine, including specifically diazepam. *See, e.g.*, *Id*. at claims 8, 17, 40. It teaches intranasal formulations where the amount of diazepam is "typically present at a weight percent of between about 0.1% to about 20% and often between 0.1% and 10% often 0.25% to 6%." *Id*. at ¶ [0102]; *see also Id*. at ¶ [0118] ("A therapeutically effective amount of diazepam in the compositions of the present invention may be, for example between about 1.0 mg and about 40.0 mg per unit dose, more preferably between about 2.0 mg and about 10.0 mg per unit dose.").

Jamieson furthers discloses benzodiazepine compositions that include tocopherols. *See, e.g.*, *id*. at claims 24, 49; *see also id.* at ¶ [0209] ("Addition of an anti-oxidant to the formulations of the present invention used for intranasal delivery of benzodiazepines may provide desirable

protective benefits to such formulations. Examples include, but are not limited to, tocopherol and derivatives thereof . . . ."). Moreover, Jamieson discloses benzodiazepine formulations containing 20% ethanol. *See id.* at Table 12A.

Jamieson recognizes problems associated with intranasally administered benzodiazepine formulations, with one of the problems being "poor bioavailability." *Id*. at ¶ [0018]. Jamieson explains the need for intranasal benzodiazepine compositions with improved properties, such as rapid absorption, time to peak concentration, and bioavailability. Thus, Jamieson also teaches the use of penetration enhancers in diazepam for intranasal spray formulations. *Id.* at ¶ [0104] ("pharmaceutical compositions comprising the benzodiazepine (e.g., clonazepam, diazepam or lorazepam) of the present invention, for example, for intranasal administration . . . may further comprise one or more components including . . . mucosa penetration enhancing agent"), ¶ [0105] ("In preferred embodiments of the present invention, the pharmaceutical compositions . . . are formulation to be sprayable."). Jamieson also recognizes that due to the "highly lipophilic nature of the benzodiazepines a combination of surfactants, strong solubilizing solvents, and carrier solutions are often used." Jamieson at [0142].

Further, Jamieson explains that "[t]ypical unit doses delivered by these spray devices for intranasal delivery are between about 50 µL to about 300 µL, often 25 µL to about 150 µL, preferably a volume of about 100 µL . . . ." *Id*. at ¶ [0127].

11. Wermeling V

U.S. Patent Application Publication No. 2004/0176359 to Wermeling (hereinafter "Wermeling V") is titled "Intranasal Benzodiazepine Compositions," and was published on September 9, 2004, and constitutes prior art under § 102(b).

Wermeling V discloses pharmaceutical compositions for intranasal administration of effective amounts of benzodiazepines, and specifically highlights the use of diazepam. Wermeling

V at Abstract, [0026]. It explains that the "principal advantages of intranasal route are non-invasive delivery, rapid drug absorption, and convenience. *Id*. at ¶ [0008]. Wermeling V continues that "there is a need for intranasal benzodiazepine compositions with improved properties, such as for example, rapid absorption and time to peak concentration." *Id*. at ¶ [0012].

Wermeling V explains that the disclosed solutions may include nasal carrier designed for the delivery of the benzodiazepine to the nasal mucosa. *Id*. at ¶ [0030]. It also discloses the use of suitable diluents for application to the nasal mucosa, which include both aqueous and non-aqueous diluents or combinations thereof. *Id*. at ¶ [0020]. Examples of diluents disclosed for use include alcohols. *Id*. at ¶ [0030]. Wermeling V continues that "the composition contains a preservative that is chosen in quantities that preserve the composition, but preferably does not cause irritation to the nasal mucosa." *Id*. at ¶ [0033]. Thereafter, Wermeling V highlights benzyl alcohol as a "suitable preservative." *Id*. at ¶ [0033].

12. Pharmacopeial Forum for Diazepam

The Pharmacopeial Forum published in 2004 and constitutes prior art under § 102(b).

The Pharmacopeial Forum is a free bimonthly journal in which USP publishes proposed revisions to USP-NF for public review and comment. New issues publish every two months at the beginning of the month. The comment period is 90-days and ends on the last day of the month. Specifically, *Pharmacopeial Forum Jan.-Feb. 2004*, 30(1):96-97 ("Pharmacopeial Forum for Diazepam") specifies impurity standards for diazepam.

13. U.S. Patent No. 6,627,211 B1 ("*Choi*")

U.S. Patent No. 6,627,211 to Choi issued September 30, 2003, and constitutes prior art under § 102(b).

U.S. Patent No. 6,627,211 to Choi is titled "Transnasal anticonvulsive compositions and modulated process." *Choi* discloses pharmaceutical compositions for transmucosal delivery of

biologically active agents, for controlling and promoting the rate and extent of transmucosal permeation and absorption of an anticonvulsive agent by coadministration of the medicament with a pharmaceutically acceptable co-solvent system comprising an aliphatic alcohol, a glycol, and water, and a biological surfactant. *Choi* at Abstract. *Choi* further discloses that specifically, compositions comprise benzodiazepine (including diazepam), adapted for intranasal administration in a solution, suspension, gel or other useful nasal formulation. *Choi* at 3:64-4:11. *Choi* addresses the need for solvent vehicles in which the solubility of the drug is high and which are non-irritating to the nasal mucosa and intranasal absorption of drugs is enhanced by co-administering a chemical adjuvant or permeation enhancers. *Choi* at 2:14-24. Further, *Choi* claims a method of administering an anticonvulsive agent (including diazepam) to a mammal by administering to the nasal mucosal membranes of the mammal a therapeutically effective amount of a pharmaceutical composition comprising said anticonvulsant and an aqueous vehicle comprising from about 30-60% by volume of an aliphatic alcohol having from 1 to 5 carbon atoms (such as ethanol), from about 30-60% by volume of a specified glycol and 0.1-5% by weight of a biological surfactant and about 10% by volume of water. *Choi* at Claim 1. Further, *Choi* also discloses intranasal composition of 2% diazepam solution in 1% sodium glycocholate (as absorption enhancer), 60% propylene glycol, 30% ethanol, and 10% water in Example 7, which had increased transnasal absorption when tested upon administering 100 µl of this formulation in spray form. *Choi* at 5:65-6:8.

14. WO2009/046444A2 ("*Costantino '444*")

WO2009/046444A2 to Costantino is titled "Formulation for intranasal administration of diazepam." Constantino '444 published on April 09, 2009 and claims priority to four provisional applications 60/977,848 (filed on October 5, 2007), 60/982,680 (filed on October 25, 2007), 60/985,918 (filed on November 6, 2007), and 60/989,370 (filed on November 20, 2007).

Costantino ’444 constitutes prior art under pre-AIA § 102(e)(1). *Costantino ’444* discloses a pharmaceutical formulation for intranasal delivery (as a spray) of diazepam, having formulation delivery vehicle that is an aqueous or non-aqueous solution, and which further comprises one or more mucosal delivery enhancing agent. *Constantino ’444* at 6:19-23. It further discloses that mucosal delivery enhancing agents may be referred to as or include carriers, solvents or co-solvents, excipients, additives, here term “carrier” covers water-containing liquid carrier which include preservatives, antioxidants (include α-tocopherol), buffering agents. *Constantino ’444* at 7:5-18. It further discloses that flavoring agents, coloring agents, may also be present in the composition. *Constantino ’444* at 16:11-15. It further discloses that a wide range of volumes may be delivered with each actuation of a nasal delivery device, ranging from about 25 µl to about 250 µl. *Constantino ’444* at 26:28-29. *Costantino ’444* further discloses that a mucosally effective dose of diazepam within the formulations discloses may be in a range from about 1mg to about 5mg, about 10 mg or about 20 mg, as needed to provide a therapeutic benefit to a subject receiving such dose. *Constantino ’444* at 10:16-19. Additionally, it discloses that pharmaceutical formulation disclosed herein may be capable of providing diazepam solubility of at least about 15 mg/ml. Diazepam solubilities greater than 100 mg/ml are also included in this disclosure. *Constantino ’444* at 10:26-31. The cosolvents may be used in a formulation disclosed herein at a concentration of about 0.1% to about 85% by weight (w/w or w/v) and cosolvents include ethanol. Further, Table 36 represents solution formulation of diazepam (#6) containing: 2.5% diazepam, 25% ethanol, 55% PEG 400, 2.5% Polysorbate 20, 17.5% SWFI. *Constantino ’444* at 17:4-13.

E. The Claims of the ’664 Patent Are Invalid as Obvious

The claims of the ’664 patent are invalid as obvious in light of the prior art discussed above, either alone, in combination, and/or with the knowledge of a POSA. It would have been obvious to a POSA as of the priority date of the ’664 patent to combine the various cited prior art. Moreover,

the prior art renders the claims of the '664 patent obvious because, to the extent a prior art reference may not expressly teach or disclose a component of the system claimed or recited in the claims of the '664 patent, such "missing" component was nevertheless known in the art and adding the well-understood "missing" component would yield predictable results, so that the subject matter of the claim as a whole would have been obvious to a POSA at the time the invention was made. *See generally KSR,* 550 U.S. 398.

The disclosures and teachings that render the claims of the '664 patent obvious are identified in the claim chart attached hereto as Exhibit A. The claim chart provides an element-by-element disclosure of where specifically, in each prior art reference, the relevant claim elements, limitations, or rationale supporting the combination(s) are found. The identifications are not meant to be exhaustive, and the inclusion of certain exemplary combinations in the claim chart does not exclude other combinations. Defendants contend that it would have been obvious to a POSA to combine any of the prior art references to practice any of the claims of the '664 patent. The prior art references are analogous art as each reference is from the same field of endeavor and is reasonably pertinent to the particular problem with which the inventors were involved, or both. To the extent Neurelis contends that an embodiment within a particular prior art reference does not fully disclose all limitations of a claim, Defendants reserve the right to rely on other embodiments in that prior art reference, or other information, to show obviousness.

1. A POSA Would Have Been Motivated to Develop Intranasal Formulations of Diazepam with a Reasonable Expectation of Success

A POSA would have been motivated to combine the teachings of the prior art references discussed above as of the priority date of the '664 patent. A motivation to combine references may be present in the nature of the problem to be solved. It was well-known in the art that the poor water solubility of diazepam created issues developing practical diazepam formulations. Indeed,

the ’664 patent acknowledges the known problem in the art regarding the inability to administer benzodiazepine drugs (e.g., diazepam) due to the limited solubility of the drug compounds as well as the problems associated with other known formulations, including oral, intravenous, and rectal dosage forms. *Supra* Section II.D.2. For example, the ’664 patent states:

> Current formulations of benzodiazepine drugs can be administered orally, rectally, or parenterally. The ability to utilize these and other types of formulations has been significantly limited due, in many cases, to solubility challenges.
>
> The oral route of administration may be considered sub-optimal due to several disadvantages. For example, the amount of time required for an orally administered benzodiazepine drug to reach therapeutically relevant concentrations in blood plasma may be rather long, such as an hour or more. Moreover, as benzodiazepine drugs pass through the liver a significant amount may be metabolized. Thus, it may require large doses to achieve therapeutic plasma levels. Furthermore, due to the nature of seizures and muscle spasms, it can be extremely difficult for either a patient or a care-giver to administer the benzodiazepine drug orally.
>
> Intravenous administration perhaps provides a faster route of administration. However intravenous administration is generally limited to trained health care professionals in tightly controlled clinical settings. Additionally, sterility must be maintained. Furthermore, administering any drug intravenously can be painful and is likely impractical for patients suffering from a phobia of needles.
>
> Suppository compositions of benzodiazepine drugs can have a rapid onset of action. However, the inconvenience of suppositories is an obvious impediment to their being administered by anyone outside a very small group of the patient's intimate acquaintances and the patient's professional medical caretakers.

’664 patent at 1:52-2:13.

Thus, the ’664 patent acknowledges that, due to the limited solubility of benzodiazepine drugs, only certain types of dosage forms were possible, including oral, intravenous, and suppository dosage forms. However, each of these dosage forms suffered from considerable shortcomings: oral dosage forms take considerable time to reach therapeutic drug levels, and suffer from significant liver metabolism; intravenous dosage form administration is primarily limited to trained health care professionals, and maintaining sterility of the dosage form; and suppository dosage forms are inconvenient to administer, given the requirement for rectal administration.

Other prior art references had also discussed these issues, noting that intravenous administration (via injection) was an acceptable method to achieve a rapid and systemic effect of the drug compound (including benzodiazepines), but require sterile syringes, skilled personal capable of initiating the intravenous injection, as well as the pain and irritation associated with administration. Cloyd at ¶0003. In view of these problems, particularly for the treatment of emergency situations such as epileptic seizures, other types of administration were preferred. *Id.* at ¶0004. While one such alternative was rectal diazepam (for the emergency treatment of epileptic seizures), the route of administration was generally considered not acceptable for school-age children and adolescents due to the unwillingness of patients and caregivers to administer the formulation rectally. *Id*. A POSA would have been aware of all of these issues in view of the prior art, and would have sought guidance on other potential dosage forms and routes of administration, especially for the treatment of emergency medical conditions (*e.g*., the use of diazepam for the treatment of emergency seizures).

(a) A POSA Was Motivated to Utilize Gwozdz, Sonne, and/or Li as Primary References for the Development of Diazepam Intranasal Formulations

Gwozdz provides the guidance discussed above, and would have been one of the primary references a POSA would look to in the development of benzodiazepine formulations with improved solubility. Gwozdz specifically states that "[p]harmaceutical solutions of the present invention can be produced by dissolving any difficult to solubilize therapeutic agent (i.e., hydrophobic or lipophilic therapeutic agents) in one or more tocopherols and/or tocotrienols and one or more alcohols and/or glycols as pharmaceutically acceptable solvents." Gwozdz at 7:29-34. In addition, Gwozdz states that the pharmaceutical solutions "are particularly useful in formulations to be administered to mucosal membranes, i.e. the nasal mucosa or lungs of a subject by any suitable means." *Id*. at 9:19-22. As such, Gwozdz was focused on formulations for nasal

administration, which provided an improvement over the known issues with oral, intravenous, and rectal formulations for benzodiazepines, as noted previously. For at least these reasons, a POSA would have looked to Gwozdz as a potential lead reference for guidance on strategies to improve the solubility of benzodiazepine drugs in an effort to develop new dosage forms, including nasally administered formulations.

Similarly, Sonne discloses "[t]he present invention is based on the surprising observation that tocopherols and derivatives thereof are excellent solvents for drugs which are substantially insoluble or sparingly soluble in water, whilst at the same time having a very low irritative potential for mucosal tissues." Sonne at 2:54-58. Sonne also explains that "[i]n one aspect, the present invention thus provides the use of a tocopherol or a derivative thereof as a solvent and/or emulsifier for substantially insoluble and sparingly soluble biologically active agents, especially in the manufacture of pharmaceutical compositions." *Id.* at 2:63-67. Sonne further explains that "[t]ransmucosal delivery is preferred however, and compositions according to the invention may be administered to mucosal membranes…*[n]asal*, rectal and oral cavity administrations are particularly preferred." *Id*. at 3:54-59. Sonne additionally teaches that tocopherols act as solvents "whilst at the same time having a very low irritative potential for mucosal tissues." *Id.* at 2:55-58.

Moreover, Sonne discloses that diazepam was one preferred drug compound, with low water solubility, that could be developed in the tocopherol-based formulations, including exemplary solution and emulsion formulations. *Id*. at 7:32 to 8:10 (Example 1, diazepam "nosedrop"); 8:11-27 (Example 1, diazepam nosedrop); 10:20-67 (Examples 8-10, diazepam emulsions); 11:1-13 (Example 11, solution of diazepam, e.g. as a nosedrop). For at least these reasons, a POSA would have also looked to Sonne as a potential lead reference for guidance on strategies to improve the solubility of benzodiazepine drugs in an effort to develop new dosage

forms, including nasally administered formulations.

Moreover, a POSA would have also viewed Li as a potential primary reference. Li discloses diazepam intranasal formulations administered in rabbits. Li at Abstract. Specifically, Li discloses that an intranasal formulation containing 2% diazepam in a carrier of 30-60% propylene glycol, 30-60% ethanol, 10% water, and 1% sodium glycholate provided a T_{max} of only 2.0 minutes, and a bioavailability of greater than 77% when compared to administration of 0.5% diazepam intravenously. *Id*. at 70-71. Consequently, a POSA would recognize that Li had already begun work to develop intranasal formulations with a quick onset of action (i.e., T_{max} of 2 minutes) that would serve as lead formulations in the effort to develop intranasal diazepam formulations.

For at least these reasons, a POSA would have been motivated by Gwozdz, Sonne, and/or Li to develop formulations with improved solubility for benzodiazepine drugs in an effort to develop new dosage forms, including nasally administered formulations suitable for emergency treatment.

(b) A Motivation and Reasonable Expectation of Success Existed to Combine the Prior Art Teachings to Pursue Carrier Systems Containing α-Tocopherol Compounds and Alcohols, Including Ethanol and Benzyl Alcohol

A POSA would know that there are historic and commercial examples that formulated diazepam with alcohols, including benzyl alcohol and ethanol, along with other solvents. In particular: i) the combination was known from commercial products Diastat and Valium injection (which was known to be used intranasally with the MAD device and known to work for the emergency treatment of seizures; *see* EMS, pp. 54-55, 69-71), both of which included ethanol and benzyl alcohol as excipients. PDR at 1012, 2676. Thus, a POSA was aware of formulations containing diazepam in combination with ethanol and benzyl alcohol in various formulations, including formulations that were administered intranasally.

Additionally, benzyl alcohol and ethanol were known to be readily miscible, meaning that a POSA would not have concerns about the two solvents being incompatible. *See* Rowe at 54, Table III; Merck Index at 189.

Further, Gwozdz expressly teaches using tocopherol in combination with one or more alcohols, i.e., ethanol and benzyl alcohol, stating "[i]n accordance with the present invention, solutions of one or more tocopherols and/or tocotrienols and one or more alcohols and/or glycols are used in the solubilization of hydrophobic or lipophilic therapeutic agents thereby providing increased bioavailability of the therapeutic agent." Gwozdz at 7:3-8.

Similarly, Sonne teaches that "[t]he compositions of the invention may be used directly as solutions of the bioactive agent in the tocopherol solvent. However such solutions are viscous, and the viscosity may be too high for certain applications, for example to achieve a sprayable formulation for nasal application…Viscosity can be reduced by addition of co-solvents such as ethanol…" Sonne at 3:60-67. Sonne discloses that tocopherols can be combined with alcohols, such as ethanol, to form a solvent system for a bioreactive agent (e.g., diazepam). Sonne's disclosure is consistent with what was known by a POSA, namely that alcohols (including ethanol and benzyl alcohol) had been used previously to intranasally administer diazepam (i.e., in the form of Valium®) as disclosed in the Florida EMS manual. *See* Florida EMS at 54-55, 69-71. For at least these reasons, a POSA would be motivated and would at least reasonably expect that alcohols (including ethanol and benzyl alcohol) and tocopherols could be combined to make a nasal formulation of diazepam, as taught by the prior art disclosures of Gwozdz, Sonne, and Li.

(c) A POSA Was Motivated with a Reasonable Expectation of Success to Combine the Teachings of Meezan with Gwozdz, Sonne, and/or Li

Moreover, a POSA was motivated to combine the teachings of Meezan related to alkyl glycosides with the pharmaceutical solutions described in Gwozdz. As explained above, Gwozdz

is directed to pharmaceutical solutions that are designed to improve the solubility of drugs with poor solubility. Gwozdz notes that the pharmaceutical solutions described therein may further incorporate additional "pharmaceutically acceptable additives," including various classes of excipients and "other biocompatible materials." Gwozdz at 10:12-16. Further, Gwozdz describes a number of prior art formulations that contained Vitamin E, a lipophilic drug, and various excipients. *See, e.g.*, *id*. at 1:9-4:10. And Gwozdz identifies certain prior art references that disclosed the use of penetration enhancers in combination with Vitamin E and other excipients.

For example, Gwozdz identified U.S. Patent No. 6,962,691 ("the '691 patent") as a prior art reference that disclosed formulations containing various excipients. *Id*. at 3:32-4:3. The '691 patent described a "medicinal spray composition" containing various ingredients, including "at least one solubilizer" and "at least one permeation enhancer." '691 patent at Abstract. According to the '691 patent, "'[s]olubilizer' refers to components that aid in the dissolution or dispersion of the drug in the formulation," including "Vitamin E." *Id*. at 3:22-26. And "'Permeation Enhancer' refers to a component used to enhance the penetration rate of drugs through the skin, preferably by temporarily diminishing the impermeability of the skin. Permeation enhancers have also been called 'accelerants' and 'sorption promoters.'" *Id*. at 3:10-16.

Accordingly, a POSA would have understood that Gwozdz disclosed intranasal pharmaceutical solution formulations containing diazepam, Vitamin E, and alcohols, where the formulations could contain additional excipients known to be useful in the prior art. Specifically, Gwozdz cited to the '691 patent as an exemplary prior art formulation, where the '691 patent identified penetration enhancers as excipients that may be particularly useful. Thus, a POSA would have also looked to additional references for guidance regarding additive compositions to improve the efficacy of the pharmaceutical solutions of Gwozdz.

Similarly, Sonne discloses that "[t]he compositions of the invention may take any of the conventional pharmaceutical forms known in the art, and may be formulated in conventional manner, optionally with one or more pharmaceutically acceptable carriers or excipients. Thus for example the compositions may take the form of ointments, creams, solutions, salves, emulsions, lotions, liniments, aerosols, sprays, drops, pessaries, suppositories, tablets, capsules or lozenges." Sonne at 6:29-35. Sonne explains that "the present invention provides the use of a tocopherol or a derivative thereof for the preparation of a composition for delivery of a substantially insoluble or sparingly soluble biologically active agent to a human or non-human animal subject," and that the "[t]he formulations according to the invention may be optimized with respect to bioadhesion, sprayability and viscosity, as desired." *Id.* at 6:36-49. In view of Sonne's teachings, a POSA again would have looked to additional references for guidance regarding additive compositions to improve the efficacy of the formulations of Sonne.

Moreover, Li discloses solvent carriers containing propylene glycol, ethanol, and water; however, Li also developed formulations containing sodium glycocholate (SGC). Li at 69. Li explains that "SGC has been one of the most extensively employed bile salts in in vitro and in vivo studies," and that SGC was "known to enhance intranasal absorption while producing minimal irritation and morphological alteration in the nasal mucosa." *Id.* at 70. Indeed, the formulations of Li that further included SGC (in addition to propylene glycol (PG), ethanol (EtOH), and water) reported an increase in bioavailability from 59.1% (for the carrier containing only 60% PG, 30% EtOH, and 10% water) to 77.3% (for the carrier containing 1% SGC, 60% PG, 30% EtOH, and 10%). *Id*. at 71 (Table 1 comparison of IN formula 1b and formula 2c). Thus, Li had already begun to experiment with the addition of absorption enhancers to diazepam intranasal solvent systems and had demonstrated that the inclusion of an absorption enhancer (1% SGC) increased

bioavailability of the intranasal formulation. However, the bioavailability was still only 77.3% of that achieved with diazepam intravenous administration, meaning a POSA would have still been motivated to look for guidance on other absorption enhancers that could further improve the bioavailability of the intranasal diazepam formulations.

Meezan provides further guidance, as it is directed to "therapeutic composition[s] containing a drug enhancing agent useful for increasing the absorption and bioavailability of the drug, while at the same time avoiding various adverse toxic effects of drug." Meezan at ¶ [0004]. While Gwozdz was focused on pharmaceutical solutions developed to improve the solubility of drugs with solubility issues, Meezan presented a distinct approach of utilizing compounds that increase the absorption (i.e., penetration enhancers) and bioavailability of drug compounds. Based on this, a POSA was motivated to apply the teachings of Meezan related to alkyl glycosides to the pharmaceutical solutions of Gwozdz, Sonne, and/or Li.

Additionally, a POSA would have expected surfactants, such as the alkyl glycosides, to increase the bioavailability of intranasal formulations. Sharma teaches that low concentrations of surfactants, including the alkyl glycosides, "are incorporated into the lipid bilayer, forming polar defects in the membrane". Sharma at 500. Sharma further discloses that "[a]lkyl glycosides are nonionic surfactants capable of enhancing glucagon or insulin absorption through the nasal, ocular or pulmonary routes." *Id.* at 501 (citing U.S. Pat. No. 5,661,130 to Meezan et al.). Ahsan proposed that the improvement in bioavailability provided by alkyl glycosides was attributable to either "increasing paracellular movement of drugs through loosened tight junctions, or by increasing transcellular drug movement through endocytic vesicles." Ahsan at 27. Sharma found that "alkylglycosides such as tetradecylmaltoside or dodecyl-maltoside administered with insulin via the nasal, ocular, or inhalational routes have shown significant reductions in blood glucose levels

in rats." Sharma at 501 (citing U.S. Pat. No. 5,661,130 to Meezan et al.). A POSA would be motivated by these teachings to include surfactant-based permeation enhancers such as alkyl glycosides to improve the nasal absorption of drugs, as the prior art established that even large drug molecules (e.g., glucagon and insulin) showed improved bioavailability when nasally administered with alkyl glycosides.

Similarly, Jamieson teaches the use of penetration enhancers in diazepam for intranasal spray formulations. Jamieson at ¶ [0104] ("pharmaceutical compositions comprising the benzodiazepine (e.g., clonazepam, diazepam or lorazepam) of the present invention, for example, for intranasal administration . . . may further comprise one or more components including . . . mucosa penetration enhancing agent").

It was well-known that larger molecules inherently have a more difficult time crossing the cell membrane than smaller molecules. If a permeation enhancer increases penetration for a large molecule, it will be expected to also increase penetration for a small molecule, simply because molecular size can be one of the primary constraints for passing through and between epithelial cells. Meezan teaches that alkyl glycosides will increase the bioavailability of small molecules, and identifies molecules having molecular weight below 1.5 kDaltons as candidates for improved bioavailability. Meezan at ¶ [0130]. Diazepam is a small molecule, having a molecular weight of 284.74. *See* PDR at 2677. Thus, a POSA would understand Meezan's teachings as motivating the use of alkyl glycosides with small molecule compounds, such as benzodiazepines, and, in particular diazepam. Meezan also discloses using alkyl glycosides in non-aqueous systems:

> Additionally, the therapeutic compositions of the invention can consist of a pharmaceutically acceptable carrier. A 'pharmaceutically acceptable carrier' is an aqueous or non-aqueous agent, for example alcoholic or oleaginous, or a mixture thereof, and can contain a surfactant,...a solvent,... Pharmaceutically acceptable carriers are well known in the art and include, for example,...oils such as olive oil or injectable organic esters...A pharmaceutically acceptable carrier can also be

selected from substances such as...benzyl alcohol,....

Meezan at ¶ 74.

Thus, a POSA would have been motivated to increase the solubility of diazepam using the solvent/carrier systems described in Gwozdz, Sonne, and/or Li. Given diazepam's potency, and in recognition of its limited water solubility, a POSA would also have been motivated to pursue strategies to enhance the absorption of diazepam, based on the teachings of Meezan. For at least these reasons, a POSA would be motivated to add Meezan's alkyl glycosides (e.g., dodecyl maltoside) to the solvent systems described in Gwozdz, Sonne, and/or Li.

Indeed, the PTAB previously found that a POSA would have been motivated to combine Gwozdz and Meezan, and rejected Neurelis's arguments to the contrary. IPR2019-00451, Paper 44 at 38-40. Specifically, Neurelis argued that "a POSA would not look to both (1) increase drug solubility and (2) use penetration enhancers to increase the permeability of the nasal mucosa in order to increase the permeation problems associated with intranasal administration" and that "a POSA would not recognize the solutions as necessarily compatible and instead would look to pursue one or the other." *Id*. But the PTAB was "not persuaded that a person of ordinary skill in the art would have been deterred from looking to both increase drug solubility and use penetration enhancers as ways to overcome problems associated with intranasal administration of low-solubility drugs." *Id*. at 39.

The PTAB also rejected Neurelis's arguments that a POSA would not have been motivated to modify Gwozdz's formulations, or to combine tocopherol with ethanol and benzyl alcohol. *Id*. at 40-43. Indeed, the PTAB held that "a person of ordinary skill in the art would have been motivated to use tocopherol along with a combination of alcohols such as ethanol and benzyl alcohol, as disclosed in Gwozdz." *Id*. at 40. And the PTAB held that "a POSA would have been

motivated to look at multiple ways of increasing intranasal delivery of drugs," and therefore would have been motivated to combine the teachings of Gwozdz and Meezan. *Id*. at 45-46.

Finally, a reasonable expectation existed that solution formulations could be successfully developed, and that alkyl glycoside compounds (including dodecyl beta-D-maltoside) could be successfully incorporated into the intranasal solvent formulations of Gwozdz, Sonne, and/or Li. Obviousness requires only a reasonable expectation of success; absolute certainty is not required. *PAR Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1198 (Fed. Cir. 2014) ("The reasonable expectation of success requirement for obviousness does not necessitate an absolute certainty for success.").

Here, Gwozdz states that the pharmaceutical solutions described therein were shown to improve the solubility of diazepam specifically, stating "[a]s a non-limiting example, the solubility of Diazepam at room temperature is less than or equal to 6.67% in 190 proof ethanol[;] [h]owever, combining tocopherol and ethanol has been found to provide solubility of the Diazepam approaching the 10% level." Gwozdz at 7:12-14. And as explained above, Gwozdz and Meezan together would have given a POSA a reasonable expectation of success that incorporating a penetration enhancer (i.e., DDM) would further improve the properties of the formulation. *See, e.g.*, Meezan at ¶ [0004]. Accordingly, a POSA would have had at least a reasonable expectation of success that intranasal solution formulations of diazepam could be made using Vitamin E, alcohols, and DDM.

To be sure, as above, the PTAB rejected Neurelis's arguments that a POSA would not have had a reasonable expectation of success during the '876 patent IPR. Specifically, Neurelis argued that the "theory of obviousness lacks a showing of a reasonable expectation of success in modifying Gwozdz to include ethanol, benzyl alcohol, tocopherol or tocotrienol, and alkyl

glycosides." IPR2019-00451, Paper 44 at 48. The PTAB disagreed, instead holding that a POSA would have reasonably expected this combination of ingredients to result in a successful diazepam spray solution formulation. *Id*. at 48-51.

Sonne discloses that the "[t]he formulations according to the invention may be optimized with respect to bioadhesion, sprayability and viscosity, as desired." Sonne at 6:36-49. Similarly, Li teaches formulations containing absorption enhancers, such as sodium glycocholate (SGC). Li at 69. Meezan teaches "therapeutic composition[s] containing a drug enhancing agent useful for increasing the absorption and bioavailability of the drug, while at the same time avoiding various adverse toxic effects of drug," (Meezan at ¶ [0004]), and that "the alkyl glycoside be nontoxic and nonionic, and that it increases the absorption of a compound when it is administered with the compound via the ocular, nasal, nasolacrimal, inhalation or pulmonary, oral cavity (sublingual or Buccal cell), or CSF delivery route." Meezan at ¶ [0054]. Consequently, Sonne and Li both teach the inclusion of additional compounds, including absorption enhancers, and Meezan teaches that the alkyl glycosides described therein can be incorporated into nasal formulations to increase absorption of the drug compound. For at least these reasons, a POSA would have at least a reasonable expectation that the alkyl glycosides of Meezan could successfully be incorporated into the solutions of Sonne and/or Li.

(d) A POSA Was Motivated with a Reasonable Expectation of Success to Combine the Teachings of Sonne and Li

As discussed above, Li represents one potential primary reference in the development of an intranasal diazepam solution to provide treatment of seizures, including the emergency treatment of seizures. Li is directed to intranasal diazepam formulations, whereby the diazepam was dissolved in a solvent system containing 30% ethanol (EtOH), 60% propylene glycol (PG), 10% water, and plus or minus 1% sodium glycholate (SGC). Li at 67. However, the total

concentration of diazepam in the solvent system was only 2% (i.e., 20 mg/ml). *Id.* at 70 (Table 1), at 71 (Table 2). This concentration is not surprising given that it was known in the art that the solubility of diazepam in propylene glycol was ~1.7% (i.e., 17 mg/ml), and the majority of the Li solution was propylene glycol. Given the limited solubility of diazepam in propylene glycol, and the fact that propylene glycol constitutes 60% of the Li intranasal solution, a POSA would expect that that it would be difficult to achieve diazepam concentrations much higher than the 2% concentration reported in Li, meaning that the amount of diazepam that could be delivered in a single nasal spray was also limited by the concentration limit.

As stated in Sonne, and as generally known in the art, the maximum volume of a nasal spray that can be administered to the nasal passage (due to the physical dimensions of the nasal passage) is about 100-200 μL (0.1-0.2 ml). *See* Sonne at 2:30-33; Wermeling, at 354 (the nasal cavity can retain 100 to 150 μL without causing immediate run-off out the front of the nose or down the naso-pharynx); *see also, e.g.*, Cloyd at ¶ [0006]. Consequently, for the intranasal diazepam solution of Li, with a diazepam contention of 2% (20 mg/ml), the administration of 100-200 μL (0.1-0.2 ml) in a single nasal spray means that it was only possible to deliver at most 2-4 mg of diazepam to the nasal passage of the patient (20 mg/ml x (0.1-0.2 ml) = 2-4 mg diazepam). It was known in the art that the treatment of status epilepticus would often require diazepam doses of 10-20 mg (when administered either rectally or intravenously). In view of this, a POSA would have recognized that, due to the diazepam solubility constraints of propylene glycol, the administration of 2-4 mg of diazepam (via the intranasal diazepam solution of Li) may not be sufficient to treat an active episode of seizure activity, and would have been motivated to find other solvents that could be utilized with diazepam, and would allow for a greater solubility of diazepam within the intranasal solution (allowing for a greater amount of diazepam to be delivered per spray

to the nasal cavity).

Sonne provides this guidance, stating that "the invention concerns the use of a tocopherol or a derivative thereof to prepare compositions having low irritability suitable for administration to mucosal membranes and which may be used efficiently to administer drugs, which are substantially insoluble or only sparingly soluble in water." Sonne at 1:8-13. In fact, Sonne discloses that diazepam was shown to have a solubility of 12% w/w in α-tocopherol. *Id.* at 9:35-60 (Table 1). Assuming a density similar to that of water (i.e., ~1.0 mg/ml), the 12% w/w solubility of diazepam in α-tocopherol corresponds to a solubility of 12% w/v (i.e., 120 mg/ml), which is significantly higher than the solubility of diazepam in propylene glycol (i.e., 20 mg/ml). Thus, a POSA would have been motivated to combine and apply the teachings of Sonne related to the use of α-tocopherol as a solvent for diazepam to Li's intranasal diazepam solution, as a POSA would reasonably expect that doing so would increase the amount of diazepam that can be delivered to the nasal passage within a spray.

(e) A Motivation and Reasonable Expectation of Success Existed to Utilize Alcohols in the Intranasal Spray Formulations of Gwozdz, Sonne, and/or Li, Despite Any Potential Irritation

While there were reports of potential irritation of the nasal mucosa resulting from the inclusion of alcohols (e.g., ethanol and benzyl alcohols) in intranasal formulations (*see, e.g.,* Wermeling IV at 6:31-39), a POSA would not have been dissuaded from their use in an emergency seizure treatment, and would have nonetheless been motivated to include alcohols in the intranasal formulations based on previous formulations that had utilized alcohols. Specifically, as discussed above, Florida EMS used diazepam intravenous solutions—which contained benzyl alcohol and ethanol—for nasal administration of diazepam in connection with the emergency treatment of seizures. *See* Florida EMS at 54-55, 69-71. Further, even if a POSA were to accept that benzyl alcohol or ethanol may cause some irritation to the nasal mucosa, a POSA would view this as an

acceptable design choice in cases of treating acute life-threatening indications, such as epileptic seizures.

2. All Claims of the ’664 Patent Are Invalid as Obvious Over Gwozdz in view of Meezan

As explained above, the ’664 patent is related to the ’546, ’414, and ’786 patents, which are the subject of IPRs filed by Padagis. *Supra* Section V.A. Additionally, a fourth patent related to the ’664, ’546, ’414, and ’786 patents was also the subject of an IPR: U.S. Patent No. 9,763,876 (“the ’876 patent’). In IPR2019-00451, the PTAB found all claims of the ’876 patent unpatentable as obvious over Gwozdz and Meezan, as well as Gwozdz, Meezan, and Cartt 2008, which was affirmed by the Federal Circuit. IPR2019-00451, Paper 44 at 68-69; *see also Neurelis, Inc. v. Aquestive Therapeutics, Inc.,* 2021 WL 4618526, at *1 (Fed. Cir. Oct. 7, 2021). Because the claims of the ’664 patent recite substantially the same subject matter found obvious in the claims of the ’876 patent, all claims of the ’664 patent are invalid as obvious over Gwozdz and Meezan, as well as Gwozdz, Meezan, and Cartt 2008.

Indeed, just like the claims of the ’664 patent, the ’876 patent recited a method of treating a patient by administering “a pharmaceutical solution for nasal administration consisting of a benzodiazepine drug, one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); ethanol and benzyl alcohol in a combined amount from about 10% to about 70% (w/w); and an alkyl glycoside.” ’876 patent at claim 1. Further, dependent claims of the ’876 patent recited that the benzodiazepine drug must be diazepam, which was present in amounts consistent with the amounts claimed in the ’664 patent. *Compare* ’876 patent at claims 6, 28, 30-33 (requiring “about 20% (w/v) of diazepam,” “about 10% (w/v) diazepam,” “diazepam from 5 to 15% (w/v),” “diazepam from 9 to 11% (w/v),” and “diazepam 10% (w/v),” respectively) *with* ’664 patent at claims 1, 3-5 (requiring “about 1 to

about 20 mg of diazepam," "about 10 mg/mL to about 250 mg/mL," "about 20 mg/mL to about 50 mg/mL," and "about 2 mg to about 10 mg," respectively). And other dependent claims of the '876 patent required the excipients (e.g., DDM, tocopherol, etc.) and amounts of those excipients recited in the claims of the '664 patent. *See, e.g.*, '876 patent at claims 1, 7-8, 11-15, 24-33. In fact, claim 28 of the '876 patent recited a solution "consist[ing] of about 56.47% (w/v) vitamin E, about 10.5% (w/v) benzyl alcohol, about 10% (w/v) diazepam, about 0.25%(w/v) dodecyl maltoside, q.s. dehydrated ethanol," and the claimed solution was found to be obvious over Gwozdz and Meezan. IPR2019-00451, Paper 44 at 68-69.

Thus, for the same reasons discussed in the PTAB's final written decision finding all claims of the '876 patent unpatentable as obvious, the claims of the '664 patent would have been obvious in view of Gwozdz and Meezan, as well as Gwozdz, Meezan, and Cartt 2008. To be sure, Padagis recently filed IPRs on the '546, '414, and '786 patents, asserting that the claims of those patents are invalid as obvious over the same prior art references relied on in the '876 patent IPR. *See, e.g.*, IPR2025-00464, Paper 2; IPR2025-00465, Paper 2; IPR2025-00466, Paper 2. And like the '664 patent, the '546, '414, and '786 patents recite subject matter that is essentially the same as the subject matter claimed in the '876 patent. The PTAB's decision to institute Padagis's IPR petitions on the '546, '414, and '786 patents underscores that point, and shows that the claims of the '664 patent would have been obvious as well. *See, e.g.*, IPR2025-00464, Paper 13; IPR2025-00465, Paper 13; IPR2025-00466, Paper 13.

Further, as noted above, Neurelis has focused its arguments in the IPRs primarily on the prior art status of Gwozdz by moving to enter a certificate of correction to the specification of the challenged patents that would purportedly indicate that Gwozdz was the product of a joint research agreement between Particle Sciences, Inc. (the applicant for Gwozdz) and Questcor, Inc. (a

predecessor to Neurelis), and is therefore unavailable as prior art. *See, e.g.*, IPR2025-00464, Paper 29 at 15-25. Padagis disagrees with Neurelis's position, the parties have briefed the issue in the '546, '414, and '786 patent IPRs, and the Board denied Neurelis' motion for leave to file a certificate of correction.[8,9] Additionally, on February 10, 2026, a certificate of correction was issued for the '664 patent, amending the patent specification to note the aforementioned joint research agreement. However, for the same reasons addressed by Padagis in the '546, '414, and '786 patent IPRs, Gwozdz is nonetheless prior art against the '664 patent, and all claims of the '664 patent are invalid as obvious.

(a) Claim 1 of the '664 Patent Would Have Been Obvious

Claim 1 of the '664 patent is invalid as obvious over the combination of Gwozdz and Meezan. As discussed above, claim 1 of the '664 patent is directed to (1) a pharmaceutical solution for nasal administration comprising: (2) about 1 to about 20 mg of diazepam; (3) dissolved in about 45% to about 85% (w/w) of one or more natural or synthetic tocopherols or tocotrienols selected from the group consisting of: α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, α-tocotrienol, β-tocotrienol, γ-tocotrienol, δ-tocotrienol, tocophersolan, any esters thereof and any combinations thereof; (4) about 25% to about 40% (w/w) of one or more alcohols selected from the group consisting of ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, and any combinations thereof; and (5) about 0.01% to about 1% (w/v) of dodecyl β-D-maltoside; (6)

[8] IPR2025-00464; IPR2025-00465; IPR2025-00466, Paper 36 (Feb. 6, 2026).

[9] Defendants question the propriety of the purported "joint research agreement" given the timing of the requests for certificate of correction on the '414, '786, and '664 patents – which came nearly two decades after the earliest claimed priority date of these patents *and* after IPRs were instituted against the '546, '414 and '786 patents. Additionally, even if a joint research agreement was in place, it does not disqualify Gwozdz as prior art, as Neurelis has not established co-ownership of Gwozdz (and U.S. Prov. App. No. 61/040,281 to which Gwozdz claims priority) between Particle Sciences, Inc. and Questcor, Inc. Lupin has requested discovery on the matter, but has yet to receive it. Defendants reserve all rights with respect to the impact of the purported joint research agreement on the arguments contained herein.

wherein the pharmaceutical composition is a solution and contains less than 1% water, and (7) wherein the pharmaceutical composition is in a pharmaceutically-acceptable spray formulation. *Supra* Section II.D.1.

The combination of Gwozdz and Meezan teaches and renders obvious each and every limitation of claim 1 of the '664 patent. As an initial matter, Gwozdz teaches pharmaceutical solution formulations, stating that "the present invention relates to a pharmaceutical solution comprising a therapeutic agent dissolved in one or more natural or synthetic tocopherols or tocotrienols, or any combination thereof and one or more alcohols or glycols, or any combinations thereof." Gwozdz at 4:13-17; '281 provisional at 4:9-13. Additionally, Gwozdz states that the pharmaceutical solutions may be utilized for nasal administration:

> Pharmaceutical solutions of the instant invention are particularly useful in formulations to be administered to mucosal membranes, i.e. the nasal mucosa or lungs of a subject by any suitable means. For many therapeutic agents, administration via the nasal route provides for faster attainment of therapeutic levels of the therapeutic agent systemically. However, many therapeutic agents are so slightly soluble in water that a therapeutically effective amount cannot be dissolved in a volume of aqueous solvent that is amenable to application to a mucosal membrane. Use of a pharmaceutical solution of the present invention, however, provides for improved ability to dissolve lipophilic and lipophilic therapeutic agents, thus providing a useful delivery system for administration of such agents to one or more mucosal membranes, including the nasal mucosal membranes. Such solutions can be administered via, for example, a metered dose inhaler or nebulizer, or in a mist sprayer.

Gwozdz at 9:19-10:2.

Thus, Gwozdz teaches pharmaceutical solutions intended for intranasal administration containing diazepam, one or more natural or synthetic tocopherols or tocotrienols, and one or more alcohols. *Id*. And Gwozdz provides a teaching of the claimed requirement of "a pharmaceutical composition for intranasal administration," and the requirement that "the pharmaceutical composition is in a pharmaceutically-acceptable spray formulation."

Further, regarding the requirement for the inclusion of "about 1 to about 20 mg of diazepam," Gwozdz teaches and renders obvious this limitation. Gwozdz states that the therapeutic agent may include various compounds, including diazepam, stating:

> Exemplary hydrophobic or lipophilic therapeutic agents which can be solubilized in accordance with the present invention include, but are in no way limited to, steroids such as Dexamethasone, 17-beta-Estradiol; benzodiazepenes such as Diazepam, alprazolam, bromazepam, chlordiazepoxidem, clonazepam, estazolam, flunitrazepam, flurazepam, lorazepam, lormetazepam, mexazolam, nitrazepam, oxazepam, temazepam, and triazolam; Rapamycin and analogues; Taxol (paclitaxel) and analogues; Actinomycin D; Prostaglandins (PGEl) ; Vitamin A; Probucol; Batimastat; Statins (HMG-CoA Reductase Inhibitors; Trapidil (and other anti-proliferative Growth Factor Inhibitors); Cytochalasin B; and microtubule binding agents such as epothilones, elutherobin and discodermolide.

Gwozdz at 8:6-18; '281 provisional at 8:5-17.

In fact, Gwozdz identified diazepam (a benzodiazepine) as a preferred therapeutic agent for use in the solubilizing solutions described therein, demonstrating that the solubility of diazepam can be increased from less than or equal to 6.67% (in ethanol) to "approaching the 10% level" (when incorporating tocopherol into the solution). Gwozdz at 7:12-16; '281 provisional at 7:10-17. Diazepam is the only therapeutic agent/drug compound identified in the entirety of Gwozdz as an example of a drug compound that can achieve increased solubility when utilized in the pharmaceutical solutions described therein. Consequently, a POSA would recognize that Gwozdz teaches diazepam as a preferred therapeutic agent, and Gwozdz teaches and renders obvious the claimed requirement for the inclusion of diazepam in the pharmaceutical solution.

Further, Gwozdz states:

> [T]he solubility of Diazepam at room temperature is less than or equal to 6.67% in 190 proof ethanol. However, combining tocopherol and ethanol has been found to provide solubility of the Diazepam approaching the 10% level. By way of illustration, at 70% tocopherol : 30% ethanol (200 proof), Diazepam is soluble to greater than or equal to 8% and at 95% tocopherol : 5% ethanol (200 proof), Diazepam is soluble at greater than or equal to 9%.

Gwozdz at 7:12-19; ’281 provisional at 7:10-17. Consequently, Gwozdz teaches that diazepam can be solubilized at concentrations up to ~8-10%, which appears to be reported in % w/v. A POSA would have understood that ~8-10% w/v correlates to ~80-100 mg/mL (i.e., ~80-100 mg of diazepam per 1 mL of solution).

In addition, a POSA would have understood that the amount of diazepam present in the pharmaceutical solution of Gwozdz can be easily modified by increasing or decreasing the volume of the pharmaceutical solution present in the intranasal spray of Gwozdz. Specifically, Gwozdz teaches and renders obvious that the diazepam may be present in the solution in concentrations of ~8-10% w/v (i.e., ~80-100 mg of diazepam/1 mL of solution). Consequently, the amount of diazepam in the pharmaceutical solution can be increased or decreased by increasing or decreasing the volume of the solution, which is a result-effective variable, and a POSA would have found it to be a routine process to simply adjust the volume of solution to include differing amounts of diazepam, including volumes that provide diazepam doses ranging from about 1 mg to about 20 mg. *See Pfizer Inc. v. Sanofi Pasteur Inc.*, 94 F.4th 1341, 1348 (Fed. Cir. 2024); *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1367-68 (Fed. Cir. 2007); *DyStar Textilfarben GmbH v. C.H. Patrick Co.*, 464 F.3d 1356, 1371 (Fed. Cir. 2006); *see also In re Luck*, 476 F.2d 650, 652-53 (CCPA 1973) (stating use of routine testing to identify optimum amounts lies within the ambit of a POSA). There is nothing in the ’664 patent suggesting that the claimed amount of “about 1 mg to about 20 mg” of diazepam provides surprising or unexpected results, or that the prior art taught away from incorporating such amounts into a pharmaceutical nasal spray formulation.

Moreover, it was well-known in the art that commercial nasal spray products typically deliver 100-200 µL (i.e., 0.1-0.2 mL) per spray.[10] As such, a solution containing ~80-100 mg of

[10] *See, e.g.*, Wermeling DP, et al., Intranasal Delivery of Antiepileptic Medications for Treatment of Seizures, Neurotherapeutics: The Journal of the American Society for Experimental

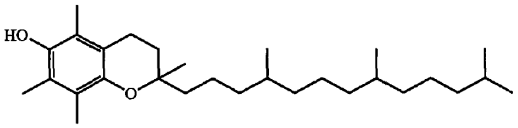
diazepam per mL of solution (as disclosed by Gwozdz), delivering 0.1-0.2 mL (i.e., 100-200 µL) per spray would deliver 8-16 mg of diazepam per spray. A diazepam dose of 8-16 mg of diazepam meets the claimed requirement of "about 1 to about 20 mg of diazepam" required by claim 1 of the '664 patent. For at least these reasons, Gwozdz and Meezan render obvious the claimed requirement for the inclusion of "about 1 to about 20 mg of diazepam."[11]

Regarding the claimed requirements of "about 45% to about 85% (w/w) of one or more natural or synthetic tocopherols or tocotrienols selected from the group consisting of: α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, α-tocotrienol, β-tocotrienol, γ-tocotrienol, δ-tocotrienol, tocophersolan, any esters thereof and any combinations thereof," and "about 25% to about 40% (w/w) of one or more alcohols selected from the group consisting of ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, and any combinations thereof," Gwozdz teaches these limitations. Specifically, Gwozdz states the following:

> The present invention is directed to the use of one or more tocopherols and/or tocotrienols and one or more alcohols and/or glycols as pharmaceutically acceptable solvents for solubilizing therapeutic agents, in particular hydrophobic or lipophilic therapeutic agents.
>
> …
>
> Tocopherols and/or tocotrienols for use in accordance with the present invention include a family of natural and synthetic compounds, also known by the generic names tocols or vitamin E. Alpha-tocopherol is the most abundant and active form of this family of compounds, and it has the following chemical structure:

Neurotherapeutics, Vol. 6, 352-353, April 2009, at p. 357, Table 3 (teaching "100-200 µL delivery volume per spray for commercial products"); and Wermeling, D, Record K, Kelly T, et al., Pharmacokinetics and pharmacodynamics of a new intranasal midazolam formulation in healthy volunteers. Anesth Analg 2006; 103: 344-349, 344 (teaching that "[t]he adult nasal cavity can only receive and retain about 100-150 µL of liquid, requiring the dose of midazolam be solubilized within this volume. A nasal formulation with a concentration of 2.5 mg per 100 µL is necessary to give a single spray per naris.").

[11] To the extent Gwozdz and Meezan do not render the claimed "about 1 to about 20 mg of diazepam" element obvious, it would have been obvious when read further in view of Cartt 2008, as explained below. *Infra* Section V.E.3.



> Other members of this family include beta-, gamma-, and delta-tocopherol, alpha-, beta-, gamma-, and delta-tocotrienols, tocopsoralen, alpha-tocopherol derivatives and/or analogs such as tocopherol acetate, phosphate, succinate, nicotinate and linoleate, as well as isomers thereof and esters thereof. Use of the phrase tocopherol (s) and/or tocotrienol (s) herein is meant to be inclusive of any member of this family alone or in combination. In one embodiment of the present invention the tocopherol (s) and/or tocotrienol (s) employed is alpha-tocopherol.

Gwozdz at 4:29-6:15; '281 provisional at 5:30-6:13.

As shown above, Gwozdz teaches that the pharmaceutical solutions described therein contain a combination of "one or more tocopherols and/or tocotrienols" and "one or more alcohols and/or glycols." Regarding the tocopherols and/or tocotrienols, Gwozdz states that "[i]n one embodiment of the present invention the tocopherol (s) and/or tocotrienol (s) employed is alpha-tocopherol." Gwozdz at 5:26-6:15; '281 provisional at 5:30-6:13. Consequently, Gwozdz teaches and renders obvious the inclusion of alpha-tocopherol, which meets the claimed requirement for the inclusion of "one or more natural or synthetic tocopherols or tocotrienols selected from the group consisting of: α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, α-tocotrienol, β-tocotrienol, γ-tocotrienol, δ-tocotrienol, tocophersolan, any esters thereof and any combinations thereof."

Regarding the "one or more alcohols selected from the group consisting of ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, and any combinations thereof" present in the pharmaceutical solutions mentioned above, Gwozdz states the following:

> Examples of alcohol (s) for use in the present invention include, but are not limited to ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, and any isomers thereof, and any combinations thereof.

Gwozdz at 6:16-19; '281 provisional at 6:14-17.

Gwozdz teaches a small number of exemplary alcohols for use in the pharmaceutical solutions, including ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, and combinations thereof. "When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007). Here, based on the small number of predictable exemplary alcohol compounds taught by Gwozdz, a POSA would have found it to be common sense and *prima facie* obvious to utilize the combination of ethanol and benzyl alcohol as the "one or more alcohols selected from the group consisting of ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, and any combinations thereof" of the Gwozdz pharmaceutical solution.

Regarding the claimed amount of "about 45% to about 85% (w/w)" of "one or more natural or synthetic tocopherols or tocotrienols" and the claimed amount of "about 25% to about 40% (w/w)" of "one or more alcohols," these limitations are disclosed and rendered obvious by Gwozdz. Gwozdz states that "[i]n some embodiments, the tocopherol (s) and/or tocotrienol (s) is in an amount from about 30% to about 99% (w/w) and the alcohol (s) and/or glycol (s) is in an amount from about 1% to about 70% (w/w)." Gwozdz at 4:17-21; '281 provisional at 4:9-17. Thus, Gwozdz expressly discloses ranges of amounts of "one or more natural or synthetic tocopherols or tocotrienols" and "one or more alcohols" that encompass the claimed ranges and amounts.

Further, "where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456 (CCPA 1955); *see also, e.g., In re Geisler*, 116 F.3d 1465, 1469–70 (Fed. Cir. 1997); *In re Woodruff*, 919 F.2d 1575, 1578 (Fed. Cir. 1990). Thus, "[n]ormally, it is to be expected

that a change in temperature, or in concentration, or in both, would be an unpatentable modification." *In re Aller*, 220 F.2d at 456. A patentee may rebut this presumption of obviousness by establishing that (1) the modification results in surprising or unexpected results; (2) the prior art taught away from the modification; or (3) the parameter being modified is not a "result-effective" variable. *E.I. DuPont de Nemours & Company v. Synvina C.V.*, 904 F.3d 996 (Fed. Cir. 2018). A result-effective variable includes any variable that can be modified to produce a different result in the claimed invention. "A recognition in the prior art that a property is affected by the variable is sufficient to find the variable result-effective." *In re Applied Materials, Inc.*, 692 F.3d 1289, 1297 (Fed. Cir. 2012); *see also E.I. DuPont de Nemours & Co.*, 904 F.3d at 1006.

Thus, to the extent Neurelis contends that the amounts and ranges of diazepam, "one or more natural or synthetic tocopherols or tocotrienols," or "one or more alcohols" are not expressly disclosed and rendered obvious by Gwozdz, arriving at the claimed amounts would have been an exercise in routine optimization of a results-effective variable.

Indeed, Gwozdz repeatedly acknowledges this, stating, for example, "[t]he present invention is directed to the use of one or more tocopherols and/or tocotrienols and one or more alcohols and/or glycols as pharmaceutically acceptable solvents for solubilizing therapeutic agents, in particular hydrophobic or lipophilic therapeutic agents." Gwozdz at 4:29-33; '281 provisional at 4:9-17.

Regarding the claimed requirement for the inclusion of "about 0.01% to about 1% (w/v) dodecyl β-D-maltoside," this limitation is taught and rendered obvious by Gwozdz and Meezan. As explained above, Gwozdz discloses that "pharmaceutically acceptable additives," including various classes of excipients and "other biocompatible materials" may be incorporated into the solution formulations. Gwozdz at 10:12-16, 12:12-22; '281 provisional at 10:4-17, 12:16-25. And

Gwozdz explains that it was known in the prior art (e.g., the '691 patent) that a "medicinal spray composition" could contain various ingredients, including "at least one solubilizer" and "at least one permeation enhancer." '691 patent at Abstract; *see also supra* section V.E.1. Further, Meezan teaches alkyl glycoside or saccharide alkyl ester compositions that provide enhanced bioavailability of therapeutic agents, thereby acting as penetration enhancers. In particular, Meezan states the following regarding the alkyl glycoside component:

> Alkyl glycosides of the present invention can include, but are not limited to: alkyl glycosides, such as octyl-, nonyl-, decyl-, undecyl-, dodecyl-, tridecyl-, tetradecyl-, pentadecyl-,hexadecyl-, heptadecyl-, and octadecyl-α- or β-D-maltoside, -glucoside or -sucroside….
>
> …
>
> Similarly, some preferred glycosides include maltose, sucrose, and glucose linked by glycosidic linkage to an alkyl chain of 9, 10, 12, 13, 14, 16, 18, 20, 22, or 24 carbon atoms, e.g., nonyl-, decyl-, dodecyl- and tetradecyl sucroside, glucoside, and maltoside, etc. These compositions are nontoxic, since they are degraded to an alcohol and an oligosaccharide, and amphipathic.

Meezan at ¶¶ [0056]-[0058]. Further, Meezan explicitly identifies alkylmaltosides, including dodecyl-beta-D-maltoside, as a preferred alkyl glycoside compound. *Id*. at ¶¶ [0092], [0156]. Thus, Meezan provides a teaching of the claimed requirement for the inclusion of "dodecyl β-D-maltoside."

Regarding the claimed requirement for the inclusion of dodecyl β-D-maltoside in an amount of "about 0.01% to about 1% (w/v)," Meezan discloses adding alkyl glycosides to formulations in amounts of "about 0.01-20%, preferably about 0.01-5%, more preferably about 0.01-2%, even more preferably 0.01-1%, and most preferably 0.01-0.125% by weight." Meezan at ¶ [0070]. Further, Meezan tested the effects of dodecyl maltoside as an absorption enhancer in amounts of 0.125%, 0.25%, 0.375%, and 0.50%. *Id*. Although the concentrations in Meezan appear to be reported as w/w concentrations, these w/w concentrations nonetheless render obvious the

claimed w/v concentrations. Based on the specific gravities of the three ingredients that constitute nearly all of the Gwozdz solution (i.e., tocopherol, ethanol, and benzyl alcohol (n-dodecyl beta-D-maltoside only constitutes a small percentage),[12] the differences between measurements of "% (w/v)" and "% (w/w)" should be small enough as to be insignificant. Therefore, Meezan discloses n-dodecyl beta-D-maltoside concentrations of 0.125%, 0.25%, 0.375%, and 0.50% (w/w), which a POSA would expect to approximate (and, at a minimum, render obvious) concentrations of ~0.125%, ~0.25%, ~0.375%, and ~0.50% (w/v) n-dodecyl beta-D-maltoside. All of these values fall within the claimed concentration range of "about 0.01% to about 1% (w/v) dodecyl β-D-maltoside," and this claim limitation is taught and rendered obvious by Gwozdz and Meezan.

Further, as explained above, Gwozdz and Meezan disclosed that the diazepam formulations were solutions, meaning that all of the ingredients were fully dissolved. Thus, the claimed requirements that the diazepam is "dissolved in" the one or more natural or synthetic tocopherols, one or more alcohols, and dodecyl β-D-maltoside, as well as the claimed requirement that "the pharmaceutical composition is a solution," is disclosed and rendered obvious by Gwozdz and Meezan. To reiterate, Gwozdz "relates to a pharmaceutical *solution* comprising a therapeutic agent dissolved in one or more natural or synthetic tocopherols or tocotrienols, or any combination thereof and one or more alcohols or glycols, or any combinations thereof." Gwozdz at 4:13-17; '281 provisional at 4:9-13 (emphasis added). Consequently, Gwozdz states that the therapeutic agent (which Gwozdz teaches to preferably be diazepam) is "dissolved in" pharmaceutical solution.

[12] Specific gravities: (i) ethanol at 20ºC = 0.8119-0.8139, and dehydrated ethanol at 20ºC = 0.7904-0.7935 (*see* Rowe, Ex. 1016, p. 14; *see also* Table II on p. 13 and Table III on p. 15); (ii) *d*-alpha tocopherol = 0.95 (*id.* at p. 28; *see also* Table I on p. 27); and (iii) benzyl alcohol at 20ºC = 1.0454 (*id*. at p. 54; *see also* Table I on p. 53).

Further, the addition of "about 0.01% to about 1% (w/v) dodecyl β-D-maltoside" to the diazepam solution, based on the teachings of Gwozdz and Meezan, would not change a POSA's expectation that the formulation would remain in solution.

Finally, regarding the requirement that pharmaceutical composition "contains less than 1% water," Gwozdz and Meezan render obvious this limitation. As a starting point, a POSA would have understood that diazepam had poor solubility in water, which led to difficulties creating formulations suitable for intranasal administration. *Supra* Section V.E.1. Indeed, the '664 patent acknowledges this point, as discussed above. *Id*. Thus, a POSA would have understood as of the priority date of the '664 patent that it would be desirable to make a solution formulation of diazepam that does not contain water, but instead utilizes a non-aqueous solvent system to overcome diazepam's known solubility challenges.

To that end, Gwozdz teaches that "many therapeutic agents are so slightly soluble in water that a therapeutically effective amount cannot be dissolved in a volume of aqueous solvent that is amenable to application to a mucosal membrane. Use of a pharmaceutical solution of the present invention, however, provides for improved ability to dissolve lipophilic and lipophilic therapeutic agents, thus providing a useful delivery system for administration of such agents to one or more mucosal membranes, including the nasal mucosal membranes." Gwozdz at 9:25-34; *see also* Gwozdz at 4:29-33; '281 provisional at 4:25-29 ("The present invention is directed to the use of one or more tocopherols and/or tocotrienols and one or more alcohols and/or glycols as pharmaceutically acceptable solvents for solubilizing therapeutic agents, in particular hydrophobic or lipophilic therapeutic agents"). In other words, Gwozdz disclosed formulations that use non-aqueous solvents (i.e., Vitamin E and alcohols) to minimize or eliminate the amount of water in the formulation, and that are suitable for dissolving lipophilic compounds like diazepam. And

Gwozdz does not discuss or teach that water should be included as an additional component of the pharmaceutical solution. Nor does Meezan disclose or teach that the dodecyl β-d-maltoside should be incorporated in combination with water.

Neurelis addressed a similar issue during the '876 patent IPR. Specifically, Neurelis argued that "[b]ecause independent claim 1 of the '876 patent excludes water from its benzodiazepine solution – through its 'consisting of' language – it does not provide a vehicle for which a surfactant such as alkyl glycoside could work to stabilize or act as a traditional penetration enhancer in a solution." IPR2019-00451, Paper 16 at 38. Thus, according to Neurelis, "a POSA would have been discouraged from selecting the alkyl glycoside as disclosed and used in Meezan '962 to add to the non-aqueous formulations of Gwozdz." *Id.* The PTAB rejected Neurelis's arguments on this point, and found that "Meezan '962 is not limited to water soluble therapeutic drugs and discloses using alkyl glycosides in aqueous or non-aqueous systems." IPR2019-00451, Paper 44 at 45-46. Accordingly, consistent with the PTAB's final written decision on the '876 patent, a POSA would have been motivated to make the claimed intranasal diazepam formulation as a non-aqueous solution (i.e., such that it contains no water, including less than 1% water).

For at least these reasons, Gwozdz and Meezan teach each and every limitation of claim 1 of the '664 patent.

Furthermore, for the reasons discussed above, a motivation existed to combine the teachings of Gwozdz and Meezan, and a POSA would have had a reasonable expectation of success. *Supra* Section V.E.1. Accordingly, claim 1 of the '664 patent is invalid as obvious in view of Gwozdz and Meezan.

(b) Claim 2 of the '664 Patent Would Have Been Obvious

Claim 2 of the '664 patent is dependent from claim 1 and recites:

2. The pharmaceutical composition of claim 1, wherein the one or more natural or synthetic tocopherols or tocotrienols is α-tocopherol.

'664 patent at claim 2.

The previous analysis establishing the obviousness of claim 1 over Gwozdz and Meezan is incorporated herein in its entirety. *Supra* Section V.E.2(a). Further, the additional limitations of dependent claim 2 would have been obvious over Gwozdz and Meezan. As discussed previously, Gwozdz states "[i]n one embodiment of the present invention the tocopherol (s) and/or tocotrienol (s) employed is alpha-tocopherol." Gwozdz at 5:26-6:15; '281 provisional at 5:30-6:13. Thus, Gwozdz teaches and renders obvious the requirement that "the one or more natural or synthetic tocopherols or tocotrienols is α-tocopherol."

For at least these reasons, Gwozdz and Meezan teach each and every limitation of claim 2, a motivation existed to combine the teachings of the prior art, and a reasonable expectation of success existed. Thus, claim 2 is invalid as obvious.

(c) Claims 3-4 of the '664 Patent Would Have Been Obvious

Claims 3-4 of the '664 patent are dependent from claim 1 and recite:

3. The pharmaceutical composition of claim 1, wherein the therapeutically effective amount of the diazepam is present in the pharmaceutical solution at a concentration of about 10 mg/mL to about 250 mg/mL.

4. The pharmaceutical composition of claim 1, wherein the diazepam is present in the pharmaceutical solution at a concentration of about 20 mg/mL to about 50 mg/mL.

The previous analysis establishing the obviousness of claim 1 over Gwozdz and Meezan is incorporated herein in its entirety. *Supra* Section V.E.2(a). Further, the additional limitations of dependent claims 3 and 4 would have been obvious over Gwozdz and Meezan.[13]

[13] To the extent Gwozdz and Meezan do not render the claimed amounts of diazepam obvious, it would have been obvious when read further in view of Cartt 2008, as explained below. *Infra* Section V.E.3.

A POSA knows and understands that the concentration range of claim 3 of "about 10 mg/mL to about 250 mg/mL" is equivalent to about 1-25% (w/v). As discussed in the analysis of claim 1, Gwozdz discloses and teaches diazepam concentrations of ~8-10% w/v. Diazepam concentrations of 8%, 9%, and 10% are all within the range of about 1-25% (w/v), and therefore meet the claimed requirement that "the therapeutically effective amount of the diazepam is present in the pharmaceutical solution at a concentration of about 10 mg/mL to about 250 mg/mL."

A POSA also knows and understands that the claimed range of "about 20 mg/mL to about 50 mg/mL" is equivalent to about 2-5% (w/v). As discussed in the analysis of claim 3, Gwozdz discloses and teaches diazepam concentrations of ~8-10% w/v. Because Gwozdz teaches that diazepam can be solubilized up to concentrations approaching 8-10%, a POSA would find it to be a simple exercise to achieve a lower concentration, such as a concentration falling in the range of about 2-5% (w/v), simply by reducing the amount of diazepam added to the solvent system. Consequently, the concentration of diazepam is merely a result-effective variable, and Gwozdz renders obvious the claimed requirement that "the diazepam is present in the pharmaceutical solution at a concentration of about 20 mg/mL to about 50 mg/mL."

Indeed, the PTAB previously held that "the disclosure of Gwozdz is not limited to administration in one nostril and administration in more than one nostril would allow for a lower concentration of drug in solution being administered in each nostril, which would avoid the potential for diazepam to precipitate out of the solution." IPR2019-00451, Paper 44 at 43. Thus, the PTAB found claims that required "from about 20 mg/mL to about 50 mg/mL" obvious in view of Gwozdz's disclosure of "diazepam solutions of greater than or equal to 8%." *Id*. (citation modified). Accordingly, for the same reasons previously considered and held by the PTAB,

dependent claims 3 and 4 of the ’664 patent would have been obvious in view of Gwozdz and Meezan.

For at least these reasons, Gwozdz and Meezan teach each and every limitation of claims 3-4, a motivation existed to combine the teachings of the prior art, and a reasonable expectation of success existed. Thus, claims 3-4 are invalid as obvious.

(d) Claim 5 of the ’664 Patent Would Have Been Obvious

Claim 5 of the ’664 patent is dependent from claim 1 and recites:

> 5. The pharmaceutical composition of claim 1, wherein the diazepam is about 2 mg to about 10 mg.

The previous analysis establishing the obviousness of claim 1 over Gwozdz and Meezan is incorporated herein in its entirety. *Supra* Section V.E.2(a). Further, the additional limitations of dependent claim 5 would have been obvious over Gwozdz and Meezan for the reasons discussed above with respect to dependent claims 3 and 4. *Supra* Section V.E.2(c).[14]

As discussed previously, the amount of diazepam present in the pharmaceutical solution of Gwozdz can be easily modified by increasing or decreasing the volume of the pharmaceutical solution present in the intranasal spray of Gwozdz. Specifically, Gwozdz teaches and renders obvious that the diazepam may be present in the solution in concentrations of ~8-10% w/v (i.e., ~80-100 mg of diazepam/1 mL of solution). Consequently, the amount of diazepam in the pharmaceutical solution can be increased or decreased by increasing or decreasing the volume of the solution, as the PTAB previously held in the ’986 patent IPR. IPR2019-00451, Paper 44 at 43. Further, the amount of diazepam present in the pharmaceutical solution of Gwozdz is a result-effective variable. “[W]here the general conditions of a claim are disclosed in the prior art, it is

[14] To the extent Gwozdz and Meezan do not render the claimed amount of diazepam obvious, it would have been obvious when read further in view of Cartt 2008, as explained below. *Infra* Section. V.E.3.

not inventive to discover the optimum or workable ranges by routine experimentation." *See In Re Aller,* 220 F.2d 454, 456 (CCPA 1955). A POSA would have found it to be a routine process to simply adjust the volume of solution to include differing amounts of diazepam, including volumes that provide diazepam doses ranging from about 2 mg to about 10 mg.

Moreover, it was well-known in the art that commercial nasal spray products typically deliver 100-200 µL (i.e., 0.1-0.2 mL) per spray.[15] As such, a solution containing ~80-100 mg of diazepam per mL of solution (as disclosed by Gwozdz), delivering 0.1-0.2 mL (i.e., 100-200 µL) per spray would deliver 8-16 mg of diazepam per spray. A diazepam dose of 8-10 mg of diazepam (as encompassed by the range of 8-16 mg) meets the claimed requirement of "about 2 to about 10 mg of diazepam." For at least these reasons, Gwozdz and Meezan render obvious the claimed requirement for the inclusion of "about 2 to about 10 mg of diazepam."

For at least these reasons, Gwozdz and Meezan teach each and every limitation of claim 5, a motivation existed to combine the teachings of the prior art, and a reasonable expectation of success existed. Thus, claim 5 is invalid as obvious.

(e) Claim 6 of the '664 Patent Would Have Been Obvious

Claim 6 of the '664 patent is dependent from claim 1 and recites:

> 6. The pharmaceutical composition of claim 1, wherein the pharmaceutical solution comprises one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof in an amount from about 60% to about 75% (w/w).

[15] *See, e.g.*, 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, at p. 357, Table 3 (teaching "100-200 µL delivery volume per spray for commercial products"); and Wermeling, D, Record K, Kelly T, et al., Pharmacokinetics and pharmacodynamics of a new intranasal midazolam formulation in healthy volunteers. Anesth Analg 2006; 103: 344-349, 344 (teaching that "[t]he adult nasal cavity can only receive and retain about 100-150 µL of liquid, requiring the dose of midazolam be solubilized within this volume. A nasal formulation with a concentration of 2.5 mg per 100 µL is necessary to give a single spray per naris.").

The previous analysis establishing the obviousness of claim 1 over Gwozdz and Meezan is incorporated herein in its entirety. *Supra* Section V.E.2(a). Further, the additional limitations of dependent claim 6 would have been obvious over Gwozdz and Meezan.

As discussed previously, Gwozdz states that "[i]n some embodiments, the tocopherol (s) and/or tocotrienol (s) is in an amount from about 30% to about 99% (w/w) and the alcohol (s) and/or glycol (s) is in an amount from about 1% to about 70% (w/w)." Gwozdz at 4:17-21; '281 provisional at 4:9-17. Thus, as explained above, Gwozdz expressly disclosed and renders obvious the claimed range of "about 60% to about 75% (w/w)." *Supra* Section V.D.1(b).

Additionally, the concentrations of the one or more natural or synthetic tocopherols or tocotrienols, as well as the combined concentration of the ethanol and benzyl alcohol, are result-effective variables, as the concentration directly impacts the solubility of the therapeutic agent (i.e., diazepam) in the pharmaceutical solution. Gwozdz repeatedly acknowledges this, stating, for example, "[t]he present invention is directed to the use of one or more tocopherols and/or tocotrienols and one or more alcohols and/or glycols as pharmaceutically acceptable solvents for solubilizing therapeutic agents, in particular hydrophobic or lipophilic therapeutic agents." Gwozdz at 4:29-33; '281 provisional at 4:25-29. Moreover, Gwozdz discloses the tocopherol in an amount of, e.g., 70-90%. Gwozdz at 7:22-25; '281 provisional at 7:18-26.

"[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *See In Re Aller,* 220 F.2d 454, 456 (CCPA 1955). Consequently, Gwozdz's teaching of the use tocopherol(s) and/or tocotrienol(s) in an amounts from about 30% to about 99% (w/w), and from 70-90% (w/w) renders obvious the claimed requirement for the inclusion of "one or more natural or synthetic tocopherols

or tocotrienols, or any combinations thereof in an amount from about 60% to about 75% (w/w)" as a matter of routine experimentation and optimization.

For at least these reasons, Gwozdz and Meezan teach each and every limitation of claim 6, a motivation existed to combine the teachings of the prior art, and a reasonable expectation of success existed. Thus, claim 6 is invalid as obvious.

(f) Claim 7 of the '664 Patent Would Have Been Obvious

Claim 7 of the '664 patent is dependent from claim 1 and recites:

> 7. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition further comprises at least one additional ingredient selected from the group consisting of stabilizers, coloring agents, pH adjusters, buffering agents, preservatives, wetting agents, flavoring agents and combinations thereof.

The previous analysis establishing the obviousness of claim 1 over Gwozdz and Meezan is incorporated herein in its entirety. *Supra* Section V.E.2(a). Further, the additional limitations of dependent claim 7 would have been obvious over Gwozdz and Meezan.

Indeed, Gwozdz explains that the formulations may contain additional pharmaceutically acceptable excipients, including various excipients recited in claim 7 (i.e., stabilizers, pH adjusters, buffering agents, etc.). Thus, Gwozdz teaches that the pharmaceutical solution may contain "at least one additional ingredient selected from the group consisting of stabilizers, coloring agents, pH adjusters, buffering agents, preservatives, wetting agents, flavoring agents and combinations thereof." Further, given the broad nature of claim 7, which recites a list of well-known and commonly used functional classes of excipients, a POSA would have been motivated to incorporate an excipient that falls within the scope of claim 7 into a diazepam solution with a reasonable expectation of success, or considered it obvious to try.

For at least these reasons, Gwozdz and Meezan teach each and every limitation of claim 7, a motivation existed to combine the teachings of the prior art, and a reasonable expectation of

success existed. Thus, claim 7 is invalid as obvious.

(g) Claims 8-10 of the ’664 Patent Would Have Been Obvious

Claims 8-10 of the ’664 patent are dependent from claim 1 and recite:

> 8. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition is about 25 μL to about 250 μL.
>
> 9. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition is about 50 μL to about 150 μL.
>
> 10. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition is about 100 μL.

The previous analysis establishing the obviousness of claim 1 over Gwozdz and Meezan is incorporated herein in its entirety. *Supra* Section V.E.2(a). Further, the additional limitations of dependent claims 8-10 would have been obvious over Gwozdz and Meezan.

As discussed previously, Gwozdz teaches pharmaceutical solutions formulated as intranasal spray formulations:

> Pharmaceutical solutions of the instant invention are particularly useful in formulations to be administered to mucosal membranes, i.e. the nasal mucosa or lungs of a subject by any suitable means. For many therapeutic agents, administration via the nasal route provides for faster attainment of therapeutic levels of the therapeutic agent systemically. However, many therapeutic agents are so slightly soluble in water that a therapeutically effective amount cannot be dissolved in a volume of aqueous solvent that is amenable to application to a mucosal membrane. Use of a pharmaceutical solution of the present invention, however, provides for improved ability to dissolve lipophilic and lipophilic therapeutic agents, thus providing a useful delivery system for administration of such agents to one or more mucosal membranes, including the nasal mucosal membranes. Such solutions can be administered via, for example, a metered dose inhaler or nebulizer, or in a mist sprayer.

Gwozdz at 9:19-10:2; ’281 provisional at 9:19-10:3. Thus, Gwozdz discloses formulations suitable for nasal administration and explains that the formulation may be administered to the nasal mucosa utilizing known delivery mechanisms, such as nasal mist sprayers. And, as explained above, a

POSA would have been motivated to develop an intranasal formulation of diazepam specifically. *Supra* Section V.E.1.

Moreover, it was well-known in the art that commercial nasal spray products typically deliver low volumes per spray, including from 25-200 µL per spray, as the human nasal cavity can only can only receive and retain about 100-150 µL of liquid.[16] Thus, a POSA motivated to develop an intranasal solution formulation of diazepam would have understood from well-accepted principles and the state of the art that it should have a volume of 25-200 µL, preferably a volume of about 100 µL. *See, e.g., KSR*, 127 S. Ct. at 1741–42 ("As our precedents make clear, however, the analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ"); *Fleming v. Cirrus Design Corp.*, 28 F.4th 1214, 1223 (Fed. Cir. 2022) (Federal Circuit explaining "that it is appropriate to consider the knowledge, creativity, and common sense of a skilled artisan in an obviousness determination"). Consequently, by teaching that the pharmaceutical solution containing diazepam is preferably administered as a nasal spray, a POSA would have understood that Gwozdz discloses that the pharmaceutical solution is administered in a spray volume of 25-200 µL, preferably at about 100 µL.[17]

For at least these reasons, Gwozdz and Meezan teach each and every limitation of claims

[16] *See, e.g.*, 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, at p. 357, Table 3 (teaching "100-200 µL delivery volume per spray for commercial products"); and Wermeling, D, Record K, Kelly T, et al., Pharmacokinetics and pharmacodynamics of a new intranasal midazolam formulation in healthy volunteers. Anesth Analg 2006; 103: 344-349, 344 (teaching that "[t]he adult nasal cavity can only receive and retain about 100-150 µL of liquid, requiring the dose of midazolam be solubilized within this volume. A nasal formulation with a concentration of 2.5 mg per 100 µL is necessary to give a single spray per naris.").

[17] To the extent Gwozdz and Meezan do not render the claimed volumes obvious, they would have been obvious when read further in view of Cartt 2008, as explained below. *Infra* SectionV.E.3.

8-10, a motivation existed to combine the teachings of the prior art, and a reasonable expectation of success existed. Thus, claims 8-10 are invalid as obvious.

(h) Claims 11-14 of the ’664 Patent Would Have Been Obvious

Claims 11-14 of the ’664 patent are dependent from claim 1 and recite:

> 11. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition contains less than 0.5% water.
>
> 12. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition contains less than 0.25% water.
>
> 13. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition contains less than 0.1% water.
>
> 14. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition contains no water.

The previous analysis establishing the obviousness of claim 1 over Gwozdz and Meezan is incorporated herein in its entirety. *Supra* Section V.E.2(a). Further, the additional limitations of dependent claims 11-14 would have been obvious over Gwozdz and Meezan.

Indeed, the only difference between claim 1 and claims 11-14 is the amount of water that the formulation can contain. For the same reasons discussed above, a POSA would have been motivated to make an intranasal solution formation of diazepam that contained as little water as possible, including no water at all. *Supra* Section V.E.2(a). To reiterate, a POSA would have understood that diazepam had poor solubility in water, which led to difficulties creating formulations suitable for intranasal administration. *Supra* Section V.E.1. Indeed, the ’664 patent acknowledges this point, as discussed above. *Id*.

Further, Gwozdz teaches that “many therapeutic agents are so slightly soluble in water that a therapeutically effective amount cannot be dissolved in a volume of aqueous solvent that is amenable to application to a mucosal membrane. Use of a pharmaceutical solution of the present invention, however, provides for improved ability to dissolve lipophilic and lipophilic therapeutic

agents, thus providing a useful delivery system for administration of such agents to one or more mucosal membranes, including the nasal mucosal membranes." Gwozdz at 9:25-34; *see also* Gwozdz at 4:29-33; '281 provisional at 4:25-29 ("The present invention is directed to the use of one or more tocopherols and/or tocotrienols and one or more alcohols and/or glycols as pharmaceutically acceptable solvents for solubilizing therapeutic agents, in particular hydrophobic or lipophilic therapeutic agents"). In other words, Gwozdz disclosed formulations that use non-aqueous solvents (i.e., Vitamin E and alcohols) to minimize the amount of water in the formulation, and that are suitable for dissolving lipophilic compounds like diazepam. And Gwozdz does not discuss or teach that water should be included as an additional component of the pharmaceutical solution. Nor does Meezan disclose or teach that the dodecyl β-d-maltoside should be incorporated in combination with water.

Finally, Neurelis addressed a similar issue during the '876 patent IPR. Specifically, Neurelis argued that "[b]ecause independent claim 1 of the '876 patent excludes water from its benzodiazepine solution – through its 'consisting of' language – it does not provide a vehicle for which a surfactant such as alkyl glycoside could work to stabilize or act as a traditional penetration enhancer in a solution." IPR2019-00451, Paper 16 at 38. Thus, according to Neurelis, "a POSA would have been discouraged from selecting the alkyl glycoside as disclosed and used in Meezan'962 to add to the non-aqueous formulations of Gwozdz." *Id.* The PTAB rejected Neurelis's arguments on this point, and found that "Meezan '962 is not limited to water soluble therapeutic drugs and discloses using alkyl glycosides in aqueous or non-aqueous systems." IPR2019-00451, Paper 44 at 45-46. Accordingly, consistent with the PTAB's final written decision on the '876 patent, a POSA would have been motivated to make the claimed intranasal diazepam

formulation as a non-aqueous solution (i.e., such that it contains no water, including less than 1% water).

For at least these reasons, Gwozdz and Meezan teach each and every limitation of claims 11-14, a motivation existed to combine the teachings of the prior art, and a reasonable expectation of success existed. Thus, claims 11-14 are invalid as obvious.

(i) Claims 15-18 of the '664 Patent Would Have Been Obvious

Claims 15-18 of the '664 patent are dependent from claim 1 and recite:

> 15. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition contains no more than 0.01% of a diazepam impurity.
>
> 16. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition contains no more than 0.01% of a diazepam impurity at 25° C. and 60% relative humidity, 30° C. and 65% relative humidity and 40° C. and 75% relative humidity.
>
> 17. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition maintains a similar average spray content at 25° C. and 60% relative humidity, 30° C. and 65% relative humidity and 40° C. and 75% relative humidity each measured at one month, three months and six months.
>
> 18. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition maintains a similar average spray content uniformity at 25° C. and 60% relative humidity and 40° C. and 75% relative humidity.

The previous analysis establishing the obviousness of claim 1 over Gwozdz and Meezan is incorporated herein in its entirety. *Supra* Section V.E.2(a). Further, the additional limitations of dependent claims 15-18 would have been obvious over Gwozdz and Meezan.

As an initial matter, Federal Circuit precedent establishes that a motivation generally exists to develop and administer the purest form of a drug compound. In *Spectrum Pharmaceuticals, Inc. v. Sandoz Inc*., the Federal Circuit stated that "[a] physician would not likely want to administer a contaminant or a less pure material to a patient if one could use a pure material."

Spectrum Pharmaceuticals, Inc. v. Sandoz Inc., 802 F.3d 1326, 1334-36 (Fed. Cir. 2015). "Thus, there is always in such cases a motivation to aim for obtaining a pure, resolved material." *Id*.

Here, a POSA would have been motivated to make intranasal diazepam solution formulations in view of Gwozdz and Meezan, and would have been motivated to ensure that the formulation was the purest form possible. Thus, a POSA would have been motivated and found it obvious to make a formulation containing no more than 0.01% of a diazepam impurity that maintained a similar average spray content uniformity, including under the claimed conditions. Thus, for at least these reasons, is the claimed stability and spray content uniformity requirements recited in claims 15-18 are invalid as obvious in view of Gwozdz and Meezan.

Further, the claimed stability and spray content uniformity limitations are inherent properties rendered obvious by Gwozdz and Meezan. The mere recitation of an inherent or latent property of an otherwise obvious formulation will not render the formulation patentable. *In re Kao*, 639 F.3d 1057, 1070 (Fed. Cir. 2011); *Santarus, Inc. v. Par Pharmaceutical, Inc.*, 694 F.3d 1344 (Fed. Cir. 2012).

Indeed, the combination of Gwozdz and Meezan renders obvious a formulation meeting each and every limitation of claim 1 of the '664 patent, namely pharmaceutical composition for intranasal administration comprising: about 1 to about 20 mg of diazepam dissolved in about 45% to about 85% (w/w) of one or more natural or synthetic tocopherols or tocotrienols selected from the group consisting of: α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, α-tocotrienol, β-tocotrienol, γ-tocotrienol, δ-tocotrienol, tocophersolan, any esters thereof and any combinations thereof, and about 25% to about 40% (w/w) of one or more alcohols selected from the group consisting of ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, and any combinations thereof, and about 0.01% to about 1% (w/v) of dodecyl β-D-maltoside, wherein the

pharmaceutical composition is a solution and contains less than 1% water, wherein the pharmaceutical composition is in a pharmaceutically-acceptable spray formulation. *Supra* Section V.E.1. Thus, the stability and spray content uniformity requirements of claims 15-18 are rendered obvious by Gwozdz and Meezan as the inherent and latent properties of an otherwise obvious formulation.

For at least these reasons, Gwozdz and Meezan teach and render obvious each and every limitation of claims 15-18, a motivation existed to combine the teachings of the prior art, and a reasonable expectation of success existed. Thus, claims 15-18 are invalid as obvious.

3. All Claims of the ’664 Patent Are Invalid as Obvious Over Gwozdz in view of Meezan and Cartt 2008

The previous analysis established the obviousness of claims 1-18 of the ’664 patent over Gwozdz and Meezan, and is incorporated herein in its entirety. *Supra* Section V.E.2. While the claims of the ’664 patent would have been obvious in view of Gwozdz and Meezan alone, certain claim limitations are expressly disclosed and further rendered obvious in view of Cartt 2008. Cartt 2008 relates to specific intranasal doses of diazepam that were found to be therapeutic, and are provided in addition to the teachings of Gwozdz and Meezan, further supporting the finding of obviousness.

Specifically, Cartt 2008 discloses nasal formulations for the administration of benzodiazepine drug compounds, including diazepam. Cartt 2008 at ¶ [0028]. Thus, a POSA would have been motivated to combine the teachings of Cartt 2008 with Gwozdz and Meezan at least because Cartt 2008 was also related to the development of intranasal diazepam formulations to overcome the known issues with other diazepam formulations.

Further, Cartt 2008 discloses exemplary doses of diazepam to be delivered to patients per dose via nasal administration, stating “[d]iazepam is a benzodiazepine drug having sedative,

tranquilizing and muscle relaxing properties. It is classified as an anxiolytic and skeletal muscle relaxant. It possesses anxiolytic, anticonvulsant, sedative, skeletal muscle relaxant and amnesic properties. The dosage of Diazepam may vary by indication, however it is expected that a therapeutic dose will be in the range of about 1 to about 20, preferably about 2 to about 10 mg per dose…." *Id*. at ¶ [0063]. Thus, to the extent the amounts and concentrations of diazepam recited in the claims of the '664 patent are not obvious in view of Gwozdz and Meezan alone, Cartt 2008 expressly disclosed that the administration of diazepam doses of about 1 mg to about 20 mg, and preferably about 2 mg to about 10 mg was found to be therapeutic. For that additional reason, a POSA would have been motivated to use the claimed amounts and concentrations of diazepam, and would have had a reasonable expectation of success.

Similarly, Cartt 2008 expressly disclosed that "[a]s a nasal formulation, diazepam may be administered in 25 to 250 µl metered sprays. In some preferred embodiments, diazepam is administered in 50 to 150 µl, especially about 100 µl, metered sprays." *Id*. at ¶ [0064]. Thus, to the extent the volumes recited in dependent claims 8-10 of the '664 patent are not obvious in view of Gwozdz and Meezan alone, Cartt 2008 expressly disclosed those limitations and would have motivated a POSA to make an intranasal diazepam formulation in a volume of 25-200 µL, preferably at about 100 µL.

Indeed, the PTAB previously held that the combination of Gwozdz, Meezan, and Cartt 2008 rendered similar limitations obvious in the '876 patent IPR. IPR2019-00451, Paper 44 at 55-56. Specifically, the PTAB held that Cartt 2008 "discloses that diazepam may be present in amounts of about 1 to about 20 mg per dose, and discloses diazepam volumes include 25-250 µl, preferably 50-150 µl, and especially about 100 µl." *Id*. (citation modified). And the PTAB rejected Neurelis's arguments that a POSA would not have been motivated "to combine the formulation of

[Cartt 2008] to the Gwozdz and/or Meezan '962 formulations" with a reasonable expectation of success. *Id*. at 57. Thus, for the same reasons discussed in the PTAB's final written decision on the '876 patent, the combination of Gwozdz, Meezan, and Cartt 2008 renders the claimed amounts and concentrations of diazepam, as well as the claimed volumes, invalid as obvious.

The remainder of the limitations of claims 1-18 of the '664 patent are rendered obvious by the prior art for the reasons previously noted, and the combination of Gwozdz, Meezan, and Cartt 2008 provide a teaching of each and every limitation of claims 1-18. *Supra* Sections V.E.1-2.

4. All Claims of the '664 Patent Are Invalid as Obvious Over Sonne in view of Meezan, Optionally Further in view of Cartt 2008, Cloyd, Florida EMS Manual, and/or USP

All claims of the '664 patent would have been obvious in view of Sonne in view of Meezan, optionally further in view of Cartt 2008, Cloyd, Florida EMS Manual, and/or USP, which are summarized above. *Supra* Section V.D. In view of this additional and alternative combination of prior art references, a POSA would have been motivated to make the claimed intranasal diazepam solution formulations, and would have had a reasonable expectation of success. *Supra* Section V.E.1.

(a) Independent Claim 1 of the '664 Patent Would Have Been Obvious

As explained above, independent claim 1 of the '664 patent recites "a pharmaceutically-acceptable spray formulation" that is a "solution" containing ranges of amounts of diazepam, tocopherols or tocotrienols, alcohols, and DDM. *Supra* Section II.D.1. For the reasons discussed above, a POSA would have been motivated to combine the teachings of Meezan with Sonne to develop an intranasal solution formulation of diazepam. *Supra* SectionV.E.1. Indeed, in view of the known shortcomings associated with rectal and intravenous diazepam formulations, it was known in the art, as evidenced by, *e.g*., the disclosures of Sonne, Cloyd, Cartt 2008, and Florida

EMS Manual, that the art had begun to explore the development of intranasal diazepam formulations for the treatment of seizures, including emergency treatment of seizures. Thus, a POSA would have been motivated to develop intranasal diazepam spray formulations to overcome issues and problems associated with existing formulations of diazepam. *See, e.g.*, Sonne at 7:25-30; Cloyd at ¶¶ [0003]-[0012]; Cartt 2008 at ¶¶ [0003]-[0008]; Florida EMS Manual at 54.

Further, a POSA would have been motivated to make a solution formulation containing the ranges and amounts of diazepam, tocopherols or tocotrienols, alcohols, and DDM recited in claim 1 of the '664 patent. For example, regarding the claimed requirement of "a pharmaceutical composition for intranasal administration …wherein the pharmaceutical composition is a solution," Sonne discloses solutions containing bioreactive agents, stating that "[t]he compositions of the invention may be used directly as solutions of the bioactive agent in the tocopherol solvent." Sonne at 3:60-61. Sonne further explains that "[n]asal, rectal and oral cavity administrations are particularly preferred" for the formulations, establishing that the Sonne formulations can be administered intranasally. In fact, Sonne specifically disclosed examples of "[a] solution of diazepam, eg. as nosedrop" containing diazepam in combination with α-Tocopherol (but with no water). *Id*. at 11:1-13. Consequently, Sonne provides a teaching of the claimed requirement of "a pharmaceutical composition for intranasal administration…wherein the pharmaceutical composition is a solution."

Regarding the requirement for the inclusion of "about 1 to about 20 mg of diazepam," Sonne discloses this limitation. Specifically, Fig. 1 of Sonne illustrates the intranasal administration of 2.5 mg diazepam. *Id*. at 7:15-18. Additionally, Examples 1, 22, and 23 of Sonne report the administration of amounts of diazepam including 2 mg, 2.5 mg, and 10 mg. *Id.* at 7:32-58; 13:56 to 14:13; and 14:63-67.

Regarding the claimed requirement for the inclusion of "about 45% to about 85% (w/w) of one or more natural or synthetic tocopherols or tocotrienols selected from the group consisting of: α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, α-tocotrienol, β-tocotrienol, γ-tocotrienol, δ-tocotrienol, tocophersolan, any esters thereof and any combinations thereof," this limitation is disclosed by Sonne. Specifically, Sonne disclosed "the use of a tocopherol or a derivative thereof as a solvent … for substantially insoluble and sparingly soluble biologically active agents, especially in the manufacture of pharmaceutical compositions" suitable for intranasal administration. *Id*. at Abstract. According to Sonne, the formulations could contain "1 to 95% (w/w) of the tocopherol or derivative thereof, preferably 20 to 95% (w/w), most preferably 35 to 80% (w/w)." *Id*. at 5:58-61. Moreover, Sonne discloses at least one exemplary solution formulation containing 10 g of α-tocopherol in a total solution weight of 25 g, equating to an α-tocopherol concentration of 40% w/w. *Id*. at 11:1-13 (Example 11).

Claim 1 of the '664 patent further requires the inclusion of "about 25% to about 40% (w/w) of one or more alcohols selected from the group consisting of ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, and any combinations thereof." Sonne discloses and renders obvious this limitation. Specifically, Sonne explained that "[t]he formulations according to the invention may be optimized with respect to bioadhesion, sprayability and viscosity, as desired" by incorporating "co-solvents" like "alcohols such as ethanol … or benzyl alcohol." *Id*. at 6:47-53. Additionally, when disclosing that the "compositions of the invention may be used directly as solutions of the bioactive agent in the tocopherol solvent," Sonne discloses that the viscosity of such a solution "may be too high for certain applications, for example to achieve a sprayable formulation for nasal application," and, because of that, "[v]iscosity can be reduced by addition of co-solvents such as ethanol…" *Id*. at 3:60-67. Consequently, based on the disclosure of Sonne, a

POSA would have bene motivated to add ethanol as a co-solvent to the α-tocopherol solution, and would reasonably expect that doing so would reduce the viscosity and allow for spray administration.

As to the specific inclusion of "about 25% to about 40% (w/w)" of the one or more alcohols, Example 11 of Sonne, directed to a solution of diazepam, incorporated 55% w/w of a co-solvent, namely triacetin (13.75 g of triacetin within a total solution weight of 25 g). *Id*. at 11:1-13. Moreover, the use of a co-solvent within the α-tocopherol solution is merely a result-effective variable, as the amount of co-solvent (e.g., ethanol) would directly impact the viscosity of the solution, as suggested by Sonne. "Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *See In Re Aller,* 220 F.2d 454, 456 (CCPA 1955) ("[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation."). As such, it was merely a matter of routine experimentation and optimization to utilize the co-solvent, including ethanol, in an amount of "about 25% to about 40% (w/w)." For at least these reasons, Sonne teaches and renders obvious the inclusion of "about 25% to about 40% (w/w) of one or more alcohols selected from the group consisting of ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, and any combinations thereof."

With regard to the requirement that "the pharmaceutical composition is a solution and contains less than 1% water, wherein the pharmaceutical composition is in a pharmaceutically-acceptable spray formulation" Sonne disclose these limitations. As noted, Sonne discloses that "[t]he compositions of the invention may be used directly as solutions of the bioactive agent in the tocopherol solvent," (*Id*. at 3:60-61) indicating that the solution does not include any water.

Further, Example 11 of Sonne, directed to "[a] solution of diazepam, eg. as nosedrop," does not include any water. Sonne at 11:1-13. Consequently, Sonne discloses the requirement that the solution "contains less than 1% water."

Further, Sonne discloses that the compositions are preferably administered via the "[n]asal" route, and that the compositions may take the form of "sprays." *Id*. at 3:58-59, 6:34-35. Consequently, Sonne discloses the claimed requirement that "the pharmaceutical composition is a solution and contains less than 1% water, wherein the pharmaceutical composition is in a pharmaceutically-acceptable spray formulation."

Finally, for the reasons already discussed above, a POSA would have been motivated to include " about 0.01% to about 1% (w/v) of dodecyl β-D-maltoside" in view of Meezan. *Supra* Section V.E.1. To reiterate, Meezan disclosed the use of alkyl glycosides in amounts of about 0.01-20%, preferably about 0.01-5%, more preferably about 0.01-2%, even more preferably 0.01-1%, and most preferably 0.01-0.125% by weight. Meezan at ¶ [0070]. Further, Meezan tested the effects of DDM specifically as an absorption enhancer in amounts of 0.125%, 0.25%, 0.375%, and 0.50%. *Id*. at ¶¶ [0146]-[0162].

A POSA also would have been motivated to make the claimed intranasal diazepam solution formulations when Sonne and Meezan are read further in view of Cloyd. Cloyd disclosed "benzodiazepine ***solutions*** that are sufficiently stable to prevent the active ingredient from precipitating during the time required for delivery across the nasal mucosal membrane." Cloyd at ¶ [0002] (emphasis added). According to Cloyd, the solution formulations contained "at least about 10 mg/ml of the benzodiazepine" where "the intranasal volume delivered to an individual in need of a benzodiazepine is … between about 50 µl to about 150 µl per nostril." *Id*. at ¶¶ [0055]-[0056].

Thus, Cloyd disclosed intranasal solution formulations containing a range of doses of diazepam, including about 10 mg of diazepam.

However, Cloyd's formulations relied on a supersaturated solution of diazepam in water and glycofurol. *See, e.g.*, *id*. at ¶ [0013]. A POSA would have understood that Cloyd's water-based (i.e., aqueous) formulations would have inherent drawbacks both because of diazepam's known solubility challenges in water and because supersaturated solutions were known to naturally convert into suspensions (i.e., where the drug is initially fully dissolved in solution, but later crashes out of solution in a solid phase). Indeed, Cloyd explained that:

> A major difficulty presented by the nasal route is the small size of the nasal cavity, such that total dosing volume (which may involve administration through both nostrils) should not generally exceed 150 µl per nostril. Assuming that a DZP dose of 10 mg would be required in adults, a highly concentrated diazepam solution is required. Since DZP's solubility in water (˜0.05 mg/ml) is very low and the dosage requirement is equal to or greater than 0.2 mg/kg, it is difficult to formulate a 100% aqueous solution of DZP for nasal use.

Id. at ¶ [0082]. Thus, consistent with a POSA's knowledge of the state of the art of diazepam solution formulations, Cloyd expressly disclosed that it was difficult to prepare aqueous solutions of diazepam with a 10 mg dose in the low volumes necessary for nasal administration. Accordingly, a POSA would have been motivated to investigate alternative, non-aqueous solution formulations of diazepam that would be better suited for a lipophilic compound like diazepam.

To that end, Sonne disclosed "the use of a tocopherol or a derivative thereof as a solvent … for substantially insoluble and sparingly soluble biologically active agents, especially in the manufacture of pharmaceutical compositions" suitable for intranasal administration. Sonne at Abstract. And Sonne specifically disclosed examples of "diazepam nosedrop" formulations containing diazepam and various excipients, including Vitamin E and α-Tocopherol. *Id*. at 7:32-8:27, 10:20-11:13. According to Sonne, the formulations could contain "1 to 95% (w/w) of the

tocopherol or derivative thereof, preferably 20 to 95% (w/w), most preferably 35 to 80% (w/w)." *Id*. at 5:58-61. Like Cloyd, Sonne disclosed examples of intranasal formulations containing various amounts of diazepam, including an example containing 10 mg of diazepam. *Id*. at 14:63-67.

Sonne also explained that "[t]he formulations according to the invention may be optimized with respect to bioadhesion, sprayability and viscosity, as desired" by incorporating "co-solvents" like "alcohols such as ethanol … or benzyl alcohol." *Id*. at 6:47-53. Thus, a POSA would have been motivated to formulate diazepam in a non-aqueous solution formulation containing Vitamin E and co-solvents (i.e., ethanol and benzyl alcohol) in view of Sonne and Cloyd.

Further, a POSA would have been motivated by Cartt 2008, Meezan, and/or USP to use the claimed amounts of diazepam, tocopherols or tocotrienols, alcohols, and DDM as excipients. For example, USP disclosed that Vitamin E and tocopherols were useful for pharmaceutical formulations. *See, e.g.*, USP at 1631.

Further, Cartt 2008 expressly disclosed intranasal formulations of diazepam with the goal of solving the same issues described in the art generally. Cartt 2008 at Abstract. Cartt 2008 disclosed that non-aqueous formulations containing "about 1 to about 20, preferably about 2 to about 10 mg per dose" of diazepam may be desirable for the reasons discussed above. *See, e.g.*, *id*. at ¶¶ [0021]-[0023], [0063]. And Cartt 2008 disclosed that "n-dodecyl β-D-maltoside" may be used as an excipient in the intranasal diazepam formulations. *See, e.g.*, *id*. at ¶ [0129].

Accordingly, a POSA would have been motivated to make a pharmaceutically acceptable spray formulation of diazepam in the form of a solution containing the amounts of diazepam, tocopherols or tocotrienols, alcohols, and DDM recited in claim 1 of the '664 patent in view of Sonne and Meezan, optionally further in view of Cartt 2008, Cloyd, USP, and/or Florida EMS

Manual. A POSA also would have had a reasonable expectation of success in view of those references for the reasons discussed above.

(b) The Dependent Claims of the '664 Patent Would Have Been Obvious

For the reasons explained above, dependent claims 2-18 would have been obvious over Sonne in view of Meezan, optionally further in view of Cartt 2008, Cloyd, Florida EMS Manual, and/or USP. *Supra* Section V.E.4(a). To be sure, the prior art disclosed each of the limitations of dependent claims 2-18 of the '664 patent, expressly or inherently, as discussed below.

Dependent claims 2 and 6 require that "the one or more natural or synthetic tocopherols or tocotrienols is α-tocopherol" (claim 2) and "the pharmaceutical solution comprises one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof in an amount from about 60% to about 75% (w/w)" (claim 6). As explained above, Sonne expressly disclosed that diazepam could be formulated for intranasal administration as a solution containing α-tocopherol, including in an amount ranging from about 40% to about 99.99% (w/w). *See, e.g.*, Sonne at 5:58-61, 7:32-8:27, 10:20-11:13. Accordingly, for the reasons discussed above, a POSA would have been motivated to develop the Sonne solution formulation containing α-tocopherol, and it would have been a matter of routine experimentation and optimization to utilize the tocopherol in an amount ranging from about 60-75% (w/w), and would have had a reasonable expectation of success. *See In Re Aller,* 220 F.2d 454, 456 (CCPA 1955) ("[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.").

Dependent claims 3-5 require the solution formulation to contain "about 10 mg/mL to about 250 mg/mL," "about 20 mg/mL to about 50 mg/mL," or "about 2 mg to about 10 mg" of diazepam. '664 patent at claims 3-5. As explained above, Sonne, Cloyd, and Cartt 2008 all

disclosed intranasal formulations containing the concentrations and amounts of diazepam recited in claims 3-5 of the '664 patent. *See, e.g.*, Sonne at 7:23-8:46, 14:63-15:33; Cloyd at ¶¶ [0013], [0055], [0103]-[0104]; Cartt 2008 at ¶¶ [0034], [0047], [0063]. Accordingly, for the reasons discussed above, a POSA would have been motivated to use the claimed concentrations and amounts of diazepam, and would have had a reasonable expectation of success.

Dependent claim 7 of the '664 patent recites that the formulation may contain "at least one additional ingredient selected from the group consisting of stabilizers, coloring agents, pH adjusters, buffering agents, preservatives, wetting agents, flavoring agents and combinations thereof." '664 patent at claim 7. As explained above, a POSA would have been motivated to include at least one of these types of excipients in an intranasal diazepam solution formulation. *Supra* Section V.E.4(a). Indeed, a POSA would have recognized that the categories of functional excipients recited in dependent claim 7 were routinely included in pharmaceutical formulations, as disclosed by Sonne, Meezan, Cloyd, and other references. *See, e.g.*, Sonne at 7:4-9, claim 10; Cloyd at ¶ [0066]; Meezan at ¶ [0074].

Indeed, Sonne discloses that "[t]he formulations according to the invention may be optimized with respect to bioadhesion, sprayability and viscosity, as desired." Sonne at 6:47-49. Additionally, Sonne states that "[t]o ensure that the formulations have a reasonable shelf-life it may be desirable to include preservatives such as benzalkonium chloride, sodium edetate, sorbic acid, potassium sorbate, phenoxyethanol, phenetanol, parabens or others known in the art. Addition of odour- or taste-masking compounds can also be desirable." Sonne at 7:4-9. Accordingly, for the reasons discussed above, a POSA would have been motivated to include an additional excipient from the list recited in dependent claim 7, and would have had a reasonable expectation of success.

Dependent claims 8-10 require the claimed diazepam formulation to be formulated in certain volumes, including at "about 100 μL." '664 patent at claims 8-10. As explained above, a POSA would have understood that intranasal administration of a pharmaceutical formulation necessarily requires the claimed volumes, and would have been motivated to use a volume of "about 100 μL" specifically. *See, e.g.*, Sonne at 7:25-30; Cloyd at ¶¶ [0055]-[0056]. Accordingly, for the reasons discussed above, a POSA would have been motivated to formulate an intranasal diazepam formulation in a volume of "about 100 μL," and would have had a reasonable expectation of success.

Dependent claims 11-14 require the claimed diazepam solution formulations to have limited amounts of water, including "no water" as required by claim 14. '664 patent at claims 11-14. As explained above, Sonne discloses that "[t]he compositions of the invention may be used directly as solutions of the bioactive agent in the tocopherol solvent," (Sonne at 3:60-61) indicating that the solution does not include any water. Further, Example 11 of Sonne, directed to "[a] solution of diazepam, eg. as nosedrop," does not include any water. Sonne at 11:1-13. While the prior art did not expressly disclose diazepam solution formulations containing the amounts of water recited in the claims of the '664 patent, a POSA would have been motivated to make non-aqueous formulations of diazepam (i.e., formulations without water) in view of the prior art. *Supra* Section V.E.4(a). Indeed, Cloyd acknowledged that there was an inherent difficulty with formulating diazepam (a lipophilic compound) in water-based formulations, particularly in the low-volume amounts required for intranasal administration. *See, e.g.*, Cloyd at ¶ [0082]. Accordingly, for the reasons discussed above, a POSA would have been motivated to develop a non-aqueous solution formulation of diazepam described in Sonne, suitable for nasal administration and would have had a reasonable expectation of success.

Finally, dependent claims 15-18 require the claimed diazepam formulation to contain no more than certain amounts of "a diazepam impurity" or to "maintain[] a similar average spray content" at certain temperatures, humidities, and times. '664 patent at claims 15-18. For the reasons explained above, a POSA would understand that these limitations are inherent properties of the otherwise obvious diazepam solution formulations. *Supra* Section V.E.2(i). Thus, dependent claims 15-18 of the '664 patent are obvious because they recite inherent properties, and are inherently disclosed in the prior art. *In re Kao*, 639 F.3d at 1070; *Santarus*, 694 F.3d at 1344.

Accordingly, for the reasons discussed above, all claims of the '664 patent would have been obvious over Sonne and Meezan, optionally further in view of Cartt 2008, Cloyd, Florida EMS Manual, and/or USP.

5. All Claims of the '664 Patent Are Invalid as Obvious over Li in view of Sonne and Meezan, Optionally further in view of Cartt 2008, Florida EMS Manual, and/or USP

All claims of the '664 patent would have been obvious over Li in view of Sonne and Meezan, optionally further in view of Cartt 2008, Florida EMS Manual, and/or USP, which are summarized above. *Supra* Section V.D. The previous analysis establishing the obviousness of all claims of the '664 patent over Sonne in view of Meezan, optionally further in view of Cartt 2008, Florida EMS Manual, and/or USP is incorporated herein in its entirety. In view of this additional and alternative combination of prior art references, a POSA would have been motivated to make the claimed intranasal diazepam solution formulations, and would have had a reasonable expectation of success, for the all the reasons noted above. *Supra* Section V.E.1.

(a) Independent Claim 1 of the '664 Patent Would Have Been Obvious

As explained above, independent claim 1 of the '664 patent recites "a pharmaceutically-acceptable spray formulation" that is a "solution" containing ranges of amounts of diazepam,

tocopherols or tocotrienols, alcohols, and DDM. *Supra* Section II.D.1. For the reasons discussed above, a POSA would have been motivated to combine the teachings of Meezan with Li and Sonne to develop an intranasal solution formulation of diazepam. *Supra* Section V.E.1. Indeed, in view of the known shortcomings associated with rectal and intravenous diazepam formulations, it was known in the art, as evidenced by, *e.g.*, the disclosures of Sonne, Cartt 2008, and Florida EMS Manual, that the art had begun to explore the development of intranasal diazepam formulations for the treatment of seizures, including emergency treatment of seizures. Consequently, a POSA would have been motivated to develop intranasal diazepam spray formulations to overcome issues and problems associated with existing formulations of diazepam. *See, e.g.*, Sonne at 7:25-30; Cartt 2008 at ¶¶ [0003]-[0008]; Florida EMS Manual at 54.

Further, a POSA would have been motivated to make a solution formulation containing the ranges and amounts of diazepam, tocopherols or tocotrienols, alcohols, and DDM recited in claim 1 of the '664 patent. For example, regarding the claimed requirement of "a pharmaceutical composition for intranasal administration…wherein the pharmaceutical composition is a solution," Li discloses intranasal diazepam solutions, stating that that "[f]or IN application, the test formulations were prepared in 30% EtOH—60% PG—10% water, plus or minus 1% SGC. All the nasal formulations were prepared just prior to the experiment by dissolving DZ (20 mg), CZ (4.2 mg), or MCA (100 mg) in 1 ml of the aforementioned vehicles." Li at 67. Li explains that the diazepam ("DZ") was "dissolved" in the vehicle, indicating that the resulting formulation was a solution. Additionally, Li states that the formulations were developed for intranasal ("IN") application. Thus, Li discloses "a pharmaceutical composition for intranasal administration…wherein the pharmaceutical composition is a solution."

Regarding the requirement for the inclusion of "about 1 to about 20 mg of diazepam," Li discloses this limitation. Specifically, as noted, Li states that 20 mg of diazepam was dissolved in 1 ml of the carrier. *Id*. at 67. Li further states that the resulting intranasal solutions provided a diazepam concentration of 20 mg/ml. *Id.* at p. 67, 70 (Table 1, reporting the 2% diazepam solution). Consequently, the formulation described by Li includes "about 20 mg of diazepam."

Further, as discussed in Section V.E.1, the maximum volume of a nasal spray that can be administered to the nasal passage (due to the physical dimensions of the nasal passage) is about 100-200 µL (0.1-0.2 ml). *See, e.g.*, Sonne at 2:30-33; Wermeling at 354 (the nasal cavity can retain 100 to 150 µL without causing immediate run-off out the front of the nose or down the naso-pharynx). Even accounting for the volume of a single spray of 0.1-0.2 ml, a single spray of the Li solution containing 20 mg/ml would include 2-4 mg of diazepam, which meets the claimed requirement of "about 2 to about 20 mg of diazepam."

Additionally, Fig. 1 of Sonne illustrates the intranasal administration of 2.5 mg diazepam (Sonne at 7:15-18), and Examples 1, 22, and 23 of Sonne report the administration of amounts of diazepam including 2 mg, 2.5 mg, and 10 mg. Sonne at 7:32-58; 13:56 to 14:13; and 14:63-67. Thus, Li and Sonne both disclose the inclusion of "about 2 to about 20 mg of diazepam."

Regarding the claimed requirement for the inclusion of "about 45% to about 85% (w/w) of one or more natural or synthetic tocopherols or tocotrienols selected from the group consisting of: α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, α-tocotrienol, β-tocotrienol, γ-tocotrienol, δ-tocotrienol, tocophersolan, any esters thereof and any combinations thereof," this limitation is disclosed and rendered obvious by Li and Sonne. As discussed, Li discloses the development of a diazepam intranasal solution, whereby the carrier vehicle contained "30% EtOH—60% PG—10% water, plus or minus 1% SGC," (Li, p. 67), which represents 60% propylene glycol (PG), 30%

ethanol (EtOH), and 10% water, plus/minus 1% sodium glycholate (SGC).[18] However, as discussed in Section V.E.1, it was known in the art that the solubility of diazepam in propylene glycol was ~1.7% (i.e., 17 mg/ml),[19] and the majority of the Li solution was propylene glycol. Given the limited solubility of diazepam in propylene glycol, and the fact that propylene glycol constitutes 60% of the Li intranasal solution, a POSA would expect that that it would be difficult to achieve diazepam concentrations much higher than the 2% concentration reported in Li, meaning that the amount of diazepam that could be delivered in a single nasal spray was also limited by the concentration limit.

Sonne provides a solution to the limited diazepam solubility of propylene glycol, disclosing that diazepam was shown to have a solubility of 12% w/w in α-tocopherol. *Id*. at 9:35-60 (Table 1). Assuming a density similar to that of water (i.e., ~1.0 mg/ml), the 12% w/w solubility of diazepam in α-tocopherol corresponds to a solubility of 12% w/v (i.e., 120 mg/ml), which is significantly higher than the solubility of diazepam in propylene glycol (i.e., 20 mg/ml), and would allow for more diazepam to be solubilized and ultimately delivered to the nasal passage in a single spray. Sonne also discloses that "the invention concerns the use of a tocopherol or a derivative thereof to prepare compositions having low irritability suitable for administration to mucosal membranes and which may be used efficiently to administer drugs, which are substantially insoluble or only sparingly soluble in water." Sonne at 1:8-13. Thus, Sonne teaches that the α-

[18] A POSA would have understood that the formulations additionally containing 1% SGC would require that the percentages of the other three components (propylene glycol, ethanol, and water) would need to be adjusted to account for the additional 1% of SGC; however, the amount of SGC is small and does not materially impact the analysis related to the amounts and concentrations disclosed by Li.

[19] Bechgaard E; Gizurarson S; Hjortkjær RK. "Solubilization of Various Benzodiazepines for Intranasal Administration, a Pilot Study." Pharmaceutical Development and Technology 2(3):293–296 (1997) (*see* p. 294, Table 1, reporting diazepam solubility in propyleneglycol of 17 mg/ml).

tocopherol solvent could be used to solubilize diazepam to a much greater extent than propylene glycol, and that α-tocopherol was shown to have low irritability and was suitable for the administration of poorly water soluble drugs (such as diazepam) to mucosal membranes.

For at least these reasons, a POSA would have been motivated to replace the 60% propylene glycol present in the Li intranasal diazepam solution with the α-tocopherol solvent taught by Sonne, and would have a reasonable expectation of success. Utilizing α-tocopherol in the same amount as was present for propylene glycol (60%) meets the claimed requirement for the inclusion of "about 45% to about 85% (w/w)" of the one or more claimed tocopherols. Additionally, Sonne also discloses that the formulations could contain "1 to 95% (w/w) of the tocopherol or derivative thereof, preferably 20 to 95% (w/w), most preferably 35 to 80% (w/w)." *Id*. at 5:58-61. Moreover, Sonne discloses at least one exemplary solution formulation containing 10 g of α-tocopherol in a total solution weight of 25 g, equating to an α-tocopherol concentration of 40% w/w. *Id*. at 11:1-13 (Example 11). Thus, Li in view of Sonne teaches and renders obvious the requirement for the inclusion of "about 45% to about 85% (w/w) of one or more natural or synthetic tocopherols or tocotrienols selected from the group consisting of: α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, α-tocotrienol, β-tocotrienol, γ-tocotrienol, δ-tocotrienol, tocophersolan, any esters thereof and any combinations thereof."

Claim 1 of the '664 patent further requires the inclusion of "about 25% to about 40% (w/w) of one or more alcohols selected from the group consisting of ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, and any combinations thereof." As noted above, Li discloses an intranasal diazepam solution containing 30% ethanol. Li at 67, 70. The inclusion of 30% ethanol in the Li intranasal solution is consistent with the disclosure of Sonne, stating the "compositions of the invention may be used directly as solutions of the bioactive agent in the tocopherol solvent,"

and discussing the "addition of co-solvents such as ethanol" to the tocopherol solvent. Sonne at 3:60-67.

With regard to the requirement that "the pharmaceutical composition is a solution and contains less than 1% water," Li in view of Sonne renders obvious this limitation. As noted, Li discloses an intranasal diazepam solution formulation. Li at 67. Additionally, Li states that the solution contains 10% water (though the percentage of water may be less in the formulations further containing 1% SGC). *Id*. at 67, 70. However, the solubility of diazepam within the solution dictates how much diazepam can be solubilized and ultimately delivered to the nasal passage of a patient (in a small volume, as only about 0.1-0.2 ml can be administered in a single spray). It was well-known that diazepam was poorly soluble in water, as explained above. *Supra* Sections V.B; V.E.1.

A POSA was motivated with a reasonable expectation of success to enhance the solubility of diazepam within the intranasal solution disclosed by Li, but would have known that the 10% water in the Li solution would adversely impact the solubility of diazepam within the solution as a whole. As such, a POSA was motivated to decrease the amount of water present in the Li intranasal diazepam formulation, as doing so would be expected to further increase the diazepam solubility. Routine experimentation would have resulted in the reduction of the amount of water in the Li formulation. *See In Re Aller,* 220 F.2d 454, 456 (CCPA 1955) ("[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation."). Consequently, the claimed requirement that the solution "contains less than 1% water," is rendered obvious as the result of routine experimentation and optimization.

Moreover, Sonne discloses that "[t]he compositions of the invention may be used directly as solutions of the bioactive agent in the tocopherol solvent," indicating that the solution does not include any water. Sonne at 3:60-61. Further, Example 11 of Sonne, directed to "[a] solution of diazepam, eg. as nosedrop," does not include any water. *Id*. at 11:1-13. The disclosure of Sonne adds to the motivation and expectation that the water component of Li's intranasal solution could be minimized, if not entirely eliminated.

Regarding the requirement that "the pharmaceutical composition is in a pharmaceutically-acceptable spray formulation," Li discloses this limitation. Specifically, Li explains that, for intranasal administration, "100 µl of the IN formulations [was administered] into each nostril within 5 s by means of a Pfeiffer spray device." Li at 67. Similarly, Sonne discloses that the compositions are preferably administered via the "[n]asal" route, and that the compositions may take the form of "sprays." Sonne at 3:58-59, 6:34-35. Consequently, Li and Sonne disclose the claimed requirement that "the pharmaceutical composition is in a pharmaceutically-acceptable spray formulation."

Finally, for the reasons already discussed above, a POSA would have been motivated to include " about 0.01% to about 1% (w/v) of dodecyl β-D-maltoside" in view of Meezan. *Supra* Section V.E.1. To reiterate, Meezan disclosed the use of alkyl glycosides in amounts of "about 0.01-20%, preferably about 0.01-5%, more preferably about 0.01-2%, even more preferably 0.01-1%, and most preferably 0.01-0.125% by weight." Meezan at ¶ [0070]. Further, Meezan tested the effects of DDM specifically as an absorption enhancer in amounts of 0.125%, 0.25%, 0.375%, and 0.50%. *Id*.

Further, Cartt 2008 expressly disclosed intranasal formulations of diazepam with the goal of solving the same issues described and known in the art. Cartt 2008 at Abstract. Cartt 2008

disclosed that non-aqueous formulations containing "about 1 to about 20, preferably about 2 to about 10 mg per dose" of diazepam may be desirable for the reasons discussed above. *See, e.g.*, *id*. at ¶¶ [0021]-[0023], [0063]. And Cartt 2008 disclosed that "n-dodecyl β-D-maltoside" may be used as an excipient in the intranasal diazepam formulations. *See, e.g.*, *id*. at ¶ [0129].

Accordingly, a POSA would have been motivated to make a pharmaceutically acceptable spray formulation of diazepam in the form of a solution containing the amounts of diazepam, tocopherols or tocotrienols, alcohols, and DDM recited in claim 1 of the '664 patent based on Li in view of Sonne and Meezan, optionally further in view of Cartt 2008, USP, and/or Florida EMS Manual. A POSA also would have had a reasonable expectation of success in view of those references for the reasons discussed above.

(b) The Dependent Claims of the '664 Patent Would Have Been Obvious

For the reasons explained above, dependent claims 2-18 would have been obvious over Li in view Sonne and Meezan, optionally further in view of Cartt 2008, Florida EMS Manual, and/or USP. *Supra* Section V.E.5(a). To be sure, the prior art disclosed each of the limitations of dependent claims 2-18 of the '664 patent, expressly or inherently, as discussed below.

Dependent claims 2 and 6 require that "the one or more natural or synthetic tocopherols or tocotrienols is α-tocopherol" (claim 2) and "the pharmaceutical solution comprises one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof in an amount from about 60% to about 75% (w/w)" (claim 6). As explained above, Sonne expressly disclosed that diazepam could be formulated for intranasal administration as a solution containing α-tocopherol, and a POSA was motivated with a reasonable expectation of success to replace the 60% propylene glycol present in Li's intranasal diazepam solution with α-tocopherol, resulting in a solution containing 60% (w/w) α-tocopherol.

Dependent claims 3-5 require the solution formulation to contain "about 10 mg/mL to about 250 mg/mL," "about 20 mg/mL to about 50 mg/mL," or "about 2 mg to about 10 mg" of diazepam. '664 patent at claims 3-5. As explained above, Li discloses that the intranasal solution contains 20 mg/ml diazepam, meeting the claimed requirements of "about 10 mg/mL to about 250 mg/mL" and "about 20 mg/mL to about 50 mg/mL." Additionally, as discussed, when the solution of Li is administered in the typical nasal spray volume of about 0.1-0.2 ml, the amount of diazepam administered to the nasal passage ranges from about 2 to about 4 mg, meeting the claimed requirement of "about 2 mg to about 10 mg" of diazepam.

Similarly, Sonne and Cartt 2008 both disclosed intranasal formulations containing the concentrations and amounts of diazepam recited in claims 3-5 of the '664 patent. *See, e.g.*, Sonne at 7:23-8:46, 14:63-15:33; Cartt 2008 at ¶¶ [0034], [0047], [0063]. Accordingly, for the reasons discussed above, a POSA would have been motivated to use the claimed concentrations and amounts of diazepam, and would have had a reasonable expectation of success.

Dependent claim 7 of the '664 patent recites that the formulation may contain "at least one additional ingredient selected from the group consisting of stabilizers, coloring agents, pH adjusters, buffering agents, preservatives, wetting agents, flavoring agents and combinations thereof." '664 patent at claim 7. Sonne discloses that "[t]he formulations according to the invention may be optimized with respect to bioadhesion, sprayability and viscosity, as desired." Sonne at 6:47-49. Additionally, Sonne states that "[t]o ensure that the formulations have a reasonable shelf-life it may be desirable to include preservatives such as benzalkonium chloride, sodium edetate, sorbic acid, potassium sorbate, phenoxyethanol, phenetanol, parabens or others known in the art. Addition of odour- or taste-masking compounds can also be desirable." *Id*. at 7:4-9.

As explained above, a POSA would have been motivated to include at least one of these types of excipients in an intranasal diazepam solution formulation. *Supra* SectionV.E.5(a). Indeed, a POSA would have recognized that the categories of functional excipients recited in dependent claim 7 were routinely included in pharmaceutical formulations, as disclosed by Sonne, Meezan, and other references. *See, e.g.*, Sonne at 7:4-9, claim 10; Meezan at ¶ [0074]. Accordingly, for the reasons discussed above, a POSA would have been motivated to include an additional excipient from the list recited in dependent claim 7, and would have had a reasonable expectation of success.

Dependent claims 8-10 require the claimed diazepam formulation to be formulated in certain volumes, including at "about 100 µL." '664 patent at claims 8-10. Li discloses that the intranasal solutions were administered intranasally in a volume of "100 µl of the IN formulations." Li at 67. Further, as explained above, a POSA would have understood that intranasal administration of a pharmaceutical formulation necessarily requires the claimed volumes, and would have been motivated to use a volume of "about 100 µL" specifically. *See, e.g.*, Sonne at 7:25-30. Accordingly, for the reasons discussed above, a POSA would have been motivated to formulate an intranasal diazepam formulation in a volume of "about 100 µL," and would have had a reasonable expectation of success.

Dependent claims 11-14 require the claimed diazepam solution formulations to have limited amounts of water, including "no water" as required by claim 14. '664 patent at claims 11-14. As explained above, a POSA was motivated with a reasonable expectation of success to enhance the solubility of diazepam within the intranasal solution disclosed by Li, but would have known that the 10% water in the Li solution would adversely impact the solubility of diazepam within the solution as a whole. As such, a POSA was motivated to decrease and eliminate the amount of water (i.e., include no water) present in the Li intranasal diazepam formulation, as doing

so would be expected to further increase the diazepam solubility. Consequently, the claimed requirement that the solution include "no water" is rendered obvious as the result of routine experimentation and optimization.

Additionally, Sonne discloses that "[t]he compositions of the invention may be used directly as solutions of the bioactive agent in the tocopherol solvent," (Sonne at 3:60-61) indicating that the solution does not include any water. Further, Example 11 of Sonne, directed to "[a] solution of diazepam, eg. as nosedrop," does not include any water. Sonne at 11:1-13. The disclosure of Sonne adds to the motivation and expectation that the water component of Li's intranasal solution could be removed entirely (i.e., include no water).

Finally, dependent claims 15-18 require the claimed diazepam formulation to contain no more than certain amounts of "a diazepam impurity" or to "maintain[] a similar average spray content" at certain temperatures, humidities, and times. '664 patent at claims 15-18. For the reasons explained above, a POSA would understand that these limitations are inherent properties of the otherwise obvious diazepam solution formulations. *Supra* Section V.E.2(i). Thus, dependent claims 15-18 of the '664 patent are obvious because they recite inherent properties, and are inherently disclosed in the prior art. *In re Kao*, 639 F.3d at 1070; *Santarus*, 694 F.3d at 1344.

Accordingly, for the reasons discussed above, all claims of the '664 patent would have been obvious over Li in view of Sonne and Meezan, optionally further in view of Cartt 2008, Florida EMS Manual, and/or USP.

6. All Claims of the '664 Patent Are Invalid as Obvious over Sonne in view of Jamieson, Li, Meezan, and/or Wermeling V

All claims of the '664 patent would have been obvious over Sonne in view of Jamieson, Li, Meezan, and/or Wermeling V, which are summarized above. *Supra* Section V.D. The previous analyses establishing the obviousness of all claims of the '664 patent over Sonne in view of

Meezan, optionally further in view of Cartt 2008, Florida EMS Manual, and/or USP as well as Li in view of Sonne and Meezan, optionally further in view of Cartt 2008, Florida EMS Manual, and/or USP are incorporated herein in their entirety. In view of this additional and alternative combination of prior art references, a POSA would have been motivated to make the claimed intranasal diazepam solution formulations, and would have had a reasonable expectation of success, for the all the reasons noted above.

(a) Independent Claim 1 of the '664 Patent Would Have Been Obvious

Sonne discloses the use of tocopherols, including vitamin E, for use in intranasal pharmaceutical formulations with benzodiazepines such as diazepam. More specifically, Sonne discloses that "[t]he present invention provides the use of a tocopherol or a derivative thereof as a ***solvent*** and/or emulsifier ***for substantially insoluble and sparingly soluble biologically active agents***, especially in the manufacture of pharmaceutical compositions. Such compositions are ***particularly suitable for*** transmucosal, and especially ***intranasal*** or rectal ***administration***, or administration via the oral cavity." Sonne at Abstract (emphasis added), 3:54-59, Example 11, Claim 4. In particular, Sonne describes representative active agents suitable for the inventions described therein, including specifically diazepam. Sonne at 5:34.

With respect to the amount of diazepam to use in intranasal formulations, Jamieson discusses generally a therapeutically effective amount of a benzodiazepine. *See, e.g.*, Jamieson at claims 8, 17, 40. More specifically, though, it teaches intranasal formulations where the amount of a benzodiazepine such as diazepam is "typically present at a weight percent of between about 0.1% to about 20% and often between 0.1% and 10% often 0.25% to 6%." *Id*. at ¶ [0102]; *see also id*. at ¶ [0118] ("A therapeutically effective amount of diazepam in the compositions of the present invention may be, for example between about 1.0 mg and about 40.0 mg per unit dose, more

preferably between about 2.0 mg and about 10.0 mg per unit dose."); *see also* Li at 67 (disclosing formulations containing 20 mg diazepam in 1 ml of vehicle).

Sonne also states that "tocopherols and derivatives thereof are excellent solvents for drugs which are substantially insoluble or sparingly soluble in water, whilst at the same time having a very low irritative potential for mucosal tissues." Sonne at 2:55-58. Thus Sonne explains that tocopherols are useful solvents for drugs such as diazepam, including because they have very low irritative potential. Jamieson also discloses the use benzodiazepine compositions that include tocopherols. *See, e.g.*, Jamieson at claims 24, 49; *see also id*. at ¶ [0209] ("Addition of an anti-oxidant to the formulations of the present invention used for intranasal delivery of benzodiazepines may provide desirable protective benefits to such formulations. Examples include, but are not limited to, tocopherol and derivatives thereof . . . ."). Thus, both Sonne and Jamieson provide guidance on how to solubilize poorly water-soluble compounds (such as diazepam), and would have been primary references that a POSA would look to for design strategies to overcome the shortcomings of oral, intravenous, and rectal benzodiazepine dosage forms. Indeed, the POSA would have had a reasonable expectation of success in using tocopherols to dissolve diazepam for intranasal administration.

With respect to the amount and type of tocopherols to use in the disclosed formulations, Sonne explains that they may contain "may contain from 1 to 99.99% (w/w), preferably 20 to 99.99%, most preferably 40 to 99.99% (w/w) of the tocopherol or tocopherol derivative solvent." Sonne at 5:55-58. Moreover, Sonne explains that tocopherols, such as those used in the claimed invention, may include alpha-tocopherol or Vitamin E. *Id*. at 3:4-10 ("Tocopherols are a range of natural and synthetic compounds, also known by the generic term Vitamin E. α-Tocopherol . . . is the most active and widely distributed in nature, and has been the most widely studied."). In

particular, Sonne discloses example compositions, including Example 11 which discloses specifically a "nosedrop solution" containing diazepam and approximately 40% α-tocopherol." *Id*. at 11:1-13. Thus, the POSA would have had a reasonable expectation of success in using amounts of tocopherols to dissolve diazepam for intranasal administration disclosed in the art.

Furthermore, both Sonne and Jamieson recognize the use of cosolvent systems for intranasal diazepam formulations. For example, Sonnne teaches cosolvents to assist in optimizing the disclosed formulations for bioadhesion, sprayability, and viscosity. *Id*. at 6:47-50 (recognizing that formulations disclosed therein may be "optimized with respect to bioadhesion, sprayability and viscosity"). Even more particularly, Sonne highlights the use of both ethanol and benzyl alcohol as co-solvents. *Id*. at 6:51-52 (disclosing ethanol and benzyl alcohol). With respect to whether and why to use such alcohol co-solvents, Sonne explains that "[t]he compositions of the invention may be used directly as solutions of the bioactive agent in the tocopherol solvent" but that "such solution are viscous, and the viscosity may be too high for certain applications, for example to achieve a sprayable formulation for nasal application." *Id*. at 3:60-64. Indeed, because of potentially high viscosity caused by the tocopherol solvent, Sonne explains that the co-solvents, such as alcohol, may be used to decrease viscosity. *Id*. at 3:65-67 ("Viscosity can be reduced by additional of co-solvents such as ethanol, but this is less desired, since solutions of this kind tend to be irritating to certain mucosal tissues.").

Jamieson contains similar disclosures related to intranasal administration of formulations that contain benzodiazepines and cosolvents. Jamieson at Abstract (inventions that "include[] benzodiazepine compositions formulated for intranasal administration, comprising a binary solvent system comprising a first solvent in which the benzodiazepine is soluble, the first solvent capable of penetrating nasal mucosal tissue, and a second solvent in which the benzodiazepine in

less soluble."). Thus, Sonne and Jamieson both provide the motivation to combine diazepam with a tocopherol (α-Tocopherol or vitamin E) for dissolution purposes, while simultaneously providing a motivation to increase the amount of cosolvents (such as ethanol and benzyl alcohol) to reduce viscosity.

With respect to the use of ethanol and benzyl alcohol, the POSA would additionally look to Li and/or Wermeling V. Li, for example, discloses the benefit of using ethanol in intranasal administration of diazepam. *See* Li at Abstract, 67. Li teaches the impact of formulations containing ethanol on absorption of diazepam. Specifically, "[t]he present study was carried out to investigate the absorption characteristics and [pharmacodynamic] response of three anticonvulsants, the benzodiazepines, [diazepam] and [clonazepam], and the new monocarbamate anticonvulsant . . . after their [intranasal] administration as solutions in aqueous cosolvent system containing various proportions of [propylene glycol] and [ethanol] in the presence of 1% [sodium glycocholate]." *Id*. at 67. The studied solutions include one that contained about 20 mg diazepam in 30% ethanol. *Id*. at 67. That formulation contained about 20 mg diazepam in about 1 ml of vehicle. *Id*. at 67. Li concludes that "[t]he peak [diazepam] concentration . . . increased significantly with increasing [ethanol] concentrations in the [intranasal] formulation (20-60%)." *Id*. at 71-72; *see also* Jamieson at Table 12A (disclosing benzodiazepine formulations containing 20% ethanol). Li also concludes that "[t]he nasal administration of [diazepam] . . . formulations in 1% SGC containing EtOH:PG:water cosolvent elicited a very fast PD response, which was less than 1.5 min. In turn, this response time appeared to be essentially identical to that seen from an IV injection of a benzodiazepine." *Id*. at 74.

Similarly, Wermeling V discloses pharmaceutical compositions for intranasal administration of effective amounts of benzodiazepines, and specifically highlights the use of

diazepam. Wermeling V at Abstract, ¶ [0026]. It further explains that the "principal advantages of intranasal route are non-invasive delivery, rapid drug absorption, and convenience." *Id*. at ¶ [0008]. Wermeling V continues that "there is a need for intranasal benzodiazepine compositions with improved properties, such as for example, rapid absorption and time to peak concentration." *Id*. at ¶ [0012]. Thus, Wermeling V provides additional motivation to use diazepam intranasal formulations. Wermeling V continues, however, by explaining that suitable diluents may include alcohols. *Id*. at ¶ [0030]. With respect specifically to benzyl alcohol, Wermeling V highlights it as a "suitable preservative" for use in its disclosed formulations. *Id*. at ¶ [0033]. Wermeling V continues that "the composition contains a preservative that is chosen in quantities that preserve the composition, but preferably does not cause irritation to the nasal mucosa." *Id*. at ¶ [0033]. Thus, the POSA would have a motivation to combine Li and Wermeling V to formulate diazepam with various alcohols in order to increase absorption and/or preservative characteristics. Based on the disclosures therein, the POSA would have had a reasonable expectation of success for the amounts taught.

Sonne also discloses solutions in spray form as a conventional form used for the compositions. Sonne at 3:54-67, 6:33-34. It recognizes that the "acceptable volume for . . . nose" administration of drugs is about 100 µl. Li also teaches that a "constraint concerning nasal administration is that a small administration volume is required; it is not generally possible to administer more than approximately 150 µl per nostril." Li at 66. Thus, the prior art taught the claimed volume of the formulation.

Moreover, Jamieson recognizes problems associated with intranasally administered benzodiazepine formulations, with one of the problems being "poor bioavailability." Jamieson at ¶ [0018]. Jamieson explains the need for intranasal benzodiazepine compositions with improved

properties, such as rapid absorption, time to peak concentration, and bioavailability. Thus, Jamieson also teaches the use of penetration enhancers in diazepam for intranasal spray formulations. *Id*. at ¶ [0104] ("pharmaceutical compositions comprising the benzodiazepine (e.g., clonazepam, diazepam or lorazepam) of the present invention, for example, for intranasal administration . . . may further comprise one or more components including . . . mucosa penetration enhancing agent"), ¶ [0105] ("In preferred embodiments of the present invention, the pharmaceutical compositions . . . are formulation to be sprayable."). Jamieson also recognizes that due to the "highly lipophilic nature of lipophilic nature of the benzodiazepines a combination of surfactants, strong solubilizing solvents, and carrier solutions are often used." *Id*. at ¶ [0142].

Similarly, Meezan discloses benefits of dodecyl-beta-D-maltoside in formulations for ocular administration. Meezan at ¶ [0156] ("[A]t least two alkylmaltosides [including dodecyl-beta-D-maltoside] are effective in achieving sufficient absorption" of the drug substance studied), Table 1. Meezan specifically teaches an alkyl glycoside (such as dodecyl-beta-D-maltoside) amount of about 0.25%. *See, e.g., id*. at ¶¶ [0150]-[0151]; *see also* Fig. 1, [0158]-[0159], Table I, and Example 6. Thus the prior art suggests the use of excipients that "increase absorption across the mucosa and/or increase[] bioavailability." '664 patent at 31:35-37.

With respect to the claimed water element, Sonne discloses that "[t]he compositions of the invention may be used directly as solutions of the bioactive agent in the tocopherol solvent," indicating that the solution does not include any water. Sonne at 3:60-61. Further, Example 11 of Sonne, directed to "[a] solution of diazepam, eg. as nosedrop," does not include any water. *Id*. at 11:1-13. Moreover, a POSA would have been motivated to make non-aqueous formulations of diazepam (i.e., formulations without water) in view of the prior art indicating the typical size of intranasal dosages at around 100 µl. Li at 66. Given it was known that diazepam is highly insoluble

in water and in view of the ~100 µl dosage amount seen in the prior art for dosages of this form, the POSA would seek to minimize the amount of water in the intranasal formulation and certainly would do so in an amount below that claimed.

The POSA would have been motivated to combine the teaching of Sonne, Jamieson, Li, and/or Wermeling to create a rapid-onset formulation containing diazepam.

First, the POSA would have recognized that intranasal administration of diazepam was a promising route of administration due to the possibility of rapid onset effect through the trans-mucosal membranes in the nose.

Second, the POSA would have sought to use a non-irritating solvent – such as the tocopherol Vitamin E – to dissolve diazepam. To balance the viscosity and to improve the time to peak concentration, the POSA would seek to use some amount of ethanol or other suitable co-solvent such as benzyl alcohol.

Furthermore, the motivation to use benzyl alcohol is compounded by the knowledge that it is a suitable preservative for intranasal benzodiazepine formulations. *See generally* Wermeling V. With respect to the specifically disclosed amounts of the claimed drug substance, tocopherol, and alcohols, those ranges were disclosed in the art as discussed above. Moreover, in seeking to develop an intranasal formulation with the appropriate viscosity, bioavailability, absorption, pharmacokinetics, and/or preservative characteristics, the POSA would need to do nothing more than routine experimentation to optimize the formulation for such characteristics. Routine experimentation would have resulted in the amounts of the claimed formulations. *See In Re Aller,* 220 F.2d 454, 456 (CCPA 1955) ("[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation."); *see also, e.g., In re Geisler*, 116 F.3d 1465, 1469–70 (Fed. Cir. 1997); *In re*

Woodruff, 919 F.2d 1575, 1578 (Fed. Cir. 1990). Thus, each limitation of claim 1 is disclosed by the combination of Sonne, Jamieson, Li, and/or Wermeling. Thus, claim 1 is obvious.

(b) The Dependent Claims of the '664 Patent Would Have Been Obvious

Dependent claim 2-18 each depend from claim 1. Thus, these claims are obvious for at least the same reasons explained above for claim 1, which discussion is incorporated herein by reference in its entirety. With respect to any additional elements in these claims, they have already been addressed above with respect to claim 1 and do not impart non-obviousness or they are addressed below in more detail.

Claim 2 requires the tocopherol be alpha-tocopherol. For the reasons already discussed above with respect to claim 1, incorporated herein by reference, this claim is obvious.

Claims 3-5 require specific amounts of diazepam. For the reasons already discussed above with respect to claim 1, incorporated herein by reference, these claims are obvious.

Claims 6 requires specific amounts of tocopherols. For the reasons already discussed above with respect to claim 1, incorporated herein by reference, this claim is obvious.

Claims 7 requires at least one additional excipient selected from the group listed therein. For the reasons already discussed above with respect to claim 1, incorporated herein by reference, this claim is obvious. Moreover, Sonne states that "[t]o ensure that the formulations have a reasonable shelf-life it may be desirable to include preservatives such as benzalkonium chloride, sodium edetate, sorbic acid, potassium sorbate, phenoxyethanol, phenetanol, parabens or others known in the art. Addition of odour- or taste-masking compounds can also be desirable." Sonne at 7:4-9. For this additional reason, claim 7 is obvious.

Claims 8-10 require specific volumes for the claimed pharmaceutical compositions. For the reasons already discussed above with respect to claim 1, incorporated herein by reference, these claims are obvious.

Claims 11-14 require specific volumes of water. For the reasons already discussed above with respect to claim 1, incorporated herein by reference, these claims are obvious.

Claims 15-18 require the claimed compositions contain no more than certain amounts of "a diazepam impurity" or to "maintain[] a similar average spray content" at certain temperatures, humidities, and times. *See* '664 patent at claims 15-18. For the reasons already discussed above with respect to claim 1, incorporated herein by reference, these claims are obvious. Additionally, a POSA would understand that these limitations are inherent properties of the otherwise obvious diazepam compositions. Dependent claims 15-18 are obvious because they recite inherent properties, and are inherently disclosed in the prior art. *See In re Kao*, 639 F.3d at 1070; *Santarus*, 694 F.3d at 1344.

7. All Claims of the '664 Patent Are Invalid as Obvious Over Gwozdz, Meezan, and Cartt 2008, in view of Pharmacopeial Forum for Diazepam

All claims of the '664 patent would have been obvious over Gwozdz, Meezan, and Cartt 2008 in view of Pharmacopeial Forum for Diazepam, which are summarized above. *Supra* Section V.D

Independent claim 1 of the '664 patent is limited to intranasal solutions comprising diazepam in a pharmaceutically-acceptable spray formulation, and containing less than 1% water. Claims 2-18 depend from claim 1. Dependent claim 2 specifies that the one or more natural or synthetic tocopherols or tocotrienols is α-tocopherol. Dependent claim 3 specifies that the therapeutically effective amount of the diazepam is present in the pharmaceutical solution at a concentration of about 10 mg/mL to about 250 mg/mL. Dependent claim 4 specifies that the

diazepam is present in the pharmaceutical solution at a concentration of about 20 mg/mL to about 50 mg/mL. Dependent claim 5 specifies that the diazepam is about 2 mg to about 10 mg. Dependent claim 6 specifies that the pharmaceutical solution comprises one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof in an amount from about 60% to about 75% (w/w). Dependent claim 7 specifies that the pharmaceutical composition further comprises at least one additional ingredient selected from the group consisting of stabilizers, coloring agents, pH adjusters, buffering agents, preservatives, wetting agents, flavoring agents and combinations thereof. Dependent claims 11-14 specify that the formulation contains less than 0.5% water, less than 0.25% water, less than 0.1% water, and no water respectively. Further dependent claims 8-10 require that the pharmaceutical composition is about 25 μL to about 250 μL, about 50 μL to about 150 μL, and about 100 μL respectively. Dependent claims 15-18 disclose that the pharmaceutical composition contains no more than 0.01% of a diazepam impurity and similar average spray content at various storage conditions, measured at specified time points. Each of these limitations are also disclosed in one or more of the combined disclosures of Gwozdz, Meezan, and Cartt 2008 described in detail above.

Each of these limitations is also disclosed in one or more of the prior art references, Gwozdz, Meezan, and Cartt 2008. Gwozdz discloses that the solutions may further contain other pharmaceutically acceptable additives such as, but not limited to, acidifying, alkalizing, buffering, chelating, complexing and solubilizing agents, antioxidants and antimicrobial preservatives, humectants, suspending and/or viscosity modifying agents, tonicity and wetting or other biocompatible materials. Gwozdz relates to non-aqueous compositions containing ethanol, and since it discloses ethanol as desirably 180 to 200 proof ethanol, i.e., in the range of 90-100%

ethanol, it would be apparent to POSA that the claimed pharmaceutical composition would contain less than 1% water depending upon the grade or amount of ethanol used.

Additionally, the Pharmacopeial Forum for Diazepam specifies impurity standards for diazepam and, amongst others, it states that the compositions should not contain more than 0.01% of diazepam related compound A as claimed. It would be obvious that the claimed composition should maintain the impurity levels of a diazepam solution—particularly compound A (NMT 0.01%)—within the limits specified in the Pharmacopeial Forum under various storage conditions in order to meet product standards and obtain regulatory approval. Furthermore, it is common knowledge to POSA to develop intranasal spray compositions that maintain a similar spray content at various storage conditions and time points. *See:* Guidance for Industry- Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products — Chemistry, Manufacturing, and Controls Documentation ("Guidance for Industry for Nasal Spray"). Additionally, it is also common knowledge that intranasal spray compositions should have spray content uniformity, and it is necessary to maintain similar spray content uniformity of intranasal spray compositions under various storage conditions and at different time points to ensure the therapeutic effectiveness of the drug. *See* Guidance for Industry for Nasal Spray.

Accordingly, for at least these reasons, the claims of the '664 patent would have been prima facie obvious over Gwozdz, Meezan, Cartt 2008 and Pharmacopeial Forum for Diazepam.

8. Secondary Considerations

Defendants contend that no secondary considerations weigh in favor of non-obviousness with respect to any of the claims of the '664 patent. Any secondary considerations that Neurelis may assert would be insufficient to overcome the strong showing of obviousness in this case with respect to the claims of the '664 patent. *See DyStar Textilfarben GmbH v. C.H. Patrick Co.*, 464 F.3d 1356, 1371 (Fed. Cir. 2006) (patent found obvious despite commercial success); *In re GPAC*

Inc., 57 F.3d 1573, 1580-81 (Fed. Cir. 1995) (same); *Pentec, Inc. v. Graphic Controls Corp.*, 776 F.2d 309, 315-17 (Fed. Cir. 1985) (same); *Pfizer*, 480 F.3d at 1371-72 (finding secondary considerations insufficient where the record establishes a strong case of obviousness); *Leapfrog Enters., Inc. v. Fisher-Price, Inc.*, 485 F.3d 1157, 1162 (Fed. Cir. 2007) ("[G]iven the strength of the prima facie obviousness showing, the evidence on secondary considerations was inadequate."); *W. Union Co. v. MoneyGram Payment Sys., Inc.*, 626 F.3d 1361, 1373 (Fed. Cir. 2010) ("[W]eak secondary considerations generally do not overcome a strong prima facie case of obviousness.").

Further, Defendants are presently unaware of any secondary considerations that are relevant to any of the claims of any of the '664 patent. Secondary considerations do not form a part of the *prima facie* case of obviousness. Rather, a patentee may try to rebut a *prima facie* case of obviousness by coming forth with purported evidence of secondary considerations. Defendants therefore have no burden at this stage to address any secondary considerations, or to come forward with any evidence rebutting such considerations. To the contrary, it is Neurelis's obligation and burden to produce evidence of so-called secondary considerations, if any, on which it intends to rely. Defendants expect that additional discovery directed to any secondary considerations Neurelis may allege will take place in accordance with the case schedule, and that the evidence will rebut any alleged or claimed secondary considerations in full. As such, if and in the event Neurelis cites to any alleged secondary considerations, Defendants reserve the right to supplement these contentions.

In addition, the PTAB previously considered certain arguments raised by Neurelis in the context of secondary considerations of non-obviousness. IPR2019-00451, Paper 44 at 51-54. Specifically, Neurelis presented "evidence of failure of others and long-felt need." *Id*. at 51. With respect to long-felt need, Neurelis argued that there was a need for intranasal formulations of

diazepam, which was met by the Valtoco product. *Id*. at 51-52. And with respect to the failure of others, Neurelis argued that other companies attempted to develop intranasal diazepam formulations, but were unsuccessful. *Id*.

The PTAB rejected both of Neurelis's arguments, noting that "we give [Neurelis's] arguments about failure of others and long-felt need very little weight in our obviousness analysis." *Id*. at 52. The PTAB specifically noted that Neurelis failed to establish a nexus between the formulations claimed by the '876 patent and the Valtoco product. *Id*. Indeed, Neurelis did not even "argue a nexus between VALTOCO … and the claims." *Id*. at 53. Thus, Neurelis has conceded that there is no nexus between the claims of its formulation patents (including the '664 patent) and the purported secondary considerations of non-obviousness it asserted.

Further, the PTAB held that "even if nexus had been shown, the objective evidence of nonobviousness identified by Patent Owner provides only limited support for nonobviousness of the challenged claims." *Id*. Indeed, the PTAB found that "benzodiazepines were delivered intranasally prior to 2009, which undercuts [Neurelis's] arguments of failure of others and long-felt need." *Id*. at 54.

Accordingly, for the reasons previously considered and addressed by the PTAB, there are no secondary considerations of non-obviousness related to the '664 patent that overcome the prima facie case of obviousness discussed above.

F. The Claims of the '664 Patent Are Invalid Under 35 U.S.C. § 112

As explained above, claim 1 of the '664 patent recites "[a] pharmaceutical composition for intranasal administration … wherein the pharmaceutical composition is in a pharmaceutically-acceptable spray formulation." '664 patent at claim 1. To the extent the claims of the '664 patent are not invalid as obvious, which they are, they are invalid for lack of written description and/or non-enablement under 35 U.S.C. § 112. Specifically, under this scenario, the specification of the

’664 patent fails to demonstrate that the inventors possessed the full scope of the claimed pharmaceutical “solution” compositions “in a pharmaceutically acceptable spray formulation,” and, if not invalid as obvious, the ’664 patent does not enable a POSA to make and use the full scope of the claimed pharmaceutical “solution” compositions “in a pharmaceutically acceptable spray formulation” without undue experimentation.

1. Lack of Written Description

As explained above, the Federal Circuit has made it clear that the specification must objectively demonstrate to a POSA that the inventor had possession of the claimed subject matter. *Supra* Section III.C.1; *see also Ariad*, 598 F.3d at 1351; *Juno Therapeutics, Inc. v. Kite Pharma, Inc.*, 10 F.4th 1330, 1336 (Fed. Cir. 2021). “For generic claims,” the Federal Circuit has “set forth a number of factors for evaluating the adequacy of the disclosure, including ‘the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, [and] the predictability of the aspect at issue.’” *Juno*, 10 F.4th at 1335 (quoting *Ariad*, 598 F.3d at 1351). And “[f]or genus claims using functional language … the written description ‘must demonstrate that the applicant has made a generic invention that achieves the claimed result and do so by showing that the applicant has invented species sufficient to support a claim to the functionally-defined genus.’” *Id.* at 1335 (quoting *Ariad*, 598 F.3d at 1351). “Generally, a genus can be sufficiently disclosed by ‘either a representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one of skill in the art can “visualize or recognize” the members of the genus.’” *Id*. at 1335 (quoting *Ariad*, 598 F.3d at 1351).

Here, the claims of the ’664 patent recite a genus of pharmaceutical compositions containing various amounts of diazepam, “one or more natural or synthetic tocopherols or tocotrienols selected from the group consisting of: α-tocopherol, β-tocopherol, γ-tocopherol, δ-

tocopherol, α-tocotrienol, β-tocotrienol, γ-tocotrienol, δ-tocotrienol, tocophersolan, any esters thereof and any combinations thereof," "one or more alcohols selected from the group consisting of ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, and any combinations thereof," and DDM, where the compositions also contain "less than 1% water." '664 patent at claim 1. Further, the claimed genus of pharmaceutical compositions must satisfy certain functional claim limitations, including that the compositions must be a "solution" and must be "in a pharmaceutically-acceptable spray formulation." *Id*. Thus, to satisfy the written description requirement, the specification of the '664 patent must demonstrate to a POSA that the inventors possessed the full scope of the claimed genus of pharmaceutical compositions that satisfy the functional requirements of the claims.

While the prior art renders the asserted genus of formulations obvious for the reasons discussed above, the specification falls well-short of demonstrating that the inventors possessed the full scope of what is claimed in the '664 patent. For example, as explained above, the specification does not contain a single working example of a pharmaceutical formulation that contains DDM. *Supra* Section II.D.2. Rather, the specification includes prophetic examples that refer to various alkyl glycosides that would still need to undergo stability and other testing necessary to assess whether the formulations are "solutions" that are "in a pharmaceutically-acceptable spray formulation." *Id*.

To be sure, the claims of the '664 patent would have been obvious in view of the prior art discussed above, which would have motivated a POSA to make the claimed formulations of diazepam with a reasonable expectation of success. *Supra* Section V.D., V.E.. Specifically, a POSA would have expected that species of formulations that fall within the broad genus claimed in the '664 patent would form "solutions" that are "in a pharmaceutically-acceptable spray

formulation." However, the standards for obviousness are different than the standards a patentee must satisfy to establish adequate written description support for a claimed invention. *Lockwood v. Am. Airlines*, Inc., 107 F.3d 1565, 1572 (Fed. Cir. 1997) ("One shows that one is in possession of the invention by describing the invention, with all its claimed limitations, not that which makes it obvious.") (citation modified). Thus, the fact that the specification of the '664 patent discloses that some embodiments within the broad genus of formulations recited in the claims may work (as disclosed in the prior art) is not sufficient to "'demonstrate that the applicant has made a generic invention that achieves the claimed result … by showing that the applicant has invented species sufficient to support a claim to the functionally-defined genus.'" *Juno*, 10 F.4th at 1335 (quoting *Ariad*, 598 F.3d at 1351).

Indeed, the specification only discloses three examples of "solutions," which were prepared using specific amounts of diazepam, α-tocopherol or Vitamin E, and ethanol. '664 patent at 42:1-43:30. Only two of those solutions were subjected to the additional tests described in Example 5, and one of those two solutions failed to meet the test specifications. '664 patent at 44:2-52:30 (Solution 00 did not "meet[] specifications" for the formation of related compound A under storage conditions of 30º C/65% relative humidity and 40º C/75% relative humidity (Table 5-2); and Solution 00 did not "meet[] specifications" for the formation of related compound B under storage conditions of 30º C/65% relative humidity and 40º C/75% relative humidity (Table 5-3)). Thus, even the limited working examples of compositions that do not fall within the scope of the claims of the '664 patent (e.g., because they did not contain DDM, as required by the claims) did not satisfy the functional requirements of the claims (i.e., they were not "solutions" that are "in a pharmaceutically-acceptable spray formulation."). And as explained above, the claims of the '664

patent encompass an almost incalculable number of pharmaceutical compositions because they may contain various types and amounts of ingredients in different permutations and combinations.

The specification's disclosure of one successful working example that does not fall within the scope of the claims, and otherwise limited guidance, fails to demonstrate that the inventors possessed the full scope of the claims. *Juno*, 10 F.4th at 1335 (quoting *Ariad*, 598 F.3d at 1351); *see also AstraZeneca AB v. Mylan Pharms. Inc.*, 2022 WL 16857400, at *19 (N.D.W. Va. Nov. 9, 2022). As noted above, however, the results described in the specification demonstrate that a POSA would expect certain species within the broad genus of formulations claimed in the '664 patent to form "solutions" that are "in a pharmaceutically-acceptable spray formulation." But disclosing enough to render the claims obvious is insufficient to provide adequate written description support for the broad genus of formulations that must meet the claimed functional requirements. *Lockwood*, 107 F.3d at 1572.

Neurelis's lack of possession of the claimed compositions is underscored by statements in the specification and arguments made during prosecution of the '664 patent. For example, the specification states that diazepam was known to suffer from "solubility challenges," and that it may be difficult to fully dissolve the drug to form a solution (instead of a suspension). *See, e.g.*, '664 patent at 1:53-56. Neurelis also specifically amended the claims of the '664 patent during prosecution to recite "solutions" that are "in a pharmaceutically-acceptable spray formulation" to overcome the examiner's obviousness rejections, and argued that a POSA would not consider the prior art formulations to be "solutions" that are "in a pharmaceutically-acceptable spray formulation" because they may not satisfy various functional requirements. *Supra* Section II.D.3. Neurelis's own statements and arguments demonstrate that it considers the claims of the '664 patent to include functional requirements that must be met by the claimed formulations. But as

explained above, to the extent the claims are not invalid as obvious, the specification of the ’664 patent fails to demonstrate to a POSA that the inventors possessed the full scope of the genus of compositions that satisfy the functional requirements required by the claims.

The written description deficiency is further and independently demonstrated with respect to dependent claims 15 and 16 of the ’664 patent. As noted above, claim 1 of the ’664 requires, among other things, “about 25% to about 40% (w/w) of one or more alcohols selected from the group consisting of ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, and any combinations thereof.” ’664 patent at claim 1. Claims 15 and 16 depend from claim 1. Claim 15 requires that the pharmaceutical composition contains no more than 0.01% of a diazepam impurity (Compound A) but does not impose any storage duration or time period. Claim 16 requires that the pharmaceutical composition contains no more than 0.01% of a diazepam impurity (Compound A) including at specified temperature and humidity conditions but does not impose any particular storage duration. A POSA reviewing the specification would therefore expect that a composition falling within claim 1 must inherently be capable of meeting the impurity requirements of claims 15 and 16.

The specification, however, affirmatively demonstrates the opposite. The patent does not describe a single working embodiment in which a diazepam solution containing “about 25% to about 40% (w/w) of one or more alcohols” (as required by claim 1) meets the impurity limits required by claims 15 and 16. The only embodiment within the claimed alcohol range—Solution 00—fails the impurity specification under at least two of the conditions. The only solution that actually satisfies the impurity limits—Solution 02—is outside the claimed alcohols range. Accordingly, a POSA would conclude that the inventors did not possess a diazepam composition

comprising "about 25% to about 40% (w/w/) of one or more alcohols" that meets the impurity limit of NMT 0.01% of Compound A, as required by claims 15 and 16.

Accordingly, to the extent that the claims are not invalid as obvious, all claims of the '664 patent are invalid for lack of written description under 35 U.S.C. § 112.

2. Non-Enablement

Claims are not enabled when, at the effective filing date of the patent, a POSA could not practice their full scope without undue experimentation. *See Wyeth & Cordis Corp. v. Abbott Labs*., 720 F.3d 1380, 1384 (Fed. Cir. 2013). As the Supreme Court explained, "the specification must enable the full scope of the invention as defined by its claims. The more one claims, the more one must enable." *Amgen Inc. v. Sanofi*, 598 U.S. 594, 610 (2023). "Although a specification does not need to describe how to make and use every possible variant of the claimed invention, when a range is claimed, there must be reasonable enablement of the scope of the range." *Amgen Inc. v. Sanofi, Aventisub LLC*, 987 F.3d 1080, 1085 (Fed. Cir. 2021) *aff'd sub nom. Amgen Inc. v. Sanofi*, 598 U.S. 594 (2023). Functional claim limitations "pose high hurdles in fulfilling the enablement requirement." *Id*. at 1087.

For the same reasons discussed above, to the extent that the claims are not invalid as obvious, the claims of the '664 patent are invalid for failing to enable a POSA to make and use the genus of pharmaceutical compositions that satisfy the functional requirements of the claims (i.e., "solutions" that are "in a pharmaceutically-acceptable spray formulation") without undue experimentation. *Supra* Section V.F.1. The specification of the '664 patent does not disclose a single example of a pharmaceutical composition that falls within the scope of the claims, let alone one that meets the functional requirements of the claims. Thus, to the extent Neurelis argues that the prior art would not have rendered the claims of the '664 patent obvious, a POSA would need to engage in undue experimentation to practice the full scope of the claims. And because the genus

of pharmaceutical compositions encompassed by the claims is extremely broad, *supra* section V.F.1, a POSA would need to conduct a significant amount of experimentation to determine which species satisfy the claimed functional requirements. *Id*.

Further, as noted above, the standards for establishing obviousness are different from the standards a patentee must satisfy to show that the claims of a patent are enabled. Indeed, the Federal Circuit has long-recognized that "claims are unpatentable when they are so broad as to read on obvious subject matter even though they likewise read on non-obvious subject matter." *In re Mraz*, 455 F.2d 1069, 1072–73, 173 USPQ 25, 28 (CCPA 1972); *see also DNT, LLC v. Sprint Spectrum, LP,* 750 F. Supp. 2d 616, 624 (E.D. Va. 2010) (holding "that simultaneous obviousness and non-enablement findings" can be "compatible."); *Pharm. Resources, Inc. v. Roxane Labs., Inc.*, 2006 WL 3231427, at *16 (D.N.J. Nov. 8, 2006) ("It is not that *no* subject matter within the claims is enabled, because some examples within the claims certainly are enabled. The point is that the specification does not enable the full scope of the claims as recited above."); *Imperial Chem. Indus., PLC v. Danbury Pharmacal, Inc.*, 777 F.Supp. 330, 373–74 (D. Del. 1991); *Cosden Oil & Chem. Co. v. Am. Hoechst Corp.*, 543 F.Supp. 522, 544 (D.Del. 1982).

Accordingly, to the extent that the claims are not invalid as obvious, the claims of the '664 patent are invalid for failing to satisfy the enablement requirement of 35 U.S.C. § 112.

G. Invalidity of the '546, '414, and '786 patents

As explained above, to ensure Padagis is complying with its *Sotera* stipulations in the IPR petitions filed in the '546, '414, and '786 patent IPRs, Padagis does not contend that the '546, '414, and '786 patents are invalid for the same grounds raised, or any grounds that reasonably could have been raised, in Padagis's IPR petitions. However, to the extent Neurelis's certificate of correction is granted in the '546, '414, and '786 patent IPRs, and if Neurelis asserts the corrected patents against Padagis (by way of a new lawsuit, an amended complaint, or otherwise), Padagis

does not waive any defenses with respect to the corrected ’546, ’414, and ’786 patents, and expressly reserves the right to contend that the corrected patents are invalid as obvious and/or anticipated (i.e., grounds that may be raised in an IPR petition) in view of the prior art and arguments discussed in these preliminary invalidity contentions.

Regardless, Padagis maintains that the ’546, ’414, and ’786 patents are invalid under at least 35 U.S.C. § 112. Additionally, Lupin asserts that the ’414 and ’786 patents are invalid under at least 35 U.S.C § 112. Specifically, to the extent the claims of the ’546, ’414, and ’786 patents are not invalid as obvious, which they are, they are invalid for lack of written description and/or non-enablement for the reasons discussed above with respect to the ’664 patent. *Supra* Section V.F. Indeed, just like the claims of the ’664 patent, the claims of the ’546, ’414, and ’786 patents recite a genus of formulations that must be “pharmaceutical solution[s] for nasal administration.” *Supra* Sections II.A.1; II.B.1; II.C.1. Although the prior art renders those broad genus claims obvious, to the extent that such claims are not invalid as obvious, the specification of the ’546, ’414, and ’786 patents fails to demonstrate to a POSA that the inventors possessed the claimed genus that meets the functional limitations. *Supra* Section V.F. Likewise, although the prior art renders those broad genus claims obvious, to the extent that such claims are not invalid as obvious, a POSA would need to engage in undue experimentation to practice the full scope of the claims, as explained above. *Id*.

Accordingly, to the extent that such claims are not invalid as obvious, all claims of the ’546, ’414, and ’786 patents are invalid for lack of written description and/or non-enablement under at least 35 U.S.C. § 112.

1. All Claims of the ’414 Patent and ’786 Patent Are Invalid as Obvious

Defendants Lupin and Amneal assert that the ’414 and ’786 patents are invalid as set forth below. As discussed above, the ’664 patent is related to the ’414 and ’786 patents, and these three

patents claim essentially the same subject matter (that is, solutions containing diazepam, tocopherols, alcohols, and alkyl glycosides). As such, the same or similar arguments discussed above with respect to obviousness of the ’664 patent support obviousness of the ’414 and ’786 patents as well. These arguments, including the specifically discussed prior art combinations, are incorporated by reference, as more fully explained below.[20]

The disclosures and teachings that render the claims of the ’414 and ’786 patents obvious are identified in the claim charts attached hereto as Exhibits B and C. The claim charts provide an element-by-element disclosure of where specifically, in each prior art reference, the relevant claim elements, limitations, or rationale supporting the combination(s) are found. The identifications are not meant to be exhaustive, and the inclusion of certain exemplary combinations in the claim chart does not exclude other combinations. Lupin contends that it would have been obvious to a POSA to combine any of the prior art references to practice any of the claims of the ’414 and ’786 patents. The prior art references are analogous art as each reference is from the same field of endeavor and is reasonably pertinent to the particular problem with which the inventors were involved, or both. To the extent Neurelis contends that an embodiment within a particular prior art reference does not fully disclose all limitations of a claim, Lupin reserves the right to rely on other embodiments in that prior art reference, or other information, to show obviousness.

(a) All Claims of the ’414 Patent Are Invalid as Obvious

Claim 1 of the ’414 patent is obvious for the same reasons discussed above with respect to, for example, claims 1 and 6 of the ’664 patent. Those discussions are incorporated herein in their entirety. As such, claim 1 is invalid as obvious.

[20] In addition, Lupin adopts the preliminary invalidity contentions with respect to the ’414 patent and ’786 patent previously served by Padagis on December 20, 2024, and fully incorporates those positions as if set forth herein.

Claims 2-4 of the ’414 patent are obvious for the same reasons discussed above with respect to, for example, claims 1 and 3-5 of the ’664 patent. Those discussions are incorporated herein in their entirety. As such, claims 2-4 are invalid as obvious.

Claim 5 of the ’414 patent is obvious for the same reasons discussed above with respect to, for example, claim 1 of the ’664 patent. Those discussions are incorporated herein in their entirety. As such, claim 5 is invalid as obvious.

Claims 6-7 of the ’414 patent are obvious for the same reasons discussed above with respect to, for example, claims 1 and 6 of the ’664 patent. Those discussions are incorporated herein in their entirety. As such, claims 6-7 are invalid as obvious.

Claims 8-9 of the ’414 patent are obvious for the same reasons discussed above with respect to, for example, claim 1 of the ’664 patent. Those discussions are incorporated herein in their entirety. As such, claims 8-9 are invalid as obvious.

Claim 10 of the ’414 patent is obvious for the same reasons discussed above with respect to, for example, claims 1 and 2 of the ’664 patent. Those discussions are incorporated herein in their entirety. As such, claim 10 is invalid as obvious.

Claim 11 of the ’414 patent is obvious for the same reasons discussed above with respect to, for example, claims 1 and 6 of the ’664 patent. Those discussions are incorporated herein in their entirety. As such, claim 11 is invalid as obvious.

Claims 12-14 of the ’414 patent are obvious for the same reasons discussed above with respect to, for example, claims 1 and 3-5 of the ’664 patent. Those discussions are incorporated herein in their entirety. As such, claims 12-14 are invalid as obvious.

Claims 15-16 of the ’414 patent are obvious for the same reasons discussed above with respect to, for example, claims 1 and 6 of the ’664 patent. Those discussions are incorporated herein in their entirety. As such, claims 15-16 are invalid as obvious.

Claims 17-18 of the ’414 patent are obvious for the same reasons discussed above with respect to, for example, claim 1 of the ’664 patent. Those discussions are incorporated herein in their entirety. As such, claims 17-18 are invalid as obvious.

* * * *

Lupin contends that no secondary considerations weigh in favor of non-obviousness with respect to any of the claims of the ’414 patent. Any secondary considerations that Neurelis may assert would be insufficient to overcome the strong showing of obviousness in this case with respect to the claims of the ’414 patent. *See DyStar Textilfarben GmbH v. C.H. Patrick Co.*, 464 F.3d 1356, 1371 (Fed. Cir. 2006) (patent found obvious despite commercial success); *In re GPAC Inc.*, 57 F.3d 1573, 1580-81 (Fed. Cir. 1995) (same); *Pentec, Inc. v. Graphic Controls Corp.*, 776 F.2d 309, 315-17 (Fed. Cir. 1985) (same); *Pfizer*, 480 F.3d at 1371-72 (finding secondary considerations insufficient where the record establishes a strong case of obviousness); *Leapfrog Enters., Inc. v. Fisher-Price, Inc.*, 485 F.3d 1157, 1162 (Fed. Cir. 2007) (“[G]iven the strength of the prima facie obviousness showing, the evidence on secondary considerations was inadequate.”); *W. Union Co. v. MoneyGram Payment Sys., Inc.*, 626 F.3d 1361, 1373 (Fed. Cir. 2010) (“[W]eak secondary considerations generally do not overcome a strong prima facie case of obviousness.”). Accordingly, all claims of the ’414 patent are invalid.

(b) All Claims of the ’786 Patent Are Invalid as Obvious

Claim 1 of the ’786 patent is obvious for the same reasons discussed above with respect to, for example, claims 1 and 6 of the ’664 patent. Those discussions are incorporated herein in their entirety. As such, claim 1 is invalid as obvious.

Claims 2-4 of the ’786 patent are obvious for the same reasons discussed above with respect to, for example, claims 1 and 3-5 of the ’664 patent. Those discussions are incorporated herein in their entirety. As such, claims 2-4 are invalid as obvious.

Claims 5-6 of the ’786 patent are obvious for the same reasons discussed above with respect to, for example, claims 1 and 6 of the ’664 patent. Those discussions are incorporated herein in their entirety. As such, claim 5-6 are invalid as obvious.

Claim 7 of the ’786 patent is obvious for the same reasons discussed above with respect to, for example, claim 1 of the ’664 patent. Those discussions are incorporated herein in their entirety. As such, claim 7 is invalid as obvious.

Claims 8-9 of the ’786 patent are obvious for the same reasons discussed above with respect to, for example, claim 1 of the ’664 patent. Those discussions are incorporated herein in their entirety. As such, claims 8-9 are invalid as obvious.

Claim 10 of the ’786 patent is obvious for the same reasons discussed above with respect to, for example, claims 1 and 2 of the ’664 patent. Those discussions are incorporated herein in their entirety. As such, claim 10 is invalid as obvious.

Claim 11 of the ’786 patent is obvious for the same reasons discussed above with respect to, for example, claims 1 and 6 of the ’664 patent. Those discussions are incorporated herein in their entirety. As such, claim 11 is invalid as obvious.

Claims 12-14 of the ’786 patent are obvious for the same reasons discussed above with respect to, for example, claims 1 and 3-5 of the ’664 patent. Those discussions are incorporated herein in their entirety. As such, claims 12-14 are invalid as obvious.

Claims 15-16 of the ’786 patent are obvious for the same reasons discussed above with respect to, for example, claims 1 and 6 of the ’664 patent. Those discussions are incorporated herein in their entirety. As such, claims 15-16 are invalid as obvious.

Claim 17 of the ’786 patent is obvious for the same reasons discussed above with respect to, for example, claim 1 of the ’664 patent. Those discussions are incorporated herein in their entirety. As such, claim 17 is invalid as obvious.

Claims 18-19 of the ’786 patent are obvious for the same reasons discussed above with respect to, for example, claim 1 of the ’664 patent. Those discussions are incorporated herein in their entirety. As such, claims 18-19 are invalid as obvious.

Claims 20-21 of the ’786 patent are obvious for the same reasons discussed above with respect to, for example, claims 1 and 3-5 of the ’664 patent. Those discussions are incorporated herein in their entirety. As such, claims 20-21 are invalid as obvious.

Claims 22-25 of the ’786 patent are obvious for the same reasons discussed above with respect to, for example, claim 1 of the ’664 patent. Those discussions are incorporated herein in their entirety. As such, claims 22-25 are invalid as obvious.

Claims 26-27 of the ’786 patent are obvious for the same reasons discussed above with respect to, for example, claims 1 and 2 of the ’664 patent. Those discussions are incorporated herein in their entirety. As such, claims 26-27 are invalid as obvious.

* * * *

Lupin contends that no secondary considerations weigh in favor of non-obviousness with respect to any of the claims of the ’786 patent. Any secondary considerations that Neurelis may assert would be insufficient to overcome the strong showing of obviousness in this case with respect to the claims of the ’786 patent. *See DyStar Textilfarben GmbH v. C.H. Patrick Co.*, 464

F.3d 1356, 1371 (Fed. Cir. 2006) (patent found obvious despite commercial success); *In re GPAC Inc.*, 57 F.3d 1573, 1580-81 (Fed. Cir. 1995) (same); *Pentec, Inc. v. Graphic Controls Corp.*, 776 F.2d 309, 315-17 (Fed. Cir. 1985) (same); *Pfizer*, 480 F.3d at 1371-72 (finding secondary considerations insufficient where the record establishes a strong case of obviousness); *Leapfrog Enters., Inc. v. Fisher-Price, Inc.*, 485 F.3d 1157, 1162 (Fed. Cir. 2007) ("[G]iven the strength of the prima facie obviousness showing, the evidence on secondary considerations was inadequate."); *W. Union Co. v. MoneyGram Payment Sys., Inc.*, 626 F.3d 1361, 1373 (Fed. Cir. 2010) ("[W]eak secondary considerations generally do not overcome a strong prima facie case of obviousness."). Accordingly, all claims of the '786 patent are invalid.

H. The Claims of the '400 Patent Are Invalid as Obvious

The claims of the '400 patent are invalid as obvious in light of the prior art discussed above, either alone, in combination, and/or with the knowledge of a POSA. It would have been obvious to a POSA as of the priority date of the '400 patent to combine the various cited prior art. Moreover, the prior art renders the claims of the '400 patent obvious because, to the extent a prior art reference may not expressly teach or disclose a component of the system claimed or recited in the claims of the '400 patent, such "missing" component was nevertheless known in the art and adding the well-understood "missing" component would yield predictable results, so that the subject matter of the claim as a whole would have been obvious to a POSA at the time the invention was made. *See generally KSR,* 550 U.S. 398.

The disclosures and teachings that render the claims of the '400 patent obvious are identified in the claim chart attached hereto as Exhibit F. The claim chart provides an element-by-element disclosure of where specifically, in each prior art reference, the relevant claim elements, limitations, or rationale supporting the combination(s) are found. The identifications are not meant to be exhaustive, and the inclusion of certain exemplary combinations in the claim chart does not

exclude other combinations. Defendants contend that it would have been obvious to a POSA to combine any of the prior art references to practice any of the claims of the ’400 patent. The prior art references are analogous art as each reference is from the same field of endeavor and is reasonably pertinent to the particular problem with which the inventors were involved, or both. To the extent Neurelis contends that an embodiment within a particular prior art reference does not fully disclose all limitations of a claim, Defendants reserve the right to rely on other embodiments in that prior art reference, or other information, to show obviousness.

1. A POSA Would Have Been Motivated to Develop Intranasal Formulations of Diazepam with a Reasonable Expectation of Success

A POSA would have been motivated to combine the teachings of the prior art references discussed above as of the priority date of the ’400 patent. A motivation to combine references may be present in the nature of the problem to be solved. It was well-known in the art that the poor water solubility of diazepam created issues developing practical diazepam formulations. Indeed, the ’400 patent acknowledges the known problem in the art regarding the inability to administer benzodiazepine drugs (e.g., diazepam) due to the limited solubility of the drug compounds as well as the problems associated with other known formulations, including oral, intravenous, and rectal dosage forms. *Supra* Section II.D.2. For example, the ’400 patent states:

> Current formulations of benzodiazepine drugs can be administered orally, rectally, or parenterally. The ability to utilize these and other types of formulations has been significantly limited due, in many cases, to solubility challenges.
>
> The oral route of administration may be considered sub-optimal due to several disadvantages. For example, the amount of time required for an orally administered benzodiazepine drug to reach therapeutically relevant concentrations in blood plasma may be rather long, such as an hour or more. Moreover, as benzodiazepine drugs pass through the liver a significant amount may be metabolized. Thus, it may require large doses to achieve therapeutic plasma levels. Furthermore, due to the nature of seizures and muscle spasms, it can be extremely difficult for either a patient or a care-giver to administer the benzodiazepine drug orally.

> Intravenous administration perhaps provides a faster route of administration. However intravenous administration is generally limited to trained health care professionals in tightly controlled clinical settings. Additionally, sterility must be maintained. Furthermore, administering any drug intravenously can be painful and is likely impractical for patients suffering from a phobia of needles.
>
> Suppository compositions of benzodiazepine drugs can have a rapid onset of action. However, the inconvenience of suppositories is an obvious impediment to their being administered by anyone outside a very small group of the patient's intimate acquaintances and the patient's professional medical caretakers.

'400 patent at 1:59-2:20.

Thus, the '400 patent acknowledges that, due to the limited solubility of benzodiazepine drugs, only certain types of dosage forms were possible, including oral, intravenous, and suppository dosage forms. However, each of these dosage forms suffered from considerable shortcomings: oral dosage forms take considerable time to reach therapeutic drug levels, and suffer from significant liver metabolism; intravenous dosage form administration is primarily limited to trained health care professionals, and maintaining sterility of the dosage form; and suppository dosage forms are inconvenient to administer, given the requirement for rectal administration.

Other prior art references had also discussed these issues, noting that intravenous administration (via injection) was an acceptable method to achieve a rapid and systemic effect of the drug compound (including benzodiazepines), but require sterile syringes, skilled personal capable of initiating the intravenous injection, as well as the pain and irritation associated with administration. Cloyd at ¶0003. In view of these problems, particularly for the treatment of emergency situations such as epileptic seizures, other types of administration were preferred. *Id.* at ¶0004. While one such alternative was rectal diazepam (for the emergency treatment of epileptic seizures), the route of administration was generally considered not acceptable for school-age children and adolescents due to the unwillingness of patients and caregivers to administer the formulation rectally. *Id*. A POSA would have been aware of all of these issues in view of the prior

art, and would have sought guidance on other potential dosage forms and routes of administration, especially for the treatment of emergency medical conditions (*e.g.*, the use of diazepam for the treatment of emergency seizures).

(a) A POSA Was Motivated to Utilize Sonne and/or Li as Primary References for the Development of Diazepam Intranasal Formulations

Sonne discloses "[t]he present invention is based on the surprising observation that tocopherols and derivatives thereof are excellent solvents for drugs which are substantially insoluble or sparingly soluble in water, whilst at the same time having a very low irritative potential for mucosal tissues." Sonne at 2:54-58. Sonne also explains that "[i]n one aspect, the present invention thus provides the use of a tocopherol or a derivative thereof as a solvent and/or emulsifier for substantially insoluble and sparingly soluble biologically active agents, especially in the manufacture of pharmaceutical compositions." *Id.* at 2:63-67. Sonne further explains that "[t]ransmucosal delivery is preferred however, and compositions according to the invention may be administered to mucosal membranes…*[n]asal*, rectal and oral cavity administrations are particularly preferred." *Id*. at 3:54-59. Sonne additionally teaches that tocopherols act as solvents "whilst at the same time having a very low irritative potential for mucosal tissues." *Id.* at 2:55-58.

Moreover, Sonne discloses that diazepam was one preferred drug compound, with low water solubility, that could be developed in the tocopherol-based formulations, including exemplary solution and emulsion formulations. *Id*. at 7:32 to 8:10 (Example 1, diazepam "nosedrop"); 8:11-27 (Example 1, diazepam nosedrop); 10:20-67 (Examples 8-10, diazepam emulsions); 11:1-13 (Example 11, solution of diazepam, e.g. as a nosedrop). For at least these reasons, a POSA would have also looked to Sonne as a potential lead reference for guidance on strategies to improve the solubility of benzodiazepine drugs in an effort to develop new dosage forms, including nasally administered formulations.

Moreover, a POSA would have also viewed Li as a potential primary reference. Li discloses diazepam intranasal formulations administered in rabbits. Li at Abstract. Specifically, Li discloses that an intranasal formulation containing 2% diazepam in a carrier of 30-60% propylene glycol, 30-60% ethanol, 10% water, and 1% sodium glycholate provided a T_{max} of only 2.0 minutes, and a bioavailability of greater than 77% when compared to administration of 0.5% diazepam intravenously. *Id*. at 70-71. Consequently, a POSA would recognize that Li had already begun work to develop intranasal formulations with a quick onset of action (i.e., T_{max} of 2 minutes) that would serve as lead formulations in the effort to develop intranasal diazepam formulations.

For at least these reasons, a POSA would have been motivated by Sonne and/or Li to develop formulations with improved solubility for benzodiazepine drugs in an effort to develop new dosage forms, including nasally administered formulations suitable for emergency treatment.

(b) A Motivation and Reasonable Expectation of Success Existed to Combine the Prior Art Teachings to Pursue Carrier Systems Containing α-Tocopherol Compounds and Alcohols, Including Ethanol and Benzyl Alcohol

A POSA would know that there are historic and commercial examples of formulating diazepam with alcohols, including benzyl alcohol and ethanol, along with other solvents. In particular the combination was known from commercial products Diastat and Valium injection (which was known to be used intranasally with the MAD device and known to work for the emergency treatment of seizures; *see* EMS, pp. 54-55, 69-71), both of which included ethanol and benzyl alcohol as excipients. PDR at 1012, 2676. Thus, a POSA was aware of formulations containing diazepam in combination with ethanol and benzyl alcohol in various formulations, including formulations that were administered intranasally.

Additionally, benzyl alcohol and ethanol were known to be readily miscible, meaning that a POSA would not have concerns about the two solvents being incompatible. *See* Rowe at 54,

Table III; Merck Index at 189.

Further, Sonne teaches that "[t]he compositions of the invention may be used directly as solutions of the bioactive agent in the tocopherol solvent. However such solutions are viscous, and the viscosity may be too high for certain applications, for example to achieve a sprayable formulation for nasal application…Viscosity can be reduced by addition of co-solvents such as ethanol…" Sonne at 3:60-67. Sonne discloses that tocopherols can be combined with alcohols, such as ethanol, to form a solvent system for a bioreactive agent (e.g., diazepam). Sonne's disclosure is consistent with what was known by a POSA, namely that alcohols (including ethanol and benzyl alcohol) had been used previously to intranasally administer diazepam (i.e., in the form of Valium®) as disclosed in the Florida EMS manual. *See* Florida EMS at 54-55, 69-71. For at least these reasons, a POSA would be motivated and would at least reasonably expect that alcohols (including ethanol and benzyl alcohol) and tocopherols could be combined to make a nasal formulation of diazepam, as taught by the prior art disclosures of Sonne and Li.

(c) A POSA Was Motivated with a Reasonable Expectation of Success to Combine the Teachings of Meezan with Sonne and/or Li

Moreover, regarding the inclusion of an "absorption enhancer," a POSA was motivated to combine the teachings of Meezan related to alkyl glycosides with the pharmaceutical solutions described in Sonne and/or Li. Sonne discloses that "[t]he compositions of the invention may take any of the conventional pharmaceutical forms known in the art, and may be formulated in conventional manner, optionally with one or more pharmaceutically acceptable carriers or excipients. Thus for example the compositions may take the form of ointments, creams, solutions, salves, emulsions, lotions, liniments, aerosols, sprays, drops, pessaries, suppositories, tablets, capsules or lozenges." Sonne at 6:29-35. Sonne explains that "the present invention provides the use of a tocopherol or a derivative thereof for the preparation of a composition for delivery of a

substantially insoluble or sparingly soluble biologically active agent to a human or non-human animal subject," and that the "[t]he formulations according to the invention may be optimized with respect to bioadhesion, sprayability and viscosity, as desired." *Id.* at 6:36-49. In view of Sonne's teachings, a POSA again would have looked to additional references for guidance regarding additive compositions to improve the efficacy of the formulations of Sonne.

Moreover, Li discloses solvent carriers containing propylene glycol, ethanol, and water; however, Li also developed formulations containing sodium glycocholate (SGC). Li at 69. Li explains that "SGC has been one of the most extensively employed bile salts in in vitro and in vivo studies," and that SGC was "known to enhance intranasal absorption while producing minimal irritation and morphological alteration in the nasal mucosa." *Id.* at 70. Indeed, the formulations of Li that further included SGC (in addition to propylene glycol (PG), ethanol (EtOH), and water) reported an increase in bioavailability from 59.1% (for the carrier containing only 60% PG, 30% EtOH, and 10% water) to 77.3% (for the carrier containing 1% SGC, 60% PG, 30% EtOH, and 10%). *Id*. at 71 (Table 1 comparison of IN formula 1b and formula 2c). Thus, Li had already begun to experiment with the addition of absorption enhancers to diazepam intranasal solvent systems and had demonstrated that the inclusion of an absorption enhancer (1% SGC) increased bioavailability of the intranasal formulation. However, the bioavailability was still only 77.3% of that achieved with diazepam intravenous administration, meaning a POSA would have still been motivated to look for guidance on other absorption enhancers that could further improve the bioavailability of the intranasal diazepam formulations.

Meezan provides further guidance, as it is directed to "therapeutic composition[s] containing a drug enhancing agent useful for increasing the absorption and bioavailability of the drug, while at the same time avoiding various adverse toxic effects of drug." Meezan at ¶ [0004].

Meezan teaches utilizing compounds that increase the absorption (i.e., penetration enhancers) and bioavailability of drug compounds. Based on this, a POSA was motivated to apply the teachings of Meezan related to alkyl glycosides to the pharmaceutical solutions of Sonne and/or Li.

Additionally, a POSA would have expected surfactants, such as the alkyl glycosides, to increase the bioavailability of intranasal formulations. Sharma teaches that low concentrations of surfactants, including the alkyl glycosides, "are incorporated into the lipid bilayer, forming polar defects in the membrane". Sharma at 500. Sharma further discloses that "[a]lkyl glycosides are nonionic surfactants capable of enhancing glucagon or insulin absorption through the nasal, ocular or pulmonary routes." *Id.* at 501 (citing U.S. Pat. No. 5,661,130 to Meezan et al.). Ahsan proposed that the improvement in bioavailability provided by alkyl glycosides was attributable to either "increasing paracellular movement of drugs through loosened tight junctions, or by increasing transcellular drug movement through endocytic vesicles." Ahsan at 27. Sharma found that "alkylglycosides such as tetradecylmaltoside or dodecyl-maltoside administered with insulin via the nasal, ocular, or inhalational routes have shown significant reductions in blood glucose levels in rats." Sharma at 501 (citing U.S. Pat. No. 5,661,130 to Meezan et al.). A POSA would be motivated by these teachings to include surfactant-based permeation enhancers such as alkyl glycosides to improve the nasal absorption of drugs, as the prior art established that even large drug molecules (e.g., glucagon and insulin) showed improved bioavailability when nasally administered with alkyl glycosides.

It was well-known that larger molecules inherently have a more difficult time crossing the cell membrane than smaller molecules. If a permeation enhancer increases penetration for a large molecule, it will be expected to also increase penetration for a small molecule, simply because molecular size can be one of the primary constraints for passing through and between epithelial

cells. Meezan teaches that alkyl glycosides will increase the bioavailability of small molecules, and identifies molecules having molecular weight below 1.5 kDaltons as candidates for improved bioavailability. Meezan at ¶ [0130]. Diazepam is a small molecule, having a molecular weight of 284.74. *See* PDR at 2677. Thus, a POSA would understand Meezan's teachings as motivating the use of alkyl glycosides with small molecule compounds, such as benzodiazepines, and, in particular diazepam. Meezan also discloses using alkyl glycosides in non-aqueous systems:

> Additionally, the therapeutic compositions of the invention can consist of a pharmaceutically acceptable carrier. A 'pharmaceutically acceptable carrier' is an aqueous or non-aqueous agent, for example alcoholic or oleaginous, or a mixture thereof, and can contain a surfactant,...a solvent,... Pharmaceutically acceptable carriers are well known in the art and include, for example,...oils such as olive oil or injectable organic esters...A pharmaceutically acceptable carrier can also be selected from substances such as...benzyl alcohol,....

Meezan at ¶ 74.

Thus, a POSA would have been motivated to increase the solubility of diazepam using the solvent/carrier systems described in Sonne and/or Li. Given diazepam's potency, and in recognition of its limited water solubility, a POSA would also have been motivated to pursue strategies to enhance the absorption of diazepam, based on the teachings of Meezan. For at least these reasons, a POSA would be motivated to add Meezan's alkyl glycosides (e.g., dodecyl maltoside) to the solvent systems described in Sonne and/or Li.

Finally, a reasonable expectation existed that solution formulations could be successfully developed, and, at least with regard to the inclusion of an "absorption enhancer," that alkyl glycoside compounds could be successfully incorporated into the intranasal solvent formulations of Sonne and/or Li. Obviousness requires only a reasonable expectation of success; absolute certainty is not required. *PAR Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1198 (Fed. Cir. 2014) ("The reasonable expectation of success requirement for obviousness does not necessitate

an absolute certainty for success."). As noted, Sonne discloses that the "[t]he formulations according to the invention may be optimized with respect to bioadhesion, sprayability and viscosity, as desired." Sonne at 6:36-49. Similarly, Li teaches formulations containing absorption enhancers, such sodium glycocholate (SGC). Li at 69. Meezan teaches "therapeutic composition[s] containing a drug enhancing agent useful for increasing the absorption and bioavailability of the drug, while at the same time avoiding various adverse toxic effects of drug," (Meezan at ¶ [0004]), and that "the alkyl glycoside be nontoxic and nonionic, and that it increases the absorption of a compound when it is administered with the compound via the ocular, nasal, nasolacrimal, inhalation or pulmonary, oral cavity (sublingual or Buccal cell), or CSF delivery route." Meezan at ¶ [0054]. Consequently, Sonne and Li both teach the inclusion of additional compounds, including absorption enhancers, and Meezan teaches that the alkyl glycosides described therein can be incorporated into nasal formulations to increase absorption of the drug compound. For at least these reasons, a POSA would have at least a reasonable expectation that the alkyl glycosides of Meezan could successfully be incorporated into the solutions of Sonne and/or Li.

(d) A POSA Was Motivated with a Reasonable Expectation of Success to Combine the Teachings of Sonne and Li

As discussed above, Li represents one potential primary reference in the development of an intranasal diazepam solution to provide treatment of seizures, including the emergency treatment of seizures. Li is directed to intranasal diazepam formulations, whereby the diazepam was dissolved in a solvent system containing 30% ethanol (EtOH), 60% propylene glycol (PG), 10% water, and plus or minus 1% sodium glycholate (SGC). Li at 67. However, the total concentration of diazepam in the solvent system was only 2% (i.e., 20 mg/ml). *Id.* at 70 (Table 1), at 71 (Table 2). This concentration is not surprising given that it was known in the art that the solubility of diazepam in propylene glycol was ~1.7% (i.e., 17 mg/ml), and the majority of the Li

solution was propylene glycol. Given the limited solubility of diazepam in propylene glycol, and the fact that propylene glycol constitutes 60% of the Li intranasal solution, a POSA would expect that that it would be difficult to achieve diazepam concentrations much higher than the 2% concentration reported in Li, meaning that the amount of diazepam that could be delivered in a single nasal spray was also limited by the concentration limit.

As stated in Sonne, and as generally known in the art, the maximum volume of a nasal spray that can be administered to the nasal passage (due to the physical dimensions of the nasal passage) is about 100-200 µL (0.1-0.2 ml). *See* Sonne at 2:30-33; Wermeling, at 354 (the nasal cavity can retain 100 to 150 µL without causing immediate run-off out the front of the nose or down the naso-pharynx); *see also, e.g.*, Cloyd at ¶ [0006]. Consequently, for the intranasal diazepam solution of Li, with a diazepam contention of 2% (20 mg/ml), the administration of 100-200 µL (0.1-0.2 ml) in a single nasal spray means that it was only possible to deliver at most 2-4 mg of diazepam to the nasal passage of the patient (20 mg/ml x (0.1-0.2 ml) = 2-4 mg diazepam). It was known in the art that the treatment of status epilepticus would often require diazepam doses of 10-20 mg (when administered either rectally or intravenously). In view of this, a POSA would have recognized that, due to the diazepam solubility constraints of propylene glycol, the administration of 2-4 mg of diazepam (via the intranasal diazepam solution of Li) may not be sufficient to treat an active episode of seizure activity, and would have been motivated to find other solvents that could be utilized with diazepam, and would allow for a greater solubility of diazepam within the intranasal solution (allowing for a greater amount of diazepam to be delivered per spray to the nasal cavity).

Sonne provides this guidance, stating that "the invention concerns the use of a tocopherol or a derivative thereof to prepare compositions having low irritability suitable for administration

to mucosal membranes and which may be used efficiently to administer drugs, which are substantially insoluble or only sparingly soluble in water." Sonne at 1:8-13. In fact, Sonne discloses that diazepam was shown to have a solubility of 12% w/w in α-tocopherol. *Id.* at 9:35-60 (Table 1). Assuming a density similar to that of water (i.e., ~1.0 mg/ml), the 12% w/w solubility of diazepam in α-tocopherol corresponds to a solubility of 12% w/v (i.e., 120 mg/ml), which is significantly higher than the solubility of diazepam in propylene glycol (i.e., 20 mg/ml). Thus, a POSA would have been motivated to combine and apply the teachings of Sonne related to the use of α-tocopherol as a solvent for diazepam to Li's intranasal diazepam solution, as a POSA would reasonably expect that doing so would increase the amount of diazepam that can be delivered to the nasal passage within a spray.

(e) A Motivation and Reasonable Expectation of Success Existed to Utilize Alcohols in the Intranasal Spray Formulations of Sonne and/or Li, Despite Any Potential Irritation

While there were reports of potential irritation of the nasal mucosa resulting from the inclusion of alcohols (e.g., ethanol and benzyl alcohols) in intranasal formulations (*see, e.g.,* Wermeling IV at 6:31-39), a POSA would not have been dissuaded from their use in an emergency seizure treatment, and would have nonetheless been motivated to include alcohols in the intranasal formulations based on previous formulations that had utilized alcohols. Specifically, as discussed above, Florida EMS used diazepam intravenous solutions—which contained benzyl alcohol and ethanol—for nasal administration of diazepam in connection with the emergency treatment of seizures. *See* Florida EMS at 54-55, 69-71. Further, even if a POSA were to accept that benzyl alcohol or ethanol may cause some irritation to the nasal mucosa, a POSA would view this as an acceptable design choice in cases of treating acute life-threatening indications, such as epileptic seizures.

2. All Claims of the ’400 Patent Are Invalid as Obvious Over Sonne Optionally in view of Meezan, Cartt 2008, Cloyd, Florida EMS Manual, and/or USP

All claims of the ’400 patent would have been obvious over Sonne optionally in view of Meezan, Cartt 2008, Cloyd, Florida EMS Manual, and/or USP, which are summarized above. *Supra* Section V.D. In view of this additional and alternative combination of prior art references, a POSA would have been motivated to make the claimed intranasal diazepam solution formulations, and would have had a reasonable expectation of success. *Supra* Section V.E.1.

(a) Independent Claim 1 of the ’400 Patent Would Have Been Obvious

Independent claim 1 of the ’400 patent recites “a pharmaceutically-acceptable spray formulation” that is a “solution” containing ranges of amounts of diazepam, tocopherols or tocotrienols, alcohols. *Supra* Section II.D.1. For the reasons discussed above, at least with regard to the inclusion of an “absorption enhancer,” a POSA would have been motivated to combine the teachings of Meezan with Sonne to develop an intranasal solution formulation of diazepam. *Supra* Section V.H.3. Indeed, in view of the known shortcomings associated with rectal and intravenous diazepam formulations, it was known in the art, as evidenced by, *e.g.*, the disclosures of Sonne, Cloyd, Cartt 2008, and Florida EMS Manual, that the art had begun to explore the development of intranasal diazepam formulations for the treatment of seizures, including emergency treatment of seizures. Thus, a POSA would have been motivated to develop intranasal diazepam spray formulations to overcome issues and problems associated with existing formulations of diazepam. *See, e.g.*, Sonne at 7:25-30; Cloyd at ¶¶ [0003]-[0012]; Cartt 2008 at ¶¶ [0003]-[0008]; Florida EMS Manual at 54.

Further, a POSA would have been motivated to make a solution formulation containing the ranges and amounts of diazepam, tocopherols or tocotrienols and alcohols recited in claim 1 of the

’400 patent. For example, regarding the claimed requirement of “a pharmaceutical composition for intranasal administration …wherein the pharmaceutical composition is a solution,” Sonne discloses solutions containing bioreactive agents, stating that “[t]he compositions of the invention may be used directly as solutions of the bioactive agent in the tocopherol solvent.” Sonne at 3:60-61. Sonne further explains that “[n]asal, rectal and oral cavity administrations are particularly preferred” for the formulations, establishing that the Sonne formulations can be administered intranasally. In fact, Sonne specifically disclosed examples of “[a] solution of diazepam, eg. as nosedrop” containing diazepam in combination with α-tocopherol (but with no water). *Id*. at 11:1-13. Consequently, Sonne provides a teaching of the claimed requirement of “a pharmaceutical composition for intranasal administration…wherein the pharmaceutical composition is a solution.”

Regarding the requirement for the inclusion of “about 1 to about 20 mg of diazepam,” Sonne discloses this limitation. Specifically, Fig. 1 of Sonne illustrates the intranasal administration of 2.5 mg diazepam. *Id*. at 7:15-18. Additionally, Examples 1, 22, and 23 of Sonne report the administration of amounts of diazepam including 2 mg, 2.5 mg, and 10 mg. *Id.* at 7:32-58; 13:56 to 14:13; and 14:63-67.

Regarding the claimed requirement that the diazepam is “dissolved in about 45% to about 85% (w/w) of one or more natural or synthetic tocopherols or tocotrienols selected from the group consisting of α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, α-tocotrienol, β-tocotrienol, γ-tocotrienol, δ-tocotrienol, tocophersolan, any esters thereof and any combinations thereof,” this limitation is disclosed by Sonne. Specifically, Sonne disclosed “the use of a tocopherol or a derivative thereof as a solvent … for substantially insoluble and sparingly soluble biologically active agents, especially in the manufacture of pharmaceutical compositions” suitable for intranasal administration. *Id*. at Abstract. According to Sonne, the formulations could contain “1

to 95% (w/w) of the tocopherol or derivative thereof, preferably 20 to 95% (w/w), most preferably 35 to 80% (w/w)." *Id*. at 5:58-61. Moreover, Sonne discloses at least one exemplary solution formulation containing 10 g of α-tocopherol in a total solution weight of 25 g, equating to an α-tocopherol concentration of 40% w/w. *Id*. at 11:1-13 (Example 11).

Claim 1 of the '400 patent further requires the inclusion of "about 25% to about 40% (w/w) of one or more alcohols selected from the group consisting of ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, and any combinations thereof." Sonne discloses and renders obvious this limitation. Specifically, Sonne explained that "[t]he formulations according to the invention may be optimized with respect to bioadhesion, sprayability and viscosity, as desired" by incorporating "co-solvents" like "alcohols such as ethanol … or benzyl alcohol." *Id*. at 6:47-53. Additionally, when disclosing that the "compositions of the invention may be used directly as solutions of the bioactive agent in the tocopherol solvent," Sonne discloses that the viscosity of such a solution "may be too high for certain applications, for example to achieve a sprayable formulation for nasal application," and, because of that, "[v]iscosity can be reduced by addition of co-solvents such as ethanol…" *Id*. at 3:60-67. Consequently, based on the disclosure of Sonne, a POSA would have bene motivated to add ethanol as a co-solvent to the α-tocopherol solution, and would reasonably expect that doing so would reduce the viscosity and allow for spray administration.

As to the specific inclusion of "about 25% to about 40% (w/w)" of the one or more alcohols, Example 11 of Sonne, directed to a solution of diazepam, incorporated 55% w/w of a co-solvent, namely triacetin (13.75 g of triacetin within a total solution weight of 25 g). *Id*. at 11:1-13. Moreover, the use of a co-solvent within the α-tocopherol solution is merely a result-effective variable, as the amount of co-solvent (e.g., ethanol) would directly impact the viscosity of the

solution, as suggested by Sonne. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *See In Re Aller,* 220 F.2d 454, 456 (CCPA 1955). As such, it was merely a matter of routine experimentation and optimization to utilize the co-solvent, including ethanol, in an amount of "about 25% to about 40% (w/w)." For at least these reasons, Sonne teaches and renders obvious the inclusion of "about 25% to about 40% (w/w) of one or more alcohols selected from the group consisting of ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, and any combinations thereof."

Regarding the claimed requirement that the pharmaceutical solution has a volume of "50 µL to 150 µL," this limitation is disclosed and rendered obvious by Sonne. Specifically, Sonne states that the formulations described therein for administration to the nose must be administered in small volumes of "about 100 µL." Sonne at 7:25-30. Similarly, Cloyd discloses that liquid compositions for intranasal administration preferably have a volume "from about 50 µl to about 150 µl." Cloyd at ¶¶ [0055]-[0056]. Thus, Sonne and Cloyd disclose and renders obvious the claimed requirement that the pharmaceutical solution has a volume of "50 µL to 150 µL."

Finally, regarding the requirement that "the pharmaceutical composition is in a pharmaceutically-acceptable spray formulation for intranasal administration," Sonne discloses that the compositions are preferably administered via the "[n]asal" route, and that the compositions may take the form of "sprays." *Id*. at 3:58-59, 6:34-35. Consequently, Sonne discloses the claimed requirement that "the pharmaceutical composition is a solution…is in a pharmaceutically-acceptable spray formulation."

A POSA also would have been motivated to make the claimed intranasal diazepam solution formulations when Sonne is read further in view of Cloyd and Meezan. Cloyd disclosed

"benzodiazepine ***solutions*** that are sufficiently stable to prevent the active ingredient from precipitating during the time required for delivery across the nasal mucosal membrane." Cloyd at ¶ [0002] (emphasis added). According to Cloyd, the solution formulations contained "at least about 10 mg/ml of the benzodiazepine" where "the intranasal volume delivered to an individual in need of a benzodiazepine is … between about 50 µl to about 150 µl per nostril." *Id*. at ¶¶ [0055]-[0056]. Thus, Cloyd disclosed intranasal solution formulations containing a range of doses of diazepam, including about 10 mg of diazepam.

However, Cloyd's formulations relied on a supersaturated solution of diazepam in water and glycofurol. *See, e.g.*, *id*. at ¶ [0013]. A POSA would have understood that Cloyd's water-based (i.e., aqueous) formulations would have inherent drawbacks both because of diazepam's known solubility challenges in water and because supersaturated solutions were known to naturally convert into suspensions (i.e., where the drug is initially fully dissolved in solution, but later crashes out of solution in a solid phase). Indeed, Cloyd explained that:

> A major difficulty presented by the nasal route is the small size of the nasal cavity, such that total dosing volume (which may involve administration through both nostrils) should not generally exceed 150 µl per nostril. Assuming that a DZP dose of 10 mg would be required in adults, a highly concentrated diazepam solution is required. Since DZP's solubility in water (˜0.05 mg/ml) is very low and the dosage requirement is equal to or greater than 0.2 mg/kg, it is difficult to formulate a 100% aqueous solution of DZP for nasal use.

Id. at ¶ [0082]. Thus, consistent with a POSA's knowledge of the state of the art of diazepam solution formulations, Cloyd expressly disclosed that it was difficult to prepare aqueous solutions of diazepam with a 10 mg dose in the low volumes necessary for nasal administration. Accordingly, a POSA would have been motivated to investigate alternative, non-aqueous solution formulations of diazepam that would be better suited for a lipophilic compound like diazepam.

To that end, Sonne disclosed "the use of a tocopherol or a derivative thereof as a solvent … for substantially insoluble and sparingly soluble biologically active agents, especially in the manufacture of pharmaceutical compositions" suitable for intranasal administration. Sonne at Abstract. And Sonne specifically disclosed examples of "diazepam nosedrop" formulations containing diazepam and various excipients, including Vitamin E and α-Tocopherol. *Id*. at 7:32-8:27, 10:20-11:13. According to Sonne, the formulations could contain "1 to 95% (w/w) of the tocopherol or derivative thereof, preferably 20 to 95% (w/w), most preferably 35 to 80% (w/w)." *Id*. at 5:58-61. Like Cloyd, Sonne disclosed examples of intranasal formulations containing various amounts of diazepam, including an example containing 10 mg of diazepam. *Id*. at 14:63-67.

Sonne also explained that "[t]he formulations according to the invention may be optimized with respect to bioadhesion, sprayability and viscosity, as desired" by incorporating "co-solvents" like "alcohols such as ethanol … or benzyl alcohol." *Id*. at 6:47-53.

Similarly, Meezan discloses formulations containing a "therapeutic composition" in "solutions," (Meezan at ¶ [0049]), and that the "compositions of the invention can consist of a pharmaceutically acceptable carrier[,] [a] 'pharmaceutically acceptable carrier' is an aqueous or non-aqueous agent, for example alcoholic or oleaginous, or a mixture thereof." Meezan at ¶ [0074]. Thus, a POSA would have been motivated to formulate diazepam in a non-aqueous solution formulation containing Vitamin E and co-solvents (i.e., ethanol and benzyl alcohol) in view of Sonne, Cloyd, and Meezan.

Further, a POSA would have been motivated by Cartt 2008, Florida EMS Manual, and/or USP to use the claimed amounts of diazepam, tocopherols or tocotrienols, and alcohols as excipients. For example, USP disclosed that Vitamin E and tocopherols were useful for pharmaceutical formulations. *See, e.g.*, USP at 1631. Similarly, as discussed above, Florida EMS

used diazepam intravenous solutions—which contained benzyl alcohol and ethanol—for nasal administration of diazepam in connection with the emergency treatment of seizures. *See* Florida EMS at 54-55, 69-71

Moreover, Cartt 2008 expressly disclosed intranasal formulations of diazepam with the goal of solving the same issues described in the art generally. Cartt 2008 at Abstract. Cartt 2008 disclosed that non-aqueous formulations containing "about 1 to about 20, preferably about 2 to about 10 mg per dose" of diazepam may be desirable for the reasons discussed above. *See, e.g.*, *id*. at ¶¶ [0021]-[0023], [0063]. And Cartt 2008 disclosed that "n-dodecyl β-D-maltoside" may be used as an excipient in the intranasal diazepam formulations. *See, e.g.*, *id*. at ¶ [0129].

Accordingly, a POSA would have been motivated to make a pharmaceutically acceptable spray formulation of diazepam in the form of a solution containing the amounts of diazepam, tocopherols or tocotrienols, and alcohols recited in claim 1 of the '400 patent over Sonne optionally in view of and Meezan, Cartt 2008, Cloyd, USP, and/or Florida EMS Manual. A POSA also would have had a reasonable expectation of success in view of those references for the reasons discussed above.

(b) Independent Claims 12 and 20 of the '400 Patent Would Have Been Obvious

Independent claims 12 and 20 are similar to claim 1, differing in only two aspects. First, claims 12 and 20 require that the one or more natural or synthetic tocopherols is α-tocopherol (whereas claim 1 more broadly recites "one or more natural or synthetic tocopherols or tocotrienols selected from the group consisting of α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, α-tocotrienol, β-tocotrienol, γ-tocotrienol, δ-tocotrienol, tocophersolan, any esters thereof and any combinations thereof"). Additionally, claim 20 requires that the pharmaceutical composition is in a volume of "about 100 µL" (whereas claim 1 and 12 recite a volume of "50 µL to 150 µL"). Sonne

optionally in view of Meezan, Cartt 2008, Cloyd, Florida EMS Manual, and/or USP disclose and render obvious these requirements.

The previous analysis establishing the obviousness of claim 1 of the '400 patent is incorporated herein in its entirety. Regarding the requirement for the inclusion of α-tocopherol, as discussed, Sonne expressly disclosed that diazepam could be formulated for intranasal administration as a solution containing α-tocopherol, including in an amount ranging from about 40% to about 99.99% (w/w). *See, e.g.*, Sonne at 5:58-61, 7:32-8:27, 10:20-11:13. Further, regarding the requirement that the pharmaceutical composition is a volume of "about 100 μL," as explained above, a POSA would have understood that intranasal administration of a pharmaceutical formulation necessarily requires the claimed volumes, and would have been motivated to use a volume of "about 100 μL" specifically. *See, e.g.*, Sonne at 7:25-30 ("administration of drugs with very low water solubility to the nose is difficult, because of the limited volume which is acceptable for the nose (about 100 μL)"); Cloyd at ¶¶ [0055]-[0056] ("the intranasal volume delivered to an individual in need of a benzodiazepine is…more particularly between about 50 μL to about 150 μL per nostril"). Accordingly, for the reasons discussed above, a POSA would have been motivated to formulate an intranasal diazepam formulation utilizing α-tocopherol as the tocopherol, and with the pharmaceutical composition in a volume of "about 100 μL," and would have had a reasonable expectation of success in doing so.

(c) The Dependent Claims of the '400 Patent Would Have Been Obvious

For the reasons explained above, dependent claims 2-11, 13-19, and 21 would have been obvious over Sonne optionally in view of Meezan, Cartt 2008, Cloyd, Florida EMS Manual, and/or USP. *Supra* Section V.H.1(a)-(b). To be sure, the prior art disclosed each of the limitations of

dependent claims 2-11, 13-19, and 21 of the ’400 patent, expressly or inherently, as discussed below.

Dependent claims 2-3, 6, and 15 require that “the natural or synthetic tocopherols or tocotrienols are selected from the group consisting of: α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, tocophersolan, any esters thereof and any combinations thereof” (claim 2); “the natural or synthetic tocopherols or tocotrienols is α-tocopherol” (claim 3); “the pharmaceutical solution comprises one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof in an amount from about 60% to about 75% (w/w)” (claim 6); and “ the pharmaceutical solution comprises α-tocopherol in an amount from about 60% to about 75% (w/w)” (claim 15). As explained above, Sonne expressly disclosed that diazepam could be formulated for intranasal administration as a solution containing α-tocopherol, including in an amount ranging from about 40% to about 99.99% (w/w). *See, e.g.*, Sonne at 5:58-61, 7:32-8:27, 10:20-11:13. Accordingly, for the reasons discussed above, a POSA would have been motivated to develop the Sonne solution formulation containing α-tocopherol, and it would have been a matter of routine experimentation and optimization to utilize the tocopherol in an amount ranging from about 60-75% (w/w), and would have had a reasonable expectation of success. *See In Re Aller,* 220 F2d 454, 456 (CCPA 1955) (“[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.”).

Dependent claim 4 requires that “the one or more alcohols is selected from the group consisting of ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, isomers thereof and any combinations thereof.” ’400 patent at claim 4. As discussed, Sonne disclosed that “[t]he formulations according to the invention may be optimized with respect to bioadhesion, sprayability

and viscosity, as desired" by incorporating "co-solvents" like "alcohols such as ethanol … or benzyl alcohol." *Id*. at 6:47-53. Additionally, when disclosing that the "compositions of the invention may be used directly as solutions of the bioactive agent in the tocopherol solvent," Sonne discloses that the viscosity of such a solution "may be too high for certain applications, for example to achieve a sprayable formulation for nasal application," and, because of that, "[v]iscosity can be reduced by addition of co-solvents such as ethanol…" *Id*. at 3:60-67. Consequently, based on the disclosure of Sonne, a POSA would have bene motivated to add ethanol and/or benzyl alcohol as a co-solvent to the α-tocopherol solution, and would reasonably expect that doing so would reduce the viscosity and allow for spray administration.

Dependent claims 5 and 13 of the '400 patent require the solution formulation to contain "about 10 mg/mL to about 250 mg/mL" of diazepam. '400 patent at claims 5, 13. Sonne discloses that diazepam was one preferred drug compound, with low water solubility, that could be developed in the tocopherol-based formulations, including exemplary solution formulations. *See* Sonne at 7:32 to 8:10 (Example 1, diazepam "nosedrop"); 8:11-27 (Example 1, diazepam nosedrop); and 11:1-13 (Example 11, solution containing diazepam and approximately 40% alpha-tocopherol, e.g. as a nosedrop). Sonne also discloses the intranasal administration of 2 mg, 2.5 mg, and 10 mg of diazepam. *See* Sonne at Fig. 1; Examples 1, 22, and 23; 7:32-58; 13:56 to 14:13; and 14:63-67. Sonne further discloses that "[t]he active substance may be present in an amount of from about 0.0001% to 50% of the total composition, preferably 0.001% to 40% (w/w)," and that that the "administration of drugs with very low water solubility to the nose is difficult, because of the limited volume which is acceptable for the nose (about 100 μL)." Sonne at 7:25-28.

Additionally, Cloyd discloses solution formulations containing "at least about 10 mg/ml of the benzodiazepine" where "the intranasal volume delivered to an individual in need of a

benzodiazepine is… between about 50 µl to about 150 µl per nostril." Cloyd at ¶¶ [0055]-[0056]. Similarly, Cartt 2008 discloses exemplary doses of diazepam to be delivered to patients per dose via nasal administration: "The dosage of Diazepam may vary by indication, however it is expected that a therapeutic dose will be in the range of about 1 to about 20, preferably about 2 to about 10 mg per dose…." Cartt 2008 at ¶ [0063].

Cartt 2008 further discloses that "[n]asal preparations are generally administered in metered sprays having volumes of less than 250 µl, preferably less than 150 µl, and ideally from 25 to 100 µl, since administration of larger volumes usually exceeds the capacity of the nasal sinuses and results in volumes in excess of about 250 µl bypassing the sinuses and flowing down the back of the throat where it is swallowed." Cartt 2008 at ¶ [0007]. Cartt 2008 specifically discloses that "[a]s a nasal formulation, diazepam may be administered in 25 to 250 µl metered sprays. In some preferred embodiments, diazepam is administered in 50 to 150 µl, especially about 100 µl, metered sprays. In some embodiments, a first metered spray is applied to a first nostril and if necessary a second metered spray is applied to a second nostril." *Id*. at ¶ [0064].

In view of these teachings, Sonne optionally in view of Meezan, Cartt 2008, Cloyd, Florida EMS Manual, and/or USP discloses and renders obvious the requirement that solution formulation contains "about 10 mg/mL to about 250 mg/mL" of diazepam. Accordingly, a POSA would have been motivated to use the claimed concentrations and amounts of diazepam, and would have had a reasonable expectation of success.

Dependent claims 7 and 16 recite that the formulation may contain "at least one additional ingredient selected from the group consisting of stabilizers, coloring agents, pH adjusters, buffering agents, preservatives, wetting agents, flavoring agents and combinations thereof." '400 patent at claims 7, 16. As explained above, a POSA would have been motivated to include at least

one of these types of excipients in an intranasal diazepam solution formulation. *Supra* Section V.H.1. Indeed, a POSA would have recognized that the categories of functional excipients recited in dependent claims 7 and 16 were routinely included in pharmaceutical formulations, as disclosed by Sonne, Meezan, Cloyd, and other references. *See, e.g.*, Sonne at 7:4-9, claim 10; Cloyd at ¶ [0066]; Meezan at ¶ [0074].

Indeed, Sonne discloses that "[t]he formulations according to the invention may be optimized with respect to bioadhesion, sprayability and viscosity, as desired." Sonne at 6:47-49. Additionally, Sonne states that "[t]o ensure that the formulations have a reasonable shelf-life it may be desirable to include preservatives such as benzalkonium chloride, sodium edetate, sorbic acid, potassium sorbate, phenoxyethanol, phenetanol, parabens or others known in the art. Addition of odour- or taste-masking compounds can also be desirable." Sonne at 7:4-9. Accordingly, for the reasons discussed above, a POSA would have been motivated to include an additional excipient from the list recited in dependent claims 7 and 16, and would have had a reasonable expectation of success.

Dependent claims 8-9, 17-18, and 21 require that "the pharmaceutical composition further comprises an absorption enhancer" (claims 8, 17, and 21) and "the absorption enhancer is present in the pharmaceutical composition at a concentration of up to 20% (w/v)" (claims 9 and 18). '400 patent at claims 8-9, 17-18, 21. Sonne discloses that bioadhesive compounds may be included in the pharmaceutical compositions, stating that "[i]t is also possible to enhance the bioadhesive properties of the formulations according to the present invention by addition of bioadhesive polymers such as: polyacrylic polymers such as carbomer and carbomer derivatives, e.g. Polycarbophil or Carbopol etc; cellulose derivatives such as hydroxymethyl-cellulose, hydroxyethylcellulose, hydroxypropyl-cellulose or sodium carboxymethylcellulose etc; natural

polymers like gelatin, sodium alginate, pectin etc; [and] more generally, any physiologically acceptable polymer showing bioadhesive characteristics may be used." Sonne at 6:59-7:3.

Regarding the requirement that the absorption enhancer is present "at a concentration up to 20% (w/v)," Sonne discloses various exemplary embodiments containing xanthan gum and poloxamer 188 (both bioadhesives compounds) in amounts including 0.025% (w/w) (xanthan gum component of Example 8); 0.03% (w/w) (xanthan gum component of Examples 9 and 10); 1% (w/w) (poloxamer 188 component of Example 9); and 3.0% (w/w) (poloxamer 188 component of Example 10). Sonne at 10:20-67. All of these bioadhesive concentrations are within the range of "up to 20%."

Further, as discussed above, Meezan teaches alkyl glycoside or saccharide alkyl ester compositions that provide enhanced bioavailability of therapeutic agents, thereby acting as penetration enhancers. In particular, Meezan states the following regarding the alkyl glycoside component:

> Alkyl glycosides of the present invention can include, but are not limited to: alkyl glycosides, such as octyl-, nonyl-, decyl-, undecyl-, dodecyl-, tridecyl-, tetradecyl-, pentadecyl-,hexadecyl-, heptadecyl-, and octadecyl-α- or β-D-maltoside, -glucoside or -sucroside….
>
> …
>
> Similarly, some preferred glycosides include maltose, sucrose, and glucose linked by glycosidic linkage to an alkyl chain of 9, 10, 12, 13, 14, 16, 18, 20, 22, or 24 carbon atoms, e.g., nonyl-, decyl-, dodecyl- and tetradecyl sucroside, glucoside, and maltoside, etc. These compositions are nontoxic, since they are degraded to an alcohol and an oligosaccharide, and amphipathic.

Meezan at ¶¶ [0056]-[0058]. Further, Meezan explicitly identifies alkylmaltosides, including dodecyl-beta-D-maltoside, as a preferred alkyl glycoside compound. *Id*. at ¶¶ [0092], [0156]. Thus, Meezan provides a teaching of the claimed requirement for the inclusion of an "absorption enhancer."

Regarding the claimed requirement for the inclusion of an absorption enhancer "at a concentration of up to 20% (w/v)," Meezan discloses adding alkyl glycosides to formulations in amounts of "about 0.01-20%, preferably about 0.01-5%, more preferably about 0.01-2%, even more preferably 0.01-1%, and most preferably 0.01-0.125% by weight." Meezan at ¶ [0070]. Further, Meezan tested the effects of dodecyl maltoside as an absorption enhancer in amounts of 0.125%, 0.25%, 0.375%, and 0.50%. *Id*. Accordingly, for the reasons discussed above, a POSA would have been motivated to include an absorption enhancer, including at concentrations up to 20% (w/v), and would have had a reasonable expectation of success.

Dependent claims 10 and 19 require the claimed diazepam formulation to be formulated in certain volumes, including at "about 100 µL." '400 patent at claims 10 and 19. As explained above, a POSA would have understood that intranasal administration of a pharmaceutical formulation necessarily requires the claimed volumes, and would have been motivated to use a volume of "about 100 µL" specifically. *See, e.g*., Sonne at 7:25-30 ("administration of drugs with very low water solubility to the nose is difficult, because of the limited volume which is acceptable for the nose (about 100 µL)"); Cloyd at ¶¶ [0055]-[0056] ("the intranasal volume delivered to an individual in need of a benzodiazepine is…more particularly between about 50 µL to about 150 µL per nostril"). Accordingly, for the reasons discussed above, a POSA would have been motivated to formulate an intranasal diazepam formulation in a volume of "about 100 µL," and would have had a reasonable expectation of success.

Dependent claims 11 and 14 require that "the therapeutically effective amount of the diazepam is about 2 mg to about 10 mg" (claim 11) and "the diazepam is about 2 mg to about 10 mg" (claim 14). '400 patent at claim 11 and 14. Fig. 1 of Sonne illustrates the intranasal administration of 2.5 mg diazepam. *Id*. at 7:15-18. Additionally, Examples 1, 22, and 23 of Sonne

report the administration of amounts of diazepam including 2 mg, 2.5 mg, and 10 mg. *Id.* at 7:32-58; 13:56 to 14:13; and 14:63-67. Additionally, Cartt 2008 discloses exemplary doses of diazepam to be delivered to patients per dose via nasal administration: "The dosage of Diazepam may vary by indication, however it is expected that a therapeutic dose will be in the range of about 1 to about 20, preferably about 2 to about 10 mg per dose…." Cartt 2008 at ¶ [0063]. Accordingly, a POSA would have been motivated to use the claimed amounts of "about 2 mg to about 10 mg" of diazepam in the pharmaceutical composition, and would have had a reasonable expectation of success.

Accordingly, for the reasons discussed above, all claims of the '400 patent would have been obvious over Sonne optionally in view of Meezan, Cartt 2008, Cloyd, Florida EMS Manual, and/or USP.

3. All Claims of the '400 Patent Are Invalid as Obvious over Li in view of Sonne Optionally Further in view of Meezan, Cartt 2008, Florida EMS Manual, and/or USP

All claims of the '400 patent would have been obvious over Li in view of Sonne, optionally further in view of Meezan, Cartt 2008, Florida EMS Manual, and/or USP, which are summarized above. *Supra* Section V.D. The previous analysis establishing the obviousness of all claims of the '400 patent over Sonne optionally in view of Meezan, Cartt 2008, Cloyd, Florida EMS Manual, and/or USP is incorporated herein in its entirety. In view of this additional and alternative combination of prior art references, a POSA would have been motivated to make the claimed intranasal diazepam solution formulations, and would have had a reasonable expectation of success, for the all the reasons noted above. *Supra* Section V.H.1.

(a) Independent Claim 1 of the '400 Patent Would Have Been Obvious

As explained above, independent claim 1 of the '400 patent recites "a pharmaceutically-acceptable spray formulation" that is a "solution" containing ranges of amounts of diazepam, tocopherols or tocotrienols, alcohols, and DDM. *Supra* Section II.G.1. For the reasons discussed above, a POSA would have been motivated to combine the teachings Li and Sonne to develop an intranasal solution formulation of diazepam. *Supra* Section V.H.1. Additionally, at least with regard to the inclusion of an absorption enhancer, a POSA would have been motivated to combine the teachings Li and Sonne with Meezan to develop an intranasal solution formulation of diazepam containing an alkyl glycoside as an absorption enhancer. *Supra* Section V.H.1.C. Indeed, in view of the known shortcomings associated with rectal and intravenous diazepam formulations, it was known in the art, as evidenced by, *e.g.*, the disclosures of Sonne, Cartt 2008, and Florida EMS Manual, that the art had begun to explore the development of intranasal diazepam formulations for the treatment of seizures, including emergency treatment of seizures. Consequently, a POSA would have been motivated to develop intranasal diazepam spray formulations to overcome issues and problems associated with existing formulations of diazepam. *See, e.g.*, Sonne at 7:25-30; Cartt 2008 at ¶¶ [0003]-[0008]; Florida EMS Manual at 54.

Further, a POSA would have been motivated to make a solution formulation containing the ranges and amounts of diazepam, tocopherols or tocotrienols, and alcohols recited in claim 1 of the '400 patent. For example, regarding the claimed requirement of "a pharmaceutical composition for intranasal administration…wherein the pharmaceutical composition is a solution," Li discloses intranasal diazepam solutions, stating that that "[f]or IN application, the test formulations were prepared in 30% EtOH—60% PG—10% water, plus or minus 1% SGC. All the nasal formulations were prepared just prior to the experiment by dissolving DZ (20 mg), CZ (4.2 mg), or MCA (100

mg) in 1 ml of the aforementioned vehicles." Li at 67. Li explains that the diazepam ("DZ") was "dissolved" in the vehicle, indicating that the resulting formulation was a solution. Additionally, Li states that the formulations were developed for intranasal ("IN") application. Thus, Li discloses "a pharmaceutical composition for intranasal administration…wherein the pharmaceutical composition is a solution."

Further, Sonne discloses solutions containing bioreactive agents, stating that "[t]he compositions of the invention may be used directly as solutions of the bioactive agent in the tocopherol solvent." Sonne at 3:60-61. Sonne further explains that "[n]asal, rectal and oral cavity administrations are particularly preferred" for the formulations, establishing that the Sonne formulations can be administered intranasally. In fact, Sonne specifically disclosed examples of "[a] solution of diazepam, eg. as nosedrop" containing diazepam in combination with α-tocopherol (but with no water). *Id*. at 11:1-13. Consequently, Sonne provides a teaching of the claimed requirement of "a pharmaceutical composition for intranasal administration…wherein the pharmaceutical composition is a solution."

Regarding the requirement for the inclusion of "about 1 to about 20 mg of diazepam," Li discloses this limitation. Specifically, as noted, Li states that 20 mg of diazepam was dissolved in 1 ml of the carrier. *Id*. at 67. Li further states that the resulting intranasal solutions provided a diazepam concentration of 20 mg/ml. *Id.* at p. 67, 70 (Table 1, reporting the 2% diazepam solution). Consequently, the formulation described by Li includes "about 20 mg of diazepam."

Further, as discussed in Section V.H.1, the maximum volume of a nasal spray that can be administered to the nasal passage (due to the physical dimensions of the nasal passage) is about 100-200 µL (0.1-0.2 ml). *See, e.g.*, Sonne at 2:30-33; Wermeling at 354 (the nasal cavity can retain 100 to 150 µL without causing immediate run-off out the front of the nose or down the naso-

pharynx). Even accounting for the volume of a single spray of 0.1-0.2 ml, a single spray of the Li solution containing 20 mg/ml would include 2-4 mg of diazepam, which meets the claimed requirement of "about 2 to about 20 mg of diazepam."

Additionally, Fig. 1 of Sonne illustrates the intranasal administration of 2.5 mg diazepam (Sonne at 7:15-18), and Examples 1, 22, and 23 of Sonne report the administration of amounts of diazepam including 2 mg, 2.5 mg, and 10 mg. Sonne at 7:32-58; 13:56 to 14:13; and 14:63-67. Thus, Li and Sonne both disclose the inclusion of "about 2 to about 20 mg of diazepam."

Regarding the claimed requirement for the inclusion of "about 45% to about 85% (w/w) of one or more natural or synthetic tocopherols or tocotrienols selected from the group consisting of: α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, α-tocotrienol, β-tocotrienol, γ-tocotrienol, δ-tocotrienol, tocophersolan, any esters thereof and any combinations thereof," this limitation is disclosed and rendered obvious by Li and Sonne. As discussed, Li discloses the development of a diazepam intranasal solution, whereby the carrier vehicle contained "30% EtOH—60% PG—10% water, plus or minus 1% SGC," (Li, p. 67), which represents 60% propylene glycol (PG), 30% ethanol (EtOH), and 10% water, plus/minus 1% sodium glycholate (SGC).[21] However, as discussed in Section V.E.1, it was known in the art that the solubility of diazepam in propylene glycol was ~1.7% (i.e., 17 mg/ml),[22] and the majority of the Li solution was propylene glycol. Given the limited solubility of diazepam in propylene glycol, and the fact that propylene glycol

[21] A POSA would have understood that the formulations additionally containing 1% SGC would require that the percentages of the other three components (propylene glycol, ethanol, and water) would need to be adjusted to account for the additional 1% of SGC; however, the amount of SGC is small and does not materially impact the analysis related to the amounts and concentrations disclosed by Li.

[22] Bechgaard E; Gizurarson S; Hjortkjær RK. "Solubilization of Various Benzodiazepines for Intranasal Administration, a Pilot Study." Pharmaceutical Development and Technology 2(3):293–296 (1997) (*see* p. 294, Table 1, reporting diazepam solubility in propyleneglycol of 17 mg/ml).

constitutes 60% of the Li intranasal solution, a POSA would expect that that it would be difficult to achieve diazepam concentrations much higher than the 2% concentration reported in Li, meaning that the amount of diazepam that could be delivered in a single nasal spray was also limited by the concentration limit.

Sonne provides a solution to the limited diazepam solubility of propylene glycol, disclosing that diazepam was shown to have a solubility of 12% w/w in α-tocopherol. *Id*. at 9:35-60 (Table 1). Assuming a density similar to that of water (i.e., ~1.0 mg/ml), the 12% w/w solubility of diazepam in α-tocopherol corresponds to a solubility of 12% w/v (i.e., 120 mg/ml), which is significantly higher than the solubility of diazepam in propylene glycol (i.e., 17 mg/ml), and would allow for more diazepam to be solubilized and ultimately delivered to the nasal passage in a single spray. Sonne also discloses that "the invention concerns the use of a tocopherol or a derivative thereof to prepare compositions having low irritability suitable for administration to mucosal membranes and which may be used efficiently to administer drugs, which are substantially insoluble or only sparingly soluble in water." Sonne at 1:8-13. Thus, Sonne teaches that the α-tocopherol solvent could be used to solubilize diazepam to a much greater extent than propylene glycol, and that α-tocopherol was shown to have low irritability and was suitable for the administration of poorly water soluble drugs (such as diazepam) to mucosal membranes.

For at least these reasons, a POSA would have been motivated to replace the 60% propylene glycol present in the Li intranasal diazepam solution with the α-tocopherol solvent taught by Sonne, and would have a reasonable expectation of success. Utilizing α-tocopherol in the same amount as was present for propylene glycol (60%) meets the claimed requirement for the inclusion of "about 45% to about 85% (w/w)" of the one or more claimed tocopherols. Additionally, Sonne also discloses that the formulations could contain "1 to 95% (w/w) of the

tocopherol or derivative thereof, preferably 20 to 95% (w/w), most preferably 35 to 80% (w/w)." *Id*. at 5:58-61. Moreover, Sonne discloses at least one exemplary solution formulation containing 10 g of α-tocopherol in a total solution weight of 25 g, equating to an α-tocopherol concentration of 40% w/w. *Id*. at 11:1-13 (Example 11). Thus, Li in view of Sonne teaches and renders obvious the requirement for the inclusion of "about 45% to about 85% (w/w) of one or more natural or synthetic tocopherols or tocotrienols selected from the group consisting of α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, α-tocotrienol, β-tocotrienol, γ-tocotrienol, δ-tocotrienol, tocophersolan, any esters thereof and any combinations thereof."

Claim 1 of the '400 patent further requires the inclusion of "about 25% to about 40% (w/w) of one or more alcohols selected from the group consisting of ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, and any combinations thereof." As noted above, Li discloses an intranasal diazepam solution containing 30% ethanol. Li at 67, 70. The inclusion of 30% ethanol in the Li intranasal solution is consistent with the disclosure of Sonne, stating the "compositions of the invention may be used directly as solutions of the bioactive agent in the tocopherol solvent," and discussing the "addition of co-solvents such as ethanol" to the tocopherol solvent. Sonne at 3:60-67.

Additionally, Meezan discloses formulations containing a "therapeutic composition" in "solutions," (Meezan at ¶ [0049]), and that the "compositions of the invention can consist of a pharmaceutically acceptable carrier[,] [a] 'pharmaceutically acceptable carrier' is an aqueous or non-aqueous agent, for example alcoholic or oleaginous, or a mixture thereof." Meezan at ¶ [0074]. Thus, a POSA would have been motivated to formulate diazepam in a non-aqueous solution formulation containing Vitamin E and co-solvents (i.e., ethanol and benzyl alcohol) in view of Li, Sonne, and Meezan.

Regarding the claimed requirement that the pharmaceutical solution has a volume of "50 µL to 150 µL," this limitation is disclosed and rendered obvious by Li and Sonne. Specifically, Li explains that, for intranasal administration, "100 µl of the IN formulations [was administered] into each nostril within 5 s by means of a Pfeiffer spray device." Li at 67. Further, Sonne states that the formulations described therein for administration to the nose must be administered in small volumes of "about 100 µL." Sonne at 7:25-30 ("administration of drugs with very low water solubility to the nose is difficult, because of the limited volume which is acceptable for the nose (about 100 µL)"). Thus, Li in view of Sonne, optionally further in view of Meezan, Cartt 2008, USP, and/or Florida EMS Manual discloses and renders obvious the claimed requirement that the pharmaceutical solution has a volume of "50 µL to 150 µL."

Regarding the requirement that "the pharmaceutical composition is in a pharmaceutically-acceptable spray formulation," Li discloses this limitation. Specifically, Li explains that, for intranasal administration, "100 µl of the IN formulations [was administered] into each nostril within 5 s by means of a Pfeiffer spray device." Li at 67. Similarly, Sonne discloses that the compositions are preferably administered via the "[n]asal" route, and that the compositions may take the form of "sprays." Sonne at 3:58-59, 6:34-35. Consequently, Li and Sonne disclose the claimed requirement that "the pharmaceutical composition is in a pharmaceutically-acceptable spray formulation."

Accordingly, a POSA would have been motivated to make a pharmaceutically acceptable spray formulation of diazepam in the form of a solution containing the amounts of diazepam, tocopherols or tocotrienols, and alcohols recited in claim 1 of the '400 patent based on Li in view of Sonne optionally further in view of Meezan, Cartt 2008, USP, and/or Florida EMS Manual. A

POSA also would have had a reasonable expectation of success in view of those references for the reasons discussed above.

(b) Independent Claims 12 and 20 of the ’400 Patent Would Have Been Obvious

Independent claims 12 and 20 are similar to claim 1, differing in only two aspects. First, claims 12 and 20 require that the one or more natural or synthetic tocopherols is α-tocopherol (whereas claim 1 more broadly recites “one or more natural or synthetic tocopherols or tocotrienols selected from the group consisting of α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, α-tocotrienol, β-tocotrienol, γ-tocotrienol, δ-tocotrienol, tocophersolan, any esters thereof and any combinations thereof”). Additionally, claim 20 requires that the pharmaceutical composition is in a volume of “about 100 µL” (whereas claim 1 and 12 recite a volume of “50 µL to 150 µL”). Li in view of Sonne, optionally further in view of Meezan, Cartt 2008, Florida EMS Manual, and/or USP disclose and render obvious these requirements.

The previous analysis establishing the obviousness of claim 1 of the ’400 patent is incorporated herein in its entirety. Regarding the requirement for the inclusion of α-tocopherol, as discussed, Sonne expressly disclosed that diazepam could be formulated for intranasal administration as a solution containing α-tocopherol, including in an amount ranging from about 40% to about 99.99% (w/w). *See, e.g.,* Sonne at 5:58-61, 7:32-8:27, 10:20-11:13. Further, regarding the requirement that the pharmaceutical composition is a volume of “about 100 µL,” Li discloses that the intranasal solutions were administered intranasally in a volume of “100 µl of the IN formulations.” Li at 67. Further, as explained above, a POSA would have understood that intranasal administration of a pharmaceutical formulation necessarily requires the claimed volumes, and would have been motivated to use a volume of “about 100 µL” specifically. *See, e.g.*, Sonne at 7:25-30. Accordingly, for the reasons discussed above, a POSA would have been

motivated to formulate an intranasal diazepam formulation containing α-tocopherol, and in a volume of "about 100 μL," and would have had a reasonable expectation of success.

(c) Dependent Claims 2-11, 13-19, and 21 of the '400 Patent Would Have Been Obvious

For the reasons explained above, dependent claims 2-11, 13-19, and 21 would have been obvious over Li in view Sonne, optionally further in view of Meezan, Cartt 2008, Florida EMS Manual, and/or USP. *Supra* Section V.E.5(a). To be sure, the prior art disclosed each of the limitations of dependent claims 2-11, 13-19, and 21 of the '400 patent, expressly or inherently, as discussed below.

Dependent claims 2-3, 6, and 15 require that "the natural or synthetic tocopherols or tocotrienols are selected from the group consisting of: α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, tocophersolan, any esters thereof and any combinations thereof" (claim 2); "the natural or synthetic tocopherols or tocotrienols is α-tocopherol" (claim 3); "the pharmaceutical solution comprises one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof in an amount from about 60% to about 75% (w/w)" (claim 6); and "the pharmaceutical solution comprises α-tocopherol in an amount from about 60% to about 75% (w/w)" (claim 15). '400 patent at claims, 2-3, 6, and 15. As explained above, Li discloses the development of a diazepam intranasal solution, whereby the carrier vehicle contained "30% EtOH—60% PG—10% water, plus or minus 1% SGC," (Li, p. 67), which represents 60% propylene glycol (PG), 30% ethanol (EtOH), and 10% water, plus/minus 1% sodium glycholate (SGC).[23] However, as discussed in Section V.E.1, a POSA would have been motivated to replace

[23] A POSA would have understood that the formulations additionally containing 1% SGC would require that the percentages of the other three components (propylene glycol, ethanol, and water) would need to be adjusted to account for the additional 1% of SGC; however, the amount of SGC is small and does not materially impact the analysis related to the amounts and concentrations disclosed by Li.

the 60% propylene glycol present in the Li intranasal diazepam solution with the α-tocopherol solvent taught by Sonne. Utilizing α-tocopherol in the same amount as was present for propylene glycol (60%) meets the claimed requirement for the inclusion of "about 60% to about 75% (w/w)" of the one or more claimed tocopherols.

Additionally, Sonne also discloses that the formulations could contain "1 to 95% (w/w) of the tocopherol or derivative thereof, preferably 20 to 95% (w/w), most preferably 35 to 80% (w/w)." *Id*. at 5:58-61. Moreover, Sonne discloses at least one exemplary solution formulation containing 10 g of α-tocopherol in a total solution weight of 25 g, equating to an α-tocopherol concentration of 40% w/w. *Id*. at 11:1-13 (Example 11). Accordingly, for the reasons discussed above, a POSA would have been motivated to develop the Sonne solution formulation containing α-tocopherol, and it would have been a matter of routine experimentation and optimization to utilize the tocopherol in an amount ranging from about 60-75% (w/w), and would have had a reasonable expectation of success. *See In Re Aller,* 220 F2d 454, 456 (CCPA 1955) ("[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.").

Dependent claim 4 requires that "the one or more alcohols is selected from the group consisting of ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, isomers thereof and any combinations thereof." '400 patent at claim 4. As discussed, Li discloses an intranasal diazepam solution containing 30% ethanol. Li at 67, 70. The inclusion of 30% ethanol in the Li intranasal solution is consistent with the disclosure of Sonne, stating the "compositions of the invention may be used directly as solutions of the bioactive agent in the tocopherol solvent," and discussing the "addition of co-solvents such as ethanol" to the tocopherol solvent. Sonne at 3:60-67. The inclusion of 30% ethanol meets the claimed requirement that "the one or more alcohols is

selected from the group consisting of ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, isomers thereof and any combinations thereof." Accordingly, for the reasons discussed above, a POSA would have been motivated to develop the Li solution containing 30% ethanol, and would have had a reasonable expectation of success.

Dependent claims 5 and 13 of the '400 patent require the solution formulation to contain "about 10 mg/mL to about 250 mg/mL" of diazepam. '400 patent at claims 5, 13. As explained above, Li discloses that the intranasal solution contains 20 mg/ml diazepam, meeting the claimed requirement that "the diazepam is present in the pharmaceutical solution at a concentration of about 10 mg/mL to about 250 mg/mL." Additionally, Sonne discloses that diazepam was one preferred drug compound, with low water solubility, that could be developed in the tocopherol-based formulations, including exemplary solution formulations. *See* Sonne at 7:32 to 8:10 (Example 1, diazepam "nosedrop"); 8:11-27 (Example 1, diazepam nosedrop); and 11:1-13 (Example 11, solution containing diazepam and approximately 40% alpha-tocopherol, e.g. as a nosedrop). Sonne also discloses the intranasal administration of 2 mg, 2.5 mg, and 10 mg of diazepam. *See* Sonne at Fig. 1; Examples 1, 22, and 23; 7:32-58; 13:56 to 14:13; and 14:63-67. Sonne further discloses that "[t]he active substance may be present in an amount of from about 0.0001% to 50% of the total composition, preferably 0.001% to 40% (w/w)," and that the "administration of drugs with very low water solubility to the nose is difficult, because of the limited volume which is acceptable for the nose (about 100 µL)." Sonne at 7:25-28.

Cartt 2008 further discloses that "[n]asal preparations are generally administered in metered sprays having volumes of less than 250 µl, preferably less than 150 µl, and ideally from 25 to 100 µl, since administration of larger volumes usually exceeds the capacity of the nasal sinuses and results in volumes in excess of about 250 µl bypassing the sinuses and flowing down

the back of the throat where it is swallowed." Cartt 2008 at ¶ [0007]. Cartt 2008 specifically discloses that "[a]s a nasal formulation, diazepam may be administered in 25 to 250 µl metered sprays. In some preferred embodiments, diazepam is administered in 50 to 150 µl, especially about 100 µl, metered sprays. In some embodiments, a first metered spray is applied to a first nostril and if necessary a second metered spray is applied to a second nostril." *Id*. at ¶ [0064].

In view of these teachings, Li in view of Sonne, optionally further in view of Meezan, Cartt 2008, Florida EMS Manual, and/or USP discloses and renders obvious the requirement that solution formulation contains "about 10 mg/mL to about 250 mg/mL" of diazepam. Accordingly, a POSA would have been motivated to use the claimed concentrations and amounts of diazepam, and would have had a reasonable expectation of success.

Dependent claims 7 and 16 recite that the formulation may contain "at least one additional ingredient selected from the group consisting of stabilizers, coloring agents, pH adjusters, buffering agents, preservatives, wetting agents, flavoring agents and combinations thereof." '400 patent at claims 7, 16. As explained above, a POSA would have been motivated to include at least one of these types of excipients in an intranasal diazepam solution formulation. *Supra* Section V.E.4(a). Indeed, a POSA would have recognized that the categories of functional excipients recited in dependent claims 7 and 16 were routinely included in pharmaceutical formulations, as disclosed by Sonne, Meezan, and other references. *See, e.g.*, Sonne at 7:4-9, claim 10; Meezan at ¶ [0074].

Indeed, Sonne discloses that "[t]he formulations according to the invention may be optimized with respect to bioadhesion, sprayability and viscosity, as desired." Sonne at 6:47-49. Additionally, Sonne states that "[t]o ensure that the formulations have a reasonable shelf-life it may be desirable to include preservatives such as benzalkonium chloride, sodium edetate, sorbic

acid, potassium sorbate, phenoxyethanol, phenetanol, parabens or others known in the art. Addition of odour- or taste-masking compounds can also be desirable." Sonne at 7:4-9. Accordingly, for the reasons discussed above, a POSA would have been motivated to include an additional excipient from the list recited in dependent claims 7 and 16, and would have had a reasonable expectation of success.

Dependent claims 8-9, 17-18, and 21 require that "the pharmaceutical composition further comprises an absorption enhancer" (claims 8, 17, and 21) and "the absorption enhancer is present in the pharmaceutical composition at a concentration of up to 20% (w/v)" (claims 9 and 18). '400 patent at claims 8-9, 17-18, 21. As discussed, Li teaches formulations containing absorption enhancers, such sodium glycocholate (SGC). Li at 69. Additionally, Sonne discloses that bioadhesive compounds may be included in the pharmaceutical compositions, stating that "[i]t is also possible to enhance the bioadhesive properties of the formulations according to the present invention by addition of bioadhesive polymers such as: polyacrylic polymers such as carbomer and carbomer derivatives, e.g. Polycarbophil or Carbopol etc; cellulose derivatives such as hydroxymethyl-cellulose, hydroxyethylcellulose, hydroxypropyl-cellulose or sodium carboxymethylcellulose etc; natural polymers like gelatin, sodium alginate, pectin etc; [and] more generally, any physiologically acceptable polymer showing bioadhesive characteristics may be used." Sonne at 6:59-7:3.

Regarding the requirement that the absorption enhancer is present "at a concentration up to 20% (w/v)," Li teaches the inclusion of SGC at a concentration of 1%. Li at 67. Further, Sonne discloses various exemplary embodiments containing xanthan gum and poloxamer 188 (both bioadhesives compounds) in amounts including 0.025% (w/w) (xanthan gum component of Example 8); 0.03% (w/w) (xanthan gum component of Examples 9 and 10); 1% (w/w) (poloxamer

188 component of Example 9); and 3.0% (w/w) (poloxamer 188 component of Example 10). Sonne at 10:20-67. All of these bioadhesive concentrations are within the range of "up to 20%."

Further, as discussed above, Meezan teaches alkyl glycoside or saccharide alkyl ester compositions that provide enhanced bioavailability of therapeutic agents, thereby acting as penetration enhancers. In particular, Meezan states the following regarding the alkyl glycoside component:

> Alkyl glycosides of the present invention can include, but are not limited to: alkyl glycosides, such as octyl-, nonyl-, decyl-, undecyl-, dodecyl-, tridecyl-, tetradecyl-, pentadecyl-,hexadecyl-, heptadecyl-, and octadecyl-α- or β-D-maltoside, -glucoside or -sucroside….
> …
> Similarly, some preferred glycosides include maltose, sucrose, and glucose linked by glycosidic linkage to an alkyl chain of 9, 10, 12, 13, 14, 16, 18, 20, 22, or 24 carbon atoms, e.g., nonyl-, decyl-, dodecyl- and tetradecyl sucroside, glucoside, and maltoside, etc. These compositions are nontoxic, since they are degraded to an alcohol and an oligosaccharide, and amphipathic.

Meezan at ¶¶ [0056]-[0058]. Further, Meezan explicitly identifies alkylmaltosides, including dodecyl-beta-D-maltoside, as a preferred alkyl glycoside compound. *Id*. at ¶¶ [0092], [0156]. Thus, Meezan provides a teaching of the claimed requirement for the inclusion of an "absorption enhancer."

Regarding the claimed requirement for the inclusion of an absorption enhancer "at a concentration of up to 20% (w/v)," Meezan discloses adding alkyl glycosides to formulations in amounts of "about 0.01-20%, preferably about 0.01-5%, more preferably about 0.01-2%, even more preferably 0.01-1%, and most preferably 0.01-0.125% by weight." Meezan at ¶ [0070]. Further, Meezan tested the effects of dodecyl maltoside as an absorption enhancer in amounts of 0.125%, 0.25%, 0.375%, and 0.50%. *Id*. Accordingly, for the reasons discussed above, a POSA would have been motivated to include an absorption enhancer, including at concentrations up to 20% (w/v), and would have had a reasonable expectation of success.

Dependent claims 10 and 19 require the claimed diazepam formulation to be formulated in certain volumes, including at "about 100 µL." '400 patent at claims 10 and 19. As discussed, Li discloses that the intranasal solutions were administered intranasally in a volume of "100 µl of the IN formulations." Li at 67. Further, a POSA would have understood that intranasal administration of a pharmaceutical formulation necessarily requires the claimed volumes, and would have been motivated to use a volume of "about 100 µL" specifically. *See, e.g.*, Sonne at 7:25-30. Accordingly, for the reasons discussed above, a POSA would have been motivated to formulate an intranasal diazepam formulation in a volume of "about 100 µL," and would have had a reasonable expectation of success.

Dependent claims 11 and 14 require that "the therapeutically effective amount of the diazepam is about 2 mg to about 10 mg" (claim 11) and "the diazepam is about 2 mg to about 10 mg" (claim 14). '400 patent at claim 11 and 14. As discussed, Li states that 20 mg of diazepam was dissolved in 1 ml of the carrier. *Id*. at 67. Li further states that the resulting intranasal solutions provided a diazepam concentration of 20 mg/ml. *Id.* at p. 67, 70 (Table 1, reporting the 2% diazepam solution). Further, as discussed, the volume of a nasal spray that can be administered to the nasal passage (due to the small physical dimensions of the nasal passage) is about 100 µL (0.1 ml). *See, e.g.*, Sonne at 2:30-33. Even accounting for the volume of a single spray of 0.1-0.2 ml, a single spray of the Li solution containing 20 mg/ml would include 2-4 mg of diazepam, which meets the claimed requirement of "about 2 to about 10 mg" of diazepam.

Additionally, Fig. 1 of Sonne illustrates the intranasal administration of 2.5 mg diazepam (Sonne at 7:15-18), and Examples 1, 22, and 23 of Sonne report the administration of amounts of diazepam including 2 mg, 2.5 mg, and 10 mg. Sonne at 7:32-58; 13:56 to 14:13; and 14:63-67. Thus, Li and Sonne both disclose the inclusion of "about 2 to about 10 mg" of diazepam.

Further, Cartt 2008 discloses exemplary doses of diazepam to be delivered to patients per dose via nasal administration: "The dosage of Diazepam may vary by indication, however it is expected that a therapeutic dose will be in the range of about 1 to about 20, preferably about 2 to about 10 mg per dose…." Cartt 2008 at ¶ [0063]. Accordingly, a POSA would have been motivated to use the claimed amounts of "about 2 mg to about 10 mg" of diazepam in the pharmaceutical composition, and would have had a reasonable expectation of success.

Accordingly, for the reasons discussed above, all claims of the '400 patent would have been obvious over Li in view of Sonne, optionally further in view of Meezan, Cartt 2008, Florida EMS Manual, and/or USP.

4. All Claims of the '400 Patent Are Invalid as Obvious over Sonne in view of Jamieson, Li, Meezan, and/or Wermeling

(a) Independent Claim 1 Is Invalid as Obvious

Sonne discloses the use of tocopherols, including vitamin E, for use in intranasal pharmaceutical formulations with benzodiazepines such as diazepam. More specifically, Sonne discloses that "[t]he present invention provides the use of a tocopherol or a derivative thereof as a ***solvent*** and/or emulsifier ***for substantially insoluble and sparingly soluble biologically active agents***, especially in the manufacture of pharmaceutical compositions. Such compositions are ***particularly suitable for*** transmucosal, and especially ***intranasal*** or rectal ***administration***, or administration via the oral cavity." Sonne at Abstract (emphasis added), 3:54-59, Example 11, Claim 4. In particular, Sonne describes representative active agents suitable for the inventions described therein, including specifically diazepam. Sonne at 5:34.

With respect to the amount of diazepam to use in intranasal formulations, Jamieson discusses generally a therapeutically effective amount of a benzodiazepine. *See, e.g.*, [Claim 8], [Claim 17]. [Claim 40]. More specifically, though, it teaches intranasal formulations where the

amount of a benzodiazepine such as diazepam is "typically present at a weight percent of between about 0.1% to about 20% and often between 0.1% and 10% often 0.25% to 6%." Jamieson [0102]; *see also* Jamieson at [0118] ("A therapeutically effective amount of diazepam in the compositions of the present invention may be, for example between about 1.0 mg and about 40.0 mg per unit dose, more preferably between about 2.0 mg and about 10.0 mg per unit dose."); *see also* Li at 67 (disclosing formulations containing 20 mg diazepam in 1 ml of vehicle).

Sonne also states that "tocopherols and derivatives thereof are excellent solvents for drugs which are substantially insoluble or sparingly soluble in water, whilst at the same time having a very low irritative potential for mucosal tissues." Sonne at 2:55-58. Thus Sonne explains that tocopherols are useful solvents for drugs such as diazepam, including because they have very low irritative potential. Jamieson also discloses the use of benzodiazepine compositions that include tocopherols. *See, e.g.*, [Claim 24], [Claim 49]; *see also* [0209] ("Addition of an anti-oxidant to the formulations of the present invention used for intranasal delivery of benzodiazepines may provide desirable protective benefits to such formulations. Examples include, but are not limited to, tocopherol and derivatives thereof . . . ."). Thus, both Sonne and Jamieson provide guidance on how to solubilize poorly water-soluble compounds (such as diazepam), and would have been primary references that a POSA would look to for design strategies to overcome the shortcomings of oral, intravenous, and rectal benzodiazepine dosage forms. Indeed, the POSA would have had a reasonable expectation of success in using tocopherols to dissolve diazepam for intranasal administration.

With respect to the amount and type of tocopherols to use in the disclosed formulations, Sonne explains that they may contain "may contain from 1 to 99.99% (w/w), preferably 20 to 99.99%, most preferably 40 to 99.99% (w/w) of the tocopherol or tocopherol derivative solvent."

Sonne at 5:55-58. Moreover, Sonne explains that tocopherols, such as those use in the claimed invention, may include alpha-tocopherol or Vitamin E. *See* Sonne at 3:4-10 ("Tocopherols are a range of natural and synthetic compounds, also known by the generic term Vitamin E. α-Tocopherol . . . is the most active and widely distributed in nature, and has been the most widely studied."). In particular, Sonne discloses example compositions, including Example 11 which discloses specifically a "nosedrop solution" containing diazepam and approximately 40% α-tocopherol." Sonne at 11:1-13. Thus, the POSA would have had a reasonable expectation of success in using amount of tocopherols to dissolve diazepam for intranasal administration disclosed in the art.

Furthermore, both Sonne and Jamieson recognize the use of cosolvent systems for intranasal diazepam formulations. For example, Sonnne teaches cosolvents to assist in optimizing the disclosed formulations for bioadhesion, sprayability, and viscosity. Sonne at 6:47-50 (recognizing that formulations disclosed therein may be "optimized with respect to bioadhesion, sprayability and viscosity"). Even more particularly, Sonne highlights the use of both ethanol and benzyl alcohol as co-solvents. Sonne at 6:51-52 (disclosing ethanol and benzyl alcohol). With respect to whether and why to use such alcohol cosolvents, Sonne explains that "[t]he compositions of the invention may be used directly as solutions of the bioactive agent in the tocopherol solvent" but that "such solution are viscous, and the viscosity may be too high for certain applications, for example to achieve a sprayable formulation for nasal application." Sonne at 3:60-64. Indeed, because of potentially high viscosity caused by the tocopherol solvent, Sonne explains that the cosolvents, such as alcohol, may be used to decrease viscosity. Sonne at 3:65-67 ("Viscosity can be reduced by additional of co-solvents such as ethanol, but this is less desired, since solutions of this kind tend to be irritating to certain mucosal tissues."). Jamieson contains similar disclosures

related to use intranasal administration of formulations that contain benzodiazepines and cosolvents. *See* Jamieson at Abstract (inventions that "include[] benzodiazepine compositions formulated for intranasal administration, comprising a binary solvent system comprising a first solvent in which the benzodiazepine is soluble, the first solvent capable of penetrating nasal mucosal tissue, and a second solvent in which the benzodiazepine in less soluble.") (emphasis added). Thus, Sonne and Jamieson both provide the motivation to combine diazepam with a tocopherol (α-Tocopherol or vitamin E) for dissolution purposes, while simultaneously providing a motivation to increase the amount of cosolvents (such as ethanol and benzyl alcohol) to reduce viscosity.

With respect to the use of ethanol and benzyl alcohol, the POSA would additionally look to Li and/or Wermeling. Li, for example, discloses the benefit of using ethanol in intranasal administration of diazepam. *See* Abstract, 67. Li teaches the impact of formulations containing ethanol on absorption of diazepam. Specifically, "[t]he present study was carried out to investigate the absorption characteristics and [pharmacodynamic] response of three anticonvulsants, the benzodiazepines, [diazepam] and [clonazepam], and the new monocarbamate anticonvulsant . . . after their [intranasal] administration as solutions in aqueous cosolvent system containing various proportions of [propylene glycol] and [ethanol] in the presence of 1% [sodium glycocholate]." Li at 66. The studied solutions include one that contained about 20 mg diazepam in 30% ethanol. Li at 67. That formulation contained about 20 mg diazepam in about 1 ml of vehicle. Li at 67. Li concludes that "[t]he peak [diazepam] concentration . . . increased significantly with increasing [ethanol] concentrations in the [intranasal] formulation (20-60%)." Li at 71-72; *see also* Jamieson at Table 12A (disclosing benzodiazepine formulations containing 20% ethanol). Li also concludes that "[t]he nasal administration of [diazepam] . . . formulations in 1% SGC containing

EtOH:PG:water cosolvent elicited a very fast PD response, which was less than 1.5 min. In turn, this response time appeared to be essentially identical to that seen from an IV injection of a benzodiazepine." Li at 74.

Similarly, Wermeling discloses pharmaceutical compositions for intranasal administration of effective amounts of benzodiazepines, and specifically highlights the use of diazepam. Wermeling at Abstract, [0026]. It further explains that the "principal advantages of intranasal route are non-invasive delivery, rapid drug absorption, and convenience." Wermeling at [0008]. Wermeling continues that "there is a need for intranasal benzodiazepine compositions with improved properties, such as for example, rapid absorption and time to peak concentration." Wermeling at [0012]. Thus Wermeling provides additional motivation to use diazepam intranasal formulations. Wermeling continues, however, by explaining that suitable diluents may include alcohols. Wermeling at [0030]. With respect specifically to benzyl alcohol, Wermeling highlights it as a "suitable preservative" for use in its disclosed formulations. Wermeling at [0033]. Wermeling continues that "the composition contains a preservative that is chosen in quantities that preserve the composition, but preferably does not cause irritation to the nasal mucosa." Wermeling at [0033]. Thus, the POSA would have a motivation to combine Li and Wermeling to formulate diazepam with various alcohols in order to increase absorption and/or preservative characteristics. Based on the disclosures therein, the POSA would have had a reasonable expectation of success for the amounts taught.

Sonne also discloses solutions in spray form as a conventional form used for the compositions. Sonne at 3:54-67, 6:33-34. It also recognizes that the "acceptable volume for . . . nose" administration of drugs is about 100 µl. Li also teaches that a "constraint concerning nasal administration is that a small administration volume is required; it is not generally possible to

administer more than approximately 150 µl per nostril." Li at 66. Thus the prior art taught the claimed volume of the formulation.

The POSA would have been motivated to combine the teaching of Sonne, Jamieson, Li, and/or Wermeling to create a rapid-onset intranasal formulation containing diazepam. First, the POSA would have recognized that intranasal administration of diazepam was a promising route of administration due to the possibility of rapid onset effect through the transmucosal membranes in the nose. *See* Sonne; Jamison; Li, Wermeling. Second, the POSA would have sought to use a non-irritating solvent – such as the tocopherol Vitamin E – to dissolve diazepam. *See* Sonne. To balance the viscosity and to improve the time to peak concentration, the POSA would seek to use some amount of ethanol or other suitable co-solvent such as benzyl alcohol. *See* Sonne, Li, Jamieson. Furthermore, the motivation to use benzyl alcohol is compounded by the knowledge that it is a suitable preservative for intranasal benzodiazepine formulations. *See* Wermeling. With respect to the specifically disclosed amounts of the claimed drug substance, tocopherol, and alcohols, those ranges were disclosed in the art as discussed above. Moreover, in seeking to develop an intranasal formulation with the appropriate viscosity, bioavailability, absorption, pharmacokinetics, and/or preservative characteristics, the POSA would need to do nothing more than routine experimentation to optimize the formulation for such characteristics. Routine experimentation would have resulted in the amounts of the claimed formulations. *See In Re Aller,* 220 F.2d 454, 456 (CCPA 1955) ("[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation."). Thus, each limitation of claim 1 is disclosed by the combination of Sonne, Jamieson, Li, and/or Wermeling. Claim 1 is obvious.

(b) Dependent Claim 2 Is Invalid as Obvious

Dependent claim 2 depends from claim 1. Thus, it is obvious for at least the same reasons explained above for claim 1, which discussion is incorporated herein by reference in its entirety. With respect to any additional elements in this claim, they have already been addressed above with respect to claim 1 and do not impart non-obviousness. Thus, claim 2 is obvious.

(c) Dependent Claim 3 Is Invalid as Obvious

Dependent claim 3 depends from claim 1. Thus, it is obvious for at least the same reasons explained above for claim 1, which discussion is incorporated herein by reference in its entirety. With respect to any additional elements in this claim, they have already been addressed above with respect to claim 1 and do not impart non-obviousness. Thus, claim 3 is obvious.

(d) Dependent Claim 4 Is Invalid as Obvious

Dependent claim 4 depends from claim 1. Thus, it is obvious for at least the same reasons explained above for claim 1, which discussion is incorporated herein by reference in its entirety. With respect to any additional elements in this claim, they have already been addressed above with respect to claim 1 and do not impart non-obviousness. Thus, claim 4 is obvious.

(e) Dependent Claim 5 Is Invalid as Obvious

Dependent claim 5 depends from claim 1. Thus, it is obvious for at least the same reasons explained above for claim 1, which discussion is incorporated herein by reference in its entirety. With respect to any additional elements in this claim, they have already been addressed above with respect to claim 1 and do not impart non-obviousness. Thus, claim 5 is obvious.

(f) Dependent Claim 6 Is Invalid as Obvious

Dependent claim 6 depends from claim 1. Thus, it is obvious for at least the same reasons explained above for claim 1, which discussion is incorporated herein by reference in its entirety.

With respect to any additional elements in this claim, they have already been addressed above with respect to claim 1 and do not impart non-obviousness. Thus, claim 6 is obvious.

(g) Dependent Claim 7 Is Invalid as Obvious

Dependent claim 7 depends from claim 1. Thus, it is obvious for at least the same reasons explained above for claim 1, which discussion is incorporated herein by reference in its entirety. With respect to any additional elements in this claim, they have already been addressed above with respect to claim 1 and do not impart non-obviousness. Thus, claim 7 is obvious.

(h) Dependent Claim 8 Is Invalid as Obvious

Dependent claim 8 depends from claim 1. Thus, it is obvious for at least the same reasons explained above for claim 1, which discussion is incorporated herein by reference in its entirety.

Moreover, Jamieson recognizes problems associated with intranasally administered benzodiazepine formulations, with one of the problems being "poor bioavailability." Jamieson at [0018]. Jamieson explains the need for intranasal benzodiazepine compositions with improved properties, such as rapid absorption, time to peak concentration, and bioavailability. Thus, Jamieson also teaches the use of penetration enhancers in diazepam for intranasal spray formulations. *See* [0104] ("pharmaceutical compositions comprising the benzodiazepine (e.g., clonazepam, diazepam or lorazepam) of the present invention, for example, for intranasal administration . . . may further comprise one or more components including . . . mucosa penetration enhancing agent"), [0105] ("In preferred embodiments of the present invention, the pharmaceutical compositions . . . are formulation to be sprayable."). Jamieson also recognizes that due to the "highly lipophilic nature of lipophilic nature of the benzodiazepines a combination of Surfactants, strong solubilizing solvents, and carrier solutions are often used." Jamieson at [0142].

Similarly, Meezan discloses benefits of dodecyl-beta-D-maltoside in formulations for ocular administration. Meezan at [0156] ("[A]t least two alkylmaltosides [including dodecyl-beta-

D-maltoside] are effective in achieving sufficient absorption" of the drug substance studied), Table 1. Meezan specifically teaches an alkyl glycoside (such as dodecyl-beta-D-maltoside) amount of about 0.25%. *See, e.g.,* Meezan at [0150]-[0151]; *see also* Fig. 1, [0158]-[0159], Table I, and Example 6. Thus the prior art suggests the use of excipients that "increase absorption across the mucosa and/or increase[] bioavailability." '400 patent at 37:31-35. Thus, claim 8 is obvious.

(i) Dependent Claim 9 Is Invalid as Obvious

Dependent claim 9 depends from claim 8. Thus, it is obvious for at least the same reasons explained above for claim 8, which discussion is incorporated herein by reference in its entirety. With respect to any additional elements in this claim, they have already been addressed above with respect to claim 8 and do not impart non-obviousness. Thus, claim 9 is obvious.

(j) Dependent Claim 10 Is Invalid as Obvious

Dependent claim 10 depends from claim 1. Thus, it is obvious for at least the same reasons explained above for claim 1, which discussion is incorporated herein by reference in its entirety. With respect to any additional elements in this claim, they have already been addressed above with respect to claim 1 and do not impart non-obviousness. Thus, claim 10 is obvious.

(k) Dependent Claim 11 Is Invalid as Obvious

Dependent claim 11 depends from claim 1. Thus, it is obvious for at least the same reasons explained above for claim 1, which discussion is incorporated herein by reference in its entirety. With respect to any additional elements in this claim, they have already been addressed above with respect to claim 1 and do not impart non-obviousness. Thus, claim 11 is obvious.

(l) Independent Claim 12 Is Invalid as Obvious

Independent claim 12 is obvious for at least the same reasons explained above for claim 1, which discussion is incorporated herein by reference in its entirety. With respect to any additional

or different elements in this claim, they have already been addressed above with respect to claim 1 and do not impart non-obviousness. Thus, claim 12 is obvious.

(m) Dependent Claim 13 Is Invalid as Obvious

Dependent claim 13 depends from claim 12. Thus, it is obvious for at least the same reasons explained above for claim 12, which discussion is incorporated herein by reference in its entirety. With respect to any additional elements in this claim, they have already been addressed above with respect to claim 12 and do not impart non-obviousness. Thus, claim 13 is obvious.

(n) Dependent Claim 14 Is Invalid as Obvious

Dependent claim 14 depends from claim 12. Thus, it is obvious for at least the same reasons explained above for claim 12, which discussion is incorporated herein by reference in its entirety. With respect to any additional elements in this claim, they have already been addressed above with respect to claim 12 and do not impart non-obviousness. Thus, claim 14 is obvious.

(o) Dependent Claim 15 Is Invalid as Obvious

Dependent claim 15 depends from claim 12. Thus, it is obvious for at least the same reasons explained above for claim 12, which discussion is incorporated herein by reference in its entirety. With respect to any additional elements in this claim, they have already been addressed above with respect to claim 12 and do not impart non-obviousness. Thus, claim 15 is obvious.

(p) Dependent Claim 16 Is Invalid as Obvious

Dependent claim 16 depends from claim 12. Thus, it is obvious for at least the same reasons explained above for claim 12, which discussion is incorporated herein by reference in its entirety. With respect to any additional elements in this claim, they have already been addressed above with respect to claim 12 and do not impart non-obviousness. Thus, claim 16 is obvious.

(q) Dependent Claim 17 Is Invalid as Obvious

Dependent claim 17 depends from claim 12. Thus, it is obvious for at least the same reasons explained above for claim 12, which discussion is incorporated herein by reference in its entirety.

Moreover, Jamieson recognizes problems associated with intranasally administered benzodiazepine formulations, with one of the problems being "poor bioavailability." Jamieson at [0018]. Jamieson explains the need for intranasal benzodiazepine compositions with improved properties, such as rapid absorption, time to peak concentration, and bioavailability. Thus, Jamieson also teaches the use of penetration enhancers in diazepam for intranasal spray formulations. *See* [0104] ("pharmaceutical compositions comprising the benzodiazepine (e.g., clonazepam, diazepam or lorazepam) of the present invention, for example, for intranasal administration . . . may further comprise one or more components including . . . mucosa penetration enhancing agent"), [0105] ("In preferred embodiments of the present invention, the pharmaceutical compositions . . . are formulation to be sprayable."). Jamieson also recognizes that due to the "highly lipophilic nature of lipophilic nature of the benzodiazepines a combination of Surfactants, strong solubilizing solvents, and carrier solutions are often used." Jamieson at [0142].

Similarly, Meezan discloses benefits of dodecyl-beta-D-maltoside in formulations for ocular administration. Meezan at [0156] ("[A]t least two alkylmaltosides [including dodecyl-beta-D-maltoside] are effective in achieving sufficient absorption" of the drug substance studied), Table 1. Meezan specifically teaches an alkyl glycoside (such as dodecyl-beta-D-maltoside) amount of about 0.25%. *See, e.g.,* Meezan at [0150]-[0151]; *see also* Fig. 1, [0158]-[0159], Table I, and Example 6. Thus the prior art suggests the use of excipients that "increase absorption across the mucosa and/or increase[] bioavailability." '400 patent at 37:31-35. Thus, claim 17 is obvious.

(r) Dependent Claim 18 Is Invalid as Obvious

Dependent claim 18 depends from claim 17. Thus, it is obvious for at least the same reasons explained above for claim 17, which discussion is incorporated herein by reference in its entirety. With respect to any additional elements in this claim, they have already been addressed above with respect to claim 17 and do not impart non-obviousness. Thus, claim 18 is obvious.

(s) Dependent Claim 19 Is Invalid as Obvious

Dependent claim 19 depends from claim 12. Thus, it is obvious for at least the same reasons explained above for claim 12, which discussion is incorporated herein by reference in its entirety. With respect to any additional elements in this claim, they have already been addressed above with respect to claim 12 and do not impart non-obviousness. Thus, claim 19 is obvious.

(t) Independent Claim 20 Is Invalid as Obvious

Independent claim 20 is obvious for at least the same reasons explained above for claim 1, which discussion is incorporated herein by reference in its entirety. With respect to any additional or different elements in this claim, they have already been addressed above with respect to claim 1 and do not impart non-obviousness. Thus, claim 20 is obvious.

(u) Dependent Claim 21 Is Invalid as Obvious

Dependent claim 21 depends from claim 20. Thus, it is obvious for at least the same reasons explained above for claim 20, which discussion is incorporated herein by reference in its entirety.

Moreover, Jamieson recognizes problems associated with intranasally administered benzodiazepine formulations, with one of the problems being "poor bioavailability." Jamieson at [0018]. Jamieson explains the need for intranasal benzodiazepine compositions with improved properties, such as rapid absorption, time to peak concentration, and bioavailability. Thus, Jamieson also teaches the use of penetration enhancers in diazepam for intranasal spray

formulations. *See* [0104] ("pharmaceutical compositions comprising the benzodiazepine (e.g., clonazepam, diazepam or lorazepam) of the present invention, for example, for intranasal administration . . . may further comprise one or more components including . . . mucosa penetration enhancing agent"), [0105] ("In preferred embodiments of the present invention, the pharmaceutical compositions . . . are formulation to be sprayable."). Jamieson also recognizes that due to the "highly lipophilic nature of lipophilic nature of the benzodiazepines a combination of Surfactants, strong solubilizing solvents, and carrier solutions are often used." Jamieson at [0142].

Similarly, Meezan discloses benefits of dodecyl-beta-D-maltoside in formulations for ocular administration. Meezan at [0156] ("[A]t least two alkylmaltosides [including dodecyl-beta-D-maltoside] are effective in achieving sufficient absorption" of the drug substance studied), Table 1. Meezan specifically teaches an alkyl glycoside (such as dodecyl-beta-D-maltoside) amount of about 0.25%. *See, e.g.,* Meezan at [0150]-[0151]; *see also* Fig. 1, [0158]-[0159], Table I, and Example 6. Thus the prior art suggests the use of excipients that "increase absorption across the mucosa and/or increase[] bioavailability." '400 patent at 37:31-35. Thus, claim 21 is obvious.

5. All Claims of the '400 Patent Are Invalid as Obvious over Sonne in view of Choi, Costantino '444, and/or Meezan

All claims of the '400 patent are obvious over U.S. Patent No. 6,193,985 B1 ("*Sonne*") in view of U.S. Patent No. US 6,627,211 B1 ("*Choi*"), PCT Publication No. WO2009/046444A2 ("*Costantino'444*"), and/or U.S. Publication No. 2006/0046962A1 ("*Meezan*").

In addition to the disclosures and teachings above, the claims of the '400 patent is further shown below to be obvious and as shown in the claim charts attached hereto as Exhibit F. *See Sections* V.A-G. Independent claim 1 of the '400 Patent is directed to a pharmaceutical composition for intranasal administration comprising: about 1 to about 20 mg of diazepam dissolved in about 45% to about 85% (w/w) of one or more natural or synthetic tocopherols or

tocotrienols selected from the group consisting of α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, α-tocotrienol, β-tocotrienol, γ-tocotrienol, δ-tocotrienol, tocophersolan, any esters thereof and any combinations thereof, and about 25% to about 40% (w/w) of one or more alcohols selected from the group consisting of ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, and any combinations thereof, wherein the pharmaceutical composition is a solution of 50 μL to 150 μL, and wherein the pharmaceutical composition is in a pharmaceutically-acceptable spray formulation for intranasal administration. Claims 2-11 directly or indirectly depend from claim 1. Claims 2-8, and 10-11 depends from claim 1. Claim 2 specifies that the natural or synthetic tocopherols or tocotrienols are selected from the group consisting of: α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, tocophersolan, any esters thereof and any combinations thereof. Claim 3 specifies that the natural or synthetic tocopherols or tocotrienols is α-tocopherol. Claim 4 specifies that the one or more alcohols is selected from the group consisting of ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, isomers thereof and any combinations thereof. Claim 5 specifies that the diazepam is present in the pharmaceutical solution at a concentration of about 10 mg/mL to about 250 mg/mL. Claim 6 specifies that the pharmaceutical solution comprises one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof in an amount from about 60% to about 75% (w/w). Claim 7 specifies that the pharmaceutical composition further comprises at least one additional ingredient selected from the group consisting of stabilizers, coloring agents, pH adjusters, buffering agents, preservatives, wetting agents, flavoring agents and combinations thereof. Claim 8 specifies that the pharmaceutical composition further comprises an absorption enhancer. Claim 9 depends from claim 8, specifies that the absorption enhancer is present in the pharmaceutical composition at a concentration of up to 20% (w/v). Claim 10 specifies that the pharmaceutical composition is about

100 μL. Claim 11 specifies that the therapeutically effective amount of the diazepam is about 2 mg to about 10 mg.

Independent claim 12 of the ’400 Patent is directed to a pharmaceutical composition for intranasal administration comprising: about 1 to about 20 mg of diazepam dissolved in about 45% to about 85% (w/w) of α-tocopherol, and about 25% to about 40% (w/w) of one or more alcohols selected from the group consisting of ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, isomers thereof and any combinations thereof, wherein the pharmaceutical composition is a solution of 50 μL to 150 μL, and wherein the pharmaceutical composition is in a pharmaceutically-acceptable spray formulation for intranasal administration. Claims 13-19 directly or indirectly depend from claim 12. Claims 13-17, and 19 depends from claim 12. Claim 13 specifies that the diazepam is present in the pharmaceutical solution at a concentration of about 10 mg/mL to about 250 mg/mL. Claim 14 specifies that the diazepam is about 2 mg to about 10 mg. Claim 15 specifies that the pharmaceutical solution comprises α-tocopherol in an amount from about 60% to about 75% (w/w). Claim 16 specifies that the pharmaceutical composition further comprises at least one additional ingredient selected from the group consisting of stabilizers, coloring agents, pH adjusters, buffering agents, preservatives, wetting agents, flavoring agents and combinations thereof. Claim 17 specifies that the pharmaceutical composition further comprises an absorption enhancer. Claim 18 depends from claim 17, specifies that the absorption enhancer is present in the pharmaceutical composition at a concentration of up to 20% (w/v). Claim 19 specifies that the pharmaceutical composition is about 100 μL.

Independent claim 20 of the ’400 Patent is directed to a pharmaceutical composition for intranasal administration comprising: about 1 to about 20 mg of diazepam dissolved in about 45% to about 85% (w/w) of α-tocopherol and about 25% to about 40% (w/w) of one or more alcohols

selected from the group consisting of ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, and any combinations thereof, wherein the pharmaceutical composition is a solution of about 100 μL, and wherein the pharmaceutical composition is in a pharmaceutically-acceptable spray formulation for intranasal administration. Claim 21 depends from claim 20, specifies that the pharmaceutical composition further comprises an absorption enhancer.

Sonne discloses a pharmaceutically acceptable solution for intranasal administration comprising about 1 to about 20 mg of diazepam dissolved in the claimed percentages of one or more natural or synthetic tocopherols or tocotrienols (including α-tocotrienol) and one or more alcohols selected from the group consisting of ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, and any combinations thereof. *Sonne* at Abstract, 3:54-59, 7:32-8:10, 13:56-14:13, 14:63-67, and Examples 1, 22, and 23. *Sonne* further discloses that an organic co-solvent such as ethanol, benzyl alcohol or triacetin can be added to optimize the sprayability and viscosity of solution. Sonne at 6:47-54. A diazepam intranasal solution as exemplified in *Sonne* in Example 11 provides for a solution of diazepam (as nosedrop) containing 5% diazepam, 40% α-tocopherol, and 55% triacetin (co-solvent). Therefore, POSA would be motivated to prepare a spray solution of diazepam using α-tocopherol and replace the organic co-solvent triacetin in Example 11 with another disclosed organic co-solvent(s) such as alcohols namely ethanol and/or benzyl alcohol. *See Sections* VI.D-G. Further *Sonne* also discloses that Cetearyl glucoside (belonging to the class of alkyl glycosides which are known to be used as effective absorption enhancers) may be safely and effectively added as surfactant in diazepam emulsions for intranasal administration (*Sonne* at 6:54-59) and it was known to a POSA that surfactants function as highly effective absorption enhancers in pharmaceutical formulations by increasing the permeability of the drug. *Sonne* also teaches that formulations for intranasal administration could also be in form of solutions (*Sonne* at

6:28-35), hence it would be obvious to a POSA to develop an intranasal diazepam solution comprising diazepam, α-tocopherol, one or more alcohols such as ethanol and/or benzyl alcohol further comprising of a surfactant/absorption enhancer, with a reasonable expectation of success. Further, a POSA would also have been aware that absorption enhancer (surfactant in an amount from about 0.01% to 20% by weight and specifically alkyl glycoside), is used to increase the absorption and bioavailability of small-molecule drug such as diazepam when administered as a spray via nasal route in solution form as taught by *Meezan*. Thus, a POSA would be motivated to include absorption enhancer (at a concentration of up to 20% w/v) as taught by *Meezan* in diazepam intranasal spray solution.

Choi and *Costantino '444* provide additional guidance on the claimed amounts of one or more alcohols. *Choi* discloses the use of vehicle containing about 30-60% of ethanol, a glycol, water, and a biological surfactant for intranasal solution composition of diazepam, which is administered in a volume of 100 µl by means of a Pfeiffer spray device. *Choi* at 2:53-58, 7:921; 7:25-28; 8:56-62. Also, *Costantino '444* discloses the intranasal delivery of about 1 mg to about 20 mg diazepam as a spray in a volume from about 25 µl to about 250 µl using about 0.1 to about 85% of cosolvent (including ethanol) as vehicle, one or more mucosal delivery enhancing agent and additional ingredients such as antioxidants (including α-tocopherol), preservatives, flavoring agents, and coloring agents. *Costantino '444* at 10:16-19, 15:22-33, 16:15-21, 16:33-17:13, 17:14-25; 26:25-29. Therefore, considering either Choi or Costantino '444, a POSA would have optimized and arrive at the claimed amounts of one or more alcohols to be included in the diazepam intranasal spray solutions taught by *Sonne*. Thus, it would be part of routine experimentation for POSA to be able to develop an intranasal spray solution of diazepam comprising α-tocopherol in an amount about 45% to about 85% w/w, one or more alcohols such as ethanol in an amount about

25% to about 40% w/w, absorption enhancer at a concentration of up to 20% w/v, and additional other ingredients as required and as set forth in the attached claim chart (*See* Exhibit F). *See Sections* VI.D-G.

6. Secondary Considerations

Defendants contend that no secondary considerations weigh in favor of non-obviousness with respect to any of the claims of the ’400 patent. Any secondary considerations that Neurelis may assert would be insufficient to overcome the strong showing of obviousness in this case with respect to the claims of the ’400 patent. *See DyStar Textilfarben GmbH v. C.H. Patrick Co.*, 464 F.3d 1356, 1371 (Fed. Cir. 2006) (patent found obvious despite commercial success); *In re GPAC Inc.*, 57 F.3d 1573, 1580-81 (Fed. Cir. 1995) (same); *Pentec, Inc. v. Graphic Controls Corp.*, 776 F.2d 309, 315-17 (Fed. Cir. 1985) (same); *Pfizer*, 480 F.3d at 1371-72 (finding secondary considerations insufficient where the record establishes a strong case of obviousness); *Leapfrog Enters., Inc. v. Fisher-Price, Inc.*, 485 F.3d 1157, 1162 (Fed. Cir. 2007) (“[G]iven the strength of the prima facie obviousness showing, the evidence on secondary considerations was inadequate.”); *W. Union Co. v. MoneyGram Payment Sys., Inc.*, 626 F.3d 1361, 1373 (Fed. Cir. 2010) (“[W]eak secondary considerations generally do not overcome a strong prima facie case of obviousness.”).

Further, Defendants are presently unaware of any secondary considerations that are relevant to any of the claims of any of the ’400 patent. Secondary considerations do not form a part of the *prima facie* case of obviousness. Rather, a patentee may try to rebut a *prima facie* case of obviousness by coming forth with purported evidence of secondary considerations. Defendants therefore have no burden at this stage to address any secondary considerations, or to come forward with any evidence rebutting such considerations. To the contrary, it is Neurelis’s obligation and burden to produce evidence of so-called secondary considerations, if any, on which it intends to rely. Defendants expect that additional discovery directed to any secondary considerations

Neurelis may allege will take place in accordance with the case schedule, and that the evidence will rebut any alleged or claimed secondary considerations in full. As such, if and in the event Neurelis cites to any alleged secondary considerations, Defendants reserve the right to supplement these contentions.

In addition, the PTAB previously considered certain arguments raised by Neurelis in the context of secondary considerations of non-obviousness. IPR2019-00451, Paper 44 at 51-54. Specifically, Neurelis presented "evidence of failure of others and long-felt need." *Id*. at 51. With respect to long-felt need, Neurelis argued that there was a need for intranasal formulations of diazepam, which was met by the Valtoco product. *Id*. at 51-52. And with respect to the failure of others, Neurelis argued that other companies attempted to develop intranasal diazepam formulations, but were unsuccessful. *Id*.

The PTAB rejected both of Neurelis's arguments, noting that "we give [Neurelis's] arguments about failure of others and long-felt need very little weight in our obviousness analysis." *Id*. at 52. The PTAB specifically noted that Neurelis failed to establish a nexus between the formulations claimed by the '876 patent and the Valtoco product. *Id*. Indeed, Neurelis did not even "argue a nexus between VALTOCO … and the claims." *Id*. at 53. Thus, Neurelis has conceded that there is no nexus between the claims of its formulation patents (including the '400 patent) and the purported secondary considerations of non-obviousness it asserted.

Further, the PTAB held that "even if nexus had been shown, the objective evidence of nonobviousness identified by Patent Owner provides only limited support for nonobviousness of the challenged claims." *Id*. Indeed, the PTAB found that "benzodiazepines were delivered intranasally prior to 2009, which undercuts [Neurelis's] arguments of failure of others and long-felt need." *Id*. at 54.

Accordingly, for the reasons previously considered and addressed by the PTAB, there are no secondary considerations of non-obviousness related to the ’400 patent that overcome the prima facie case of obviousness discussed above.

I. The Claims of the ’400 Patent Are Invalid Under 35 U.S.C. § 112

As explained above, claim 1 of the ’400 patent recites “[a] pharmaceutical composition for intranasal administration … wherein the pharmaceutical composition is in a pharmaceutically-acceptable spray formulation.” ’400 patent at claim 1. To the extent the claims of the ’400 patent are not invalid as obvious, which they are, they are invalid for lack of written description and/or non-enablement under 35 U.S.C. § 112. Specifically, under this scenario, the specification of the ’400 patent fails to demonstrate that the inventors possessed the full scope of the claimed pharmaceutical “solution” compositions “in a pharmaceutically acceptable spray formulation,” and, if not invalid as obvious, the ’400 patent does not enable a POSA to make and use the full scope of the claimed pharmaceutical “solution” compositions “in a pharmaceutically acceptable spray formulation” without undue experimentation.

1. Lack of Written Description

As explained above, the Federal Circuit has made it clear that the specification must objectively demonstrate to a POSA that the inventor had possession of the claimed subject matter. *Supra* Section III.C.1; *see also Ariad*, 598 F.3d at 1351; *Juno Therapeutics, Inc. v. Kite Pharma, Inc.*, 10 F.4th 1330, 1336 (Fed. Cir. 2021). “For generic claims,” the Federal Circuit has “set forth a number of factors for evaluating the adequacy of the disclosure, including ‘the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, [and] the predictability of the aspect at issue.’” *Juno*, 10 F.4th at 1335 (quoting *Ariad*, 598 F.3d at 1351). And “[f]or genus claims using functional language … the written description ‘must demonstrate that the applicant has made a generic invention that achieves the

claimed result and do so by showing that the applicant has invented species sufficient to support a claim to the functionally-defined genus.'" *Id.* at 1335 (quoting *Ariad*, 598 F.3d at 1351). "Generally, a genus can be sufficiently disclosed by 'either a representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one of skill in the art can "visualize or recognize" the members of the genus.'" *Id*. at 1335 (quoting *Ariad*, 598 F.3d at 1351).

Here, the claims of the '400 patent recite a genus of pharmaceutical compositions containing various amounts of diazepam, "one or more natural or synthetic tocopherols or tocotrienols selected from the group consisting of α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, α-tocotrienol, β-tocotrienol, γ-tocotrienol, δ-tocotrienol, tocophersolan, any esters thereof and any combinations thereof," and "one or more alcohols selected from the group consisting of ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, and any combinations thereof." '400 patent at claim 1. Further, the claimed genus of pharmaceutical compositions must satisfy certain functional claim limitations, including that the compositions must be a "solution" and must be "in a pharmaceutically-acceptable spray formulation." *Id*. Thus, to satisfy the written description requirement, the specification of the '400 patent must demonstrate to a POSA that the inventors possessed the full scope of the claimed genus of pharmaceutical compositions that satisfy the functional requirements of the claims.

While the prior art renders the claimed genus of formulations obvious for the reasons discussed above, the specification falls well-short of demonstrating that the inventors possessed the full scope of what is claimed in the '400 patent.

To be sure, the claims of the '400 patent would have been obvious in view of the prior art discussed above, which would have motivated a POSA to make the claimed formulations of

diazepam with a reasonable expectation of success. *Supra* Section V.D, V.E.. Specifically, a POSA would have expected that species of formulations that fall within the broad genus claimed in the '400 patent would form "solutions" that are "in a pharmaceutically-acceptable spray formulation." However, the standards for obviousness are different than the standards a patentee must satisfy to establish adequate written description support for a claimed invention. *Lockwood v. Am. Airlines*, Inc., 107 F.3d 1565, 1572 (Fed. Cir. 1997) ("One shows that one is in possession of the invention by describing the invention, with all its claimed limitations, not that which makes it obvious.") (citation modified). Thus, the fact that the specification of the '400 patent discloses that some embodiments within the broad genus of formulations recited in the claims may work (as disclosed in the prior art) is not sufficient to "'demonstrate that the applicant has made a generic invention that achieves the claimed result … by showing that the applicant has invented species sufficient to support a claim to the functionally-defined genus.'" *Juno*, 10 F.4th at 1335 (quoting *Ariad*, 598 F.3d at 1351).

Indeed, the specification only discloses three examples of "solutions," which were prepared using specific amounts of diazepam, α-tocopherol or Vitamin E, and ethanol. '400 patent at 42:27-43:56. Only two of those solutions were subjected to the additional tests described in Example 5, and one of those two solutions failed to meet the test specifications. '400 patent at 44:28-52:30 (Solution 00 did not "meet[] specifications" for the formation of related compound A under storage conditions of 30º C/65% relative humidity and 40º C/75% relative humidity (Table 5-2); and Solution 00 did not "meet[] specifications" for the formation of related compound B under storage conditions of 30º C/65% relative humidity and 40º C/75% relative humidity (Table 5-3)). Thus, even among the limited working examples of compositions developed and tested in the examples of the '400 patent, certain solutions failed to satisfy the functional requirements of the claims (i.e.,

they were not "solutions" that are "in a pharmaceutically-acceptable spray formulation."). And as explained above, the claims of the '400 patent encompass an almost incalculable number of pharmaceutical compositions because they may contain various types and amounts of ingredients in different permutations and combinations.

The specification's minimal disclosure of formulations and testing fails to demonstrate that the inventors possessed the full scope of the claims. *Juno*, 10 F.4th at 1335 (quoting *Ariad*, 598 F.3d at 1351); *see also AstraZeneca AB v. Mylan Pharms. Inc.*, 2022 WL 16857400, at *19 (N.D.W. Va. Nov. 9, 2022). As noted above, the prior art renders obvious a solution formulation meeting the claimed requirements. However, the specification's disclosure of a small number of embodiments within the broad genus of formulations claimed in the '400 patent (i.e., "solutions" that are "in a pharmaceutically-acceptable spray formulation") does not establish adequate written description support for the broad genus of formulations that must meet the claimed functional requirements. *Lockwood*, 107 F.3d at 1572.

Neurelis's lack of possession of the claimed compositions is underscored by statements in the specification and arguments made during prosecution of the '400 patent. For example, the specification states that diazepam was known to suffer from "solubility challenges," and that it may be difficult to fully dissolve the drug to form a solution (instead of a suspension). *See, e.g.*, '400 patent at 1:53-56. Neurelis also specifically amended the claims of the '664 patent during prosecution to recite "solutions" that are "in a pharmaceutically-acceptable spray formulation" to overcome the examiner's obviousness rejections, and argued that a POSA would not consider the prior art formulations to be "solutions" that are "in a pharmaceutically-acceptable spray formulation" because they may not satisfy various functional requirements. *Supra* Section II.D.3. Neurelis's own statements and arguments demonstrate that it considers the claims of the '400

patent to include functional requirements that must be met by the claimed formulations. But as explained above, to the extent the claims are not invalid as obvious, the specification of the ’400 patent fails to demonstrate to a POSA that the inventors possessed the full scope of the genus of compositions that satisfy the functional requirements required by the claims.

2. Non-Enablement

Claims are not enabled when, at the effective filing date of the patent, a POSA could not practice their full scope without undue experimentation. *See Wyeth & Cordis Corp. v. Abbott Labs*., 720 F.3d 1380, 1384 (Fed. Cir. 2013). As the Supreme Court explained, “the specification must enable the full scope of the invention as defined by its claims. The more one claims, the more one must enable.” *Amgen Inc. v. Sanofi*, 598 U.S. 594, 610 (2023). “Although a specification does not need to describe how to make and use every possible variant of the claimed invention, when a range is claimed, there must be reasonable enablement of the scope of the range.” *Amgen Inc. v. Sanofi, Aventisub LLC*, 987 F.3d 1080, 1085 (Fed. Cir. 2021) *aff’d sub nom. Amgen Inc. v. Sanofi*, 598 U.S. 594 (2023). Functional claim limitations “pose high hurdles in fulfilling the enablement requirement.” *Id*. at 1087.

For the same reasons discussed above, to the extent that the claims are not invalid as obvious, the claims of the ’400 patent are invalid for failing to enable a POSA to make and use the genus of pharmaceutical compositions that satisfy the functional requirements of the claims (i.e., “solutions” that are “in a pharmaceutically-acceptable spray formulation”) without undue experimentation. *Supra* Section V.F.1. Thus, to the extent Neurelis argues that the prior art would not have rendered the claims of the ’400 patent obvious, a POSA would need to engage in undue experimentation to practice the full scope of the claims. And because the genus of pharmaceutical compositions encompassed by the claims is extremely broad, *supra* section V.F.1, a POSA would

need to conduct a significant amount of experimentation to determine which species satisfy the claimed functional requirements. *Id*.

Further, as noted above, the standards for establishing obviousness are different from the standards a patentee must satisfy to show that the claims of a patent are enabled. Indeed, the Federal Circuit has long-recognized that "claims are unpatentable when they are so broad as to read on obvious subject matter even though they likewise read on non-obvious subject matter." *In re Mraz*, 455 F.2d 1069, 1072–73, 173 USPQ 25, 28 (CCPA 1972); *see also DNT, LLC v. Sprint Spectrum, LP,* 750 F. Supp. 2d 616, 624 (E.D. Va. 2010) (holding "that simultaneous obviousness and non-enablement findings" can be "compatible."); *Pharm. Resources, Inc. v. Roxane Labs., Inc.*, 2006 WL 3231427, at *16 (D.N.J. Nov. 8, 2006) ("It is not that *no* subject matter within the claims is enabled, because some examples within the claims certainly are enabled. The point is that the specification does not enable the full scope of the claims as recited above."); *Imperial Chem. Indus., PLC v. Danbury Pharmacal, Inc.*, 777 F.Supp. 330, 373–74 (D. Del. 1991); *Cosden Oil & Chem. Co. v. Am. Hoechst Corp.*, 543 F.Supp. 522, 544 (D.Del. 1982).

Accordingly, to the extent that the claims are not invalid as obvious, the claims of the '400 patent are invalid for failing to satisfy the enablement requirement of 35 U.S.C. § 112.

VI. INVALIDITY OF THE '852 AND '061 PATENTS

A. The Priority Date of the '852 and '061 Patents

As explained above, the earliest possible priority date for the '852 and '061 patents is June 13, 2012. *Supra* Section II.E-C. While the '852 and '061 patents purport to claim priority to earlier-filed provisional applications, Neurelis unambiguously stated to the examiner during prosecution that the '852 and '061 patents are only entitled to a priority date of June 13, 2012. *See, e.g.*, Neurelis-02049980-50015 (explaining that the claims are entitled to a priority date of June 13, 2012 and that "[a]pplicant submits that the present claims should be allowed immediately and be

granted a natural term of twenty years (i.e., until June 13, 2032)."); Neurelis-02053602-623 ("Applicant's objective in filing this Track One application is the ensure that the Examiner is aware of everything considered to be material in this case's history and the prior art and to establish the patentability of ***the present claims with a priority date of June 13, 2012***, and a natural term of twenty years (i.e., until June 13, 2032).") (emphasis added). Accordingly, Defendants understand that the claims of the '852 and '061 patents have a priority date of no earlier than June 13, 2012.

B. Background of Technology

As explained above, the '852 and '061 patents have a priority date of no earlier than June 13, 2012. *Supra* Section VI.A. Accordingly, a POSA would have been aware of the background and state of the art discussed above with respect to the '664 patent, which has an earlier priority date of March 27, 2009. *Supra* Section V.A-C.

Further, a POSA would have been aware of additional information published between March 27, 2009 and June 12, 2012. For example, a POSA would have been aware of the disclosures of the original specification of the '414, '786, and '664 patents filed and published in 2009, which is prior art against the '852 and '061 patents. Accordingly, a POSA would have been aware of the intranasally available diazepam formulations, and their use for the treatment of seizures, described in the specification of the '414, '786, and '664 patents. *Supra* Section II.D.2.

In addition, a POSA would have been aware of a Neurelis-sponsored clinical trial that was being performed "to assess the bioavailability and pharmacokinetics of two formulations of diazepam after intranasal (nasal spray) and injectable diazepam after intravenous (I.V.) administration." Clinical Trial No. NCT01364558.[24] Neurelis's clinical trial, NCT01364558

[24] Clinical trial number NCT01364558 was first posted (i.e., made publicly available) by June 2, 2011, and thus was published more than one year before the June 13, 2012 priority date of the '852 and '061 patents. *See, e.g.*, https://clinicaltrials.gov/study/NCT01364558.

("NCT '558"), described three arms and interventions, which sought to investigate "the absolute bioavailability of two intranasal diazepam formulations." *Id*. One intranasal diazepam formulation was described by NCT '558 as a "solution" while the other was referred to as a "suspension." *Id*. According to NCT '558, "[t]he two nasal formulations will be given as 10 mg doses." *Id*.

The results of that clinical trial were subsequently published in an abstract in October 2011, and presented in December 2011 during a poster session at the American Epilepsy Society annual meeting. Agarwal at 220.[25] Consistent with the NCT '558 clinical trial, the Agarwal Abstract disclosed that "[t]he primary objective of this study was to compare the bioavailability and pharmacokinetics (PK) of two novel intranasal (IN) diazepam (DZP) formulations versus intravenous (IV) administration in healthy volunteers." *Id*. The Agarwal Abstract explained that the 10 mg doses of the intranasal diazepam solution formulation resulted in a "[b]ioavailability" that "approached 100% and was significantly ($p<0.05$) greater than the IN suspension, as was Cmax." *Id*. Further, "[m]edian time to maximum concentration (Tmax) was 1hr and 1.5hr for suspension and formulation, respectively. The mean $T_{1/2}$ was similar for all three formulations. Both investigational intranasal formulations were well tolerated." *Id*.

Neurelis likewise issued several press releases in 2011 and 2012 to report that the intranasal solution formulation of diazepam was being tested,[26] resulted in encouraging pharmacokinetic and

[25] The Agarwal abstract was initially published on October 4, 2011 and later published and presented in poster-form at the American Epilepsy Society annual meeting in December 2011. *See* Suresh K. Agarwal, *A Pilot Study Assessing the Bioavailability and Pharmacokinetics of Diazepam after Intranasal And Intravenous Administration in Healthy Volunteers*, 12 EPILEPSY CURRENTS 220, 220 (2011); *see also* https://aesnet.org/abstractslisting/a-pilot-study-assessing-the-bioavailability-and-pharmacokinetics-of-diazepam-after-intranasal-and-intravenous-administration-in-healthy-volunteers.

[26] https://www.prnewswire.com/news-releases/neurelis-announces-completion-of-dosing-in-study-of-intranasal-diazepam-120272699.html

bioavailability data,[27] and that Neurelis's related investigational new drug ("IND") application was cleared and further clinical trials could proceed.[28] Specifically, on June 14, 2011, Neurelis reported that:

> Comparative analysis of the lead intranasal formulation, NRL-1, revealed promising pharmacokinetic results. In its evaluation of a 10 mg diazepam dose in the NRL-1 intranasal solution formulation, the study showed the following:
>
> - NRL-1 is well-tolerated, with only mild adverse events reported
> - Similar bioavailability to intravenous administration of diazepam (100% vs. 96%)
> - Tmax of 1.5 hours.
> - Cmax of approximately 272 ng/ml.
> - These values are comparable to those reported in the literature for Diastat® (rectal diazepam gel) at equivalent doses. Diastat is the only approved therapy for the at home treatment of acute repetitive seizures.

June 14, 2011 Press Release. The June 14, 2011 Press Release continued by explaining that:

> "The results from this pilot study are very encouraging," commented Jim Cloyd, PharmD, University of Minnesota professor and principal investigator of the study, "The only approved drug to treat breakthrough seizures outside the hospital is diazepam rectal gel, a therapy that many older children and adults decline to use. The ability to quickly and efficiently deliver, via intranasal administration, clinically relevant diazepam levels offers a more acceptable method of rescue therapy. The bioavailability and relatively low variability in exposure of the intranasal diazepam solution exceeded our expectations. We look forward to further development of this important therapy."

Id. Finally, Neurelis explained that:

> NRL-01 (intranasal diazepam) is a proprietary formulation of diazepam delivered via a commercially available nasal sprayer. It is being developed for the management of patients who require intermittent use of diazepam to control bouts of acute repetitive seizure activity. There are over 2.7 million people with epilepsy in the United States with approximately 200,000 new patients diagnosed each year. It is estimated that between 30% to 40% of these patients are uncontrolled on oral therapy and are at-risk for acute repetitive seizures. Studies have shown that

[27] https://www.prnewswire.com/news-releases/neurelis-announces-positive-results-from-phase-1-pharmacokinetic-study-of-nrl-01-intranasal-diazepam-123834469.html

[28] https://www.prnewswire.com/news-releases/neurelis-announces-fda-allowance-of-ind-application-for-nrl-1-a-novel-intranasal-diazepam-formulation-138802279.html

> prolonged or repetitive seizures can cause neurological damage and dramatically increase the risk of changes in neuropsychological function or even death.

Id.

References that may be relied upon to demonstrate the state of the art as of the priority date of the ’852 and ’061 patents (i.e., June 13, 2012) include all references listed above with respect to the ’664 patent, *supra* sections V.A-D, as well as the references discussed in this section.

C. Identification of Invalidating Prior Art

Defendants identify the following prior art that, alone or in combination with other references, renders obvious the claims of the ’852 and ’061 patents. Defendants reserve the right to rely upon additional prior art or documents as discovery progresses, to the extent not addressed herein. Defendants reserve the right to rely on all prior art cited or discussed during the prosecution of any of the Asserted Patents and any patent claiming priority to any of the Asserted Patents or to which any of the Asserted Patents claim priority. As such, Defendants incorporate by reference, in full, all prior art references cited in any of the Asserted Patents or in any of the prosecution histories of any of the Asserted Patents and any patent claiming priority to any of the Asserted Patents or to which any of the Asserted Patents claim priority. Defendants further reserve the right to identify and rely on additional art or teachings or disclosures within the art in the event that Defendants’ evaluation of the prior art teachings or disclosures is in any way contested.

Defendants reserve the right to rely on these cited or uncited references as well as other teachings or disclosures in the field to demonstrate the state of art and/or the knowledge and level of skills of a POSA at the relevant times. Defendants intend to rely upon each reference in its entirety to the extent relevant and/or appropriate, including references cited in and/or referenced within the references identified below.

Prior art not included in these Preliminary Invalidity Contentions may become relevant depending upon the positions Neurelis asserts (*e.g.*, the infringement or claim construction positions asserted by Neurelis), the claim constructions adopted by the Court, and the priority date(s) determined for any of the Asserted Patents. In addition, Defendants may uncover additional prior art and/or relevant information during discovery. Defendants reserve the right to supplement, modify, or amend these Preliminary Invalidity Contentions with additional prior art, or different versions of the references listed herein, as discovery continues in light of information provided by Neurelis concerning its infringement allegations, claim constructions, or alleged earliest priority dates of the Asserted Patents, or in light of the Court's claim construction or other rulings and orders.

The following table summarizes the prior art references that Defendants contend renders the claims of the '852 and '061 patents obvious:

Prior Art Reference[29]	**Effective Publication Date**	**Short Cite**
WIPO Pub. No. WO 2009/120933 to Gwozdz et al.	March 28, 2008	Gwozdz
U.S. Pub. No. 2006/0046962 to Meezan et al.	March 2, 2006	Meezan
U.S. Pub. No. 2008/0279784 to Cartt et al.	November 13, 2008	Cartt 2008
U.S. Pub. No. 2009/0258865 to Cartt et al.	October 15, 2009	Cartt 2009
U.S. Pub. No. 2012/0252793 to Bream et al.	October 4, 2012	Bream
U.S. Patent No. 8,859,546	November, 25, 2014	'546
USP 23/NF 18, Ed., "United States Pharmacopeia. The National Formulary," The United States Pharmacopoeial Convention Inc., Rockville, 1995	1995	USP

[29] Defendants reserve the right to rely on any Invalidating Prior Art reference in combination with any other Invalidating Prior Art reference consistent with the disclosures provided herein. Specific combinations of Invalidating Prior Art references discussed below are exemplary only.

Prior Art Reference[29]	Effective Publication Date	Short Cite
Clinical Trial No. NCT01364558	June 2, 2011	NCT '558
Agarwal, *A Pilot Study Assessing the Bioavailability and Pharmacokinetics of Diazepam After Intranasal and Intravenous Administration in Healthy Volunteers*, 12 EPILEPSY CURRENTS (2011)	October 4, 2011	Agarwal
Press Release, Neurelis, Inc., *Neurelis Announces Positive Results from Phase 1 Pharmacokinetic Study of NRL-01 (intranasal diazepam)* (June 14, 2011), https://www.prnewswire.com/news-releases/neurelis-announces-positive-results-from-phase-1-pharmacokinetic-study-of-nrl-01-intranasal-diazepam-123834469.html	June 14, 2011	Neurelis Press Release
Press Release, Neurelis, Inc., *Neurelis Announces Completion of Dosing in Study of Intranasal Diazepam* (April 20, 2011), https://www.prnewswire.com/news-releases/neurelis-announces-completion-of-dosing-in-study-of-intranasal-diazepam-120272699.html	April 20, 2011	Neurelis April Press Release
Diastat Prescribing Information (Sep. 2005)	September 2005	Diastat Label

D. Preliminary Summary of the Prior Art References

1. Gwozdz, Meezan, Cartt 2008, and USP

Gwozdz, Meezan, Cartt 2008, and USP are summarized above and incorporated by reference here. *Supra* Section V.D.

2. Diastat Label

Diastat was initially approved by the FDA in 2005, and thus the corresponding drug product insert or label for Diastat is prior art against the '852 and '061 patents under § 102(b).

The Diastat Label disclosed a "rectal gel" formulation containing 5 mg/mL of diazepam. Diastat Label at 1. Thus, Diastat was "a gel formulation of diazepam intended for rectal administration in the management of selected, refractory, patients with epilepsy, on stable

regimens of AEDs, who require intermittent use of diazepam to control bouts of increased seizure activity." *Id*. Further, the Diastat Label explained that:

> Evidence to support the use of diazepam rectal gel was adduced in two controlled trials (see CLINICAL PHARMACOLOGY, CLINICAL STUDIES subsection) that enrolled patients with partial onset or generalized convulsive seizures who were identified jointly by their caregivers and physicians as suffering intermittent and periodic episodes of markedly increased seizure activity, sometimes heralded by nonconvulsive symptoms, that for the individual patient were characteristic and were deemed by the prescriber to be of a kind for which a benzodiazepine would ordinarily be administered acutely. Although these clusters or bouts of seizures differed among patients, for any individual patient the clusters of seizure activity were not only stereotypic but were judged by those conducting and participating in these studies to be distinguishable from other seizures suffered by that patient. The conclusion that a patient experienced such unique episodes of seizure activity was based on historical information.

Id.

3. Cartt 2009

U.S. Pub. No. 2009/0258865 to Cartt et al. titled "Administration of Benzodiazepine Compositions" was published on October 15, 2009. Cartt 2009 constitutes prior art against the '852 and '061 patents under § 102(b).

Cartt 2009 is related to and shares a specification with the '664 patent, which was summarized above. *Supra* Section II.D.2. To reiterate, Cartt 2009 is directed to "pharmaceutical compositions comprising one or more benzodiazepine drugs for nasal administration, methods for producing and for using such compositions." Cartt 2009 at Abstract. Specifically, Cartt 2009 discloses pharmaceutical compositions for nasal administration that contain "a benzodiazepine drug; one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); and one or more alcohols or glycols, or any combinations thereof, in an amount from about 5% to about 70% (w/w), preferably about 10% to about 70% (w/w) in a pharmaceutically-acceptable formulation for administration to one or more

nasal mucosal membranes of the patient." *Id*. at ¶ [0010]. The pharmaceutical compositions may also contain an alkyl glycoside, such as DDM. *Id*. at ¶¶ [0019], [0138], [0142]-[0143], [0210].

Further, Cartt 2009 discloses that the benzodiazepine-containing intranasal formulations are "useful in preventing, treating, or ameliorating the symptoms of … seizures (such as those caused by epilepsy)." *Id*. at ¶ [0003]; *see also, id.* at ¶ [0086]. "The dosage of diazepam may vary by indication, however it is expected that a therapeutic dose will be in the range of about 1 to about 20, preferably about 2 to about 10 mg per dose…" *Id*. at ¶ [0086]. Cart 2009 also discloses that the intranasal spray may be a solution that is administered in a "volume from about 10 μL to 200 μL" and "into at least one nostril" or "each nostril." *Id*. at ¶¶ [0028]-[0029]. "In some preferred embodiments, diazepam is administered in 50 to 150 μL, especially about 100 μL, metered sprays." *Id*. at ¶¶ [0147]-[0148].

4. NCT '558

Clinical Trial No. NCT01364558 was first posted by at least June 2, 2011 and thus constitutes prior art against the '852 and '061 patents under § 102(b).

NCT '558 was being performed "to assess the bioavailability and pharmacokinetics of two formulations of diazepam after intranasal (nasal spray) and injectable diazepam after intravenous (I.V.) administration." NCT '558. NCT '558 described three arms and interventions, which sought to investigate "the absolute bioavailability of two intranasal diazepam formulations" for the treatment of "epilepsy." *Id*. One intranasal diazepam formulation was described by NCT '558 as a "solution" while the other was referred to as a "suspension." *Id*. According to NCT '558, "[t]he two nasal formulations will be given as 10 mg doses." *Id*.

5. Agarwal

Agarwal, an abstract titled "A Pilot Study Assessing the Bioavailability and Pharmacokinetics of Diazepam After Intranasal and Intravenous Administration in Healthy

Volunteers" was published on October 4, 2011 and thus constitutes prior art against the '852 and '061 patents under § 102(a).

Agarwal disclosed the results of the NCT '558 clinical trial. Agarwal at 220. Consistent with the NCT '558 clinical trial, the Agarwal Abstract disclosed that "[t]he primary objective of this study was to compare the bioavailability and pharmacokinetics (PK) of two novel intranasal (IN) diazepam (DZP) formulations versus intravenous (IV) administration in healthy volunteers." *Id*. The Agarwal Abstract explained that the 10 mg doses of the intranasal diazepam solution formulation resulted in a "[b]ioavailability" that "approached 100% and was significantly ($p<0.05$) greater than the IN suspension, as was Cmax." *Id*. Further, "[m]edian time to maximum concentration (Tmax) was 1hr and 1.5hr for suspension and formulation, respectively. The mean $T_{1/2}$ was similar for all three formulations. Both investigational intranasal formulations were well tolerated." *Id*.

6. Neurelis Press Release

The Neurelis Press Release, titled "Neurelis Announces Positive Results from Phase 1 Pharmacokinetic Study of NRL-01 (intranasal diazepam)" was published on June 14, 2011, and thus constitutes prior art against the '852 and '061 patents under § 102(a).

In the Neurelis Press Release, Neurelis announced the results of the NCT '558 clinical trial. Neurelis Press Release. Specifically, Neurelis reported that:

> Comparative analysis of the lead intranasal formulation, NRL-1, revealed promising pharmacokinetic results. In its evaluation of a 10 mg diazepam dose in the NRL-1 intranasal solution formulation, the study showed the following:
>
> - NRL-1 is well-tolerated, with only mild adverse events reported
> - Similar bioavailability to intravenous administration of diazepam (100% vs. 96%)
> - Tmax of 1.5 hours.
> - Cmax of approximately 272 ng/ml.

- These values are comparable to those reported in the literature for Diastat® (rectal diazepam gel) at equivalent doses. Diastat is the only approved therapy for the at home treatment of acute repetitive seizures.

Id. The Neurelis Press Release continued by explaining that:

> "The results from this pilot study are very encouraging," commented Jim Cloyd, PharmD, University of Minnesota professor and principal investigator of the study, "The only approved drug to treat breakthrough seizures outside the hospital is diazepam rectal gel, a therapy that many older children and adults decline to use. The ability to quickly and efficiently deliver, via intranasal administration, clinically relevant diazepam levels offers a more acceptable method of rescue therapy. The bioavailability and relatively low variability in exposure of the intranasal diazepam solution exceeded our expectations. We look forward to further development of this important therapy."

Id. Finally, Neurelis explained that:

> NRL-01 (intranasal diazepam) is a proprietary formulation of diazepam delivered via a commercially available nasal sprayer. It is being developed for the management of patients who require intermittent use of diazepam to control bouts of acute repetitive seizure activity. There are over 2.7 million people with epilepsy in the United States with approximately 200,000 new patients diagnosed each year. It is estimated that between 30% to 40% of these patients are uncontrolled on oral therapy and are at-risk for acute repetitive seizures. Studies have shown that prolonged or repetitive seizures can cause neurological damage and dramatically increase the risk of changes in neuropsychological function or even death.

Id.

7. Bream

U.S. Pub. No. 2012/0252793 to Bream et al. titled "Intranasal Benzodiazepine Pharmaceutical Compositions" was published on October 4, 2012. Bream constitutes prior art against the '852 and '061 patents under § 102(b).

Bream discloses pharmaceutical compositions for intranasal spray administration of a therapeutically effective amount of a benzodiazepine active agent, particularly diazepam, for the treatment of seizures. It discloses that intranasal treatment can be easily and safely administered by a patient or a caregiver and can improve the management of seizure emergencies. It further states that the disclosed compositions can provide greater bioavailability of the benzodiazepine

compared to intravenously and/or rectally administered formulations. It further describes that the intranasal diazepam composition may be formulated as a nonaqueous solution and provides methods for treating and/or preventing seizures, including acute repetitive seizures ("ARS"). It defines ARS as a cluster or number of primary generalized and/or partial seizures that occur over a short period of time, e.g., 30 minutes or less, 20 minutes or less, 15 minutes or less, 10 minutes or less, or 5 minutes or less, in which the subject may regain consciousness between seizures. It further discloses pharmaceutical compositions comprising diazepam in an amount from about 1% to about 15% by weight. It also discloses dosages of 5, 10, or 20 mg administered once or twice daily. It further discloses that the pharmaceutical composition can be delivered in any suitable administration volume from about 50 μL to 150 μL, particularly about 100 μL. It also discloses that the benzodiazepine is introduced into one or both nasal passages of a subject and is absorbed into the systemic circulation. Additionally, it discloses pharmaceutical compositions including alcohol (exemplary alcohols include, but are not limited to, ethanol) in an amount from about 0% to about 10% by weight, preservatives (including benzyl alcohol) in an amount of about 2% by weight or less, and an absorption enhancer, such as an agent that opens tight junctions (including surfactants).

E. The Claims of the '852 and '061 Patents Are Invalid as Obvious Over Gwozdz in view of Meezan, Cartt 2008, and USP, optionally in view of the Diastat Label

The disclosures and teachings that render the claims of the '852 and '061 patents obvious are discussed below and also identified in the claim charts attached hereto as Exhibits D and E. The claim charts provide an element-by-element disclosure of where specifically, in each prior art reference, the relevant claim elements, limitations, or rationale supporting the combination(s) are found. The identifications are not meant to be exhaustive, and the inclusion of certain exemplary combinations in the claim chart does not exclude other combinations. Defendants contend that it

would have been obvious to a POSA to combine any of the prior art references to practice any of the claims of the ’852 and ’061 patents. The prior art references are analogous art as each reference is from the same field of endeavor and is reasonably pertinent to the particular problem with which the inventors were involved, or both. To the extent Neurelis contends that an embodiment within a particular prior art reference does not fully disclose all limitations of a claim, Defendants reserve the right to rely on other embodiments in that prior art reference, or other information, to show obviousness.

1. A POSA Would Have Been Motivated to Develop Intranasal Formulations of Diazepam for the Treatment of Seizure Activity in Epilepsy Patients with a Reasonable Expectation of Success

A POSA would have been motivated to combine the teachings of Gwozdz, Meezan, Cartt 2008, and USP as of the priority date of the ’852 and ’061 patents. As explained above, a POSA would have been motivated to develop intranasal formulations of diazepam well before the priority date of the ’852 and ’061 patents. *Supra* Sections V.B; VI.B. For those same reasons, a POSA would have remained motivated to develop intranasal formulations of diazepam in view of Gwozdz, Meezan, Cartt 2008, and USP as of June 13, 2012.

Further, a POSA would have been motivated to use intranasal diazepam formulations for the treatment of intermittent, stereotypic episodes of seizure activity in epilepsy patients. For example, Cartt 2008 explained that diazepam was known to be useful for the treatment of seizures. Cartt 2008 at ¶ [0003]. However, oral formulations of diazepam were “considered sub-optimal for acute treatment of seizures.” *Id*. at ¶ [0004]. “[I]ntravenous administration is generally limited to trained health care professionals (e.g. nurses)” and as a result “the intravenous administration of benzodiazepines for acute treatment of seizure is limited to tightly controlled clinical settings.” *Id*. at ¶ [0005]. Finally, “[s]uppository formulations” were considered inconvenient and “unlikely to gain widespread acceptance as a means for acute treatment of seizure in adults outside controlled

clinical environments." *Id*. at ¶ [0006].

Against that backdrop, Cartt 2008 explained that "[n]asal formulations of benzodiazepines have been suggested for the acute treatment of seizure." *Id*. at ¶ [0007]. Thus, a POSA would have been motivated to develop intranasal formulations of diazepam for the treatment of acute seizure activity in epilepsy patients (i.e., intermittent, stereotypic episodes of seizure activity in epilepsy patients) in view of Cartt 2008.[30] In addition, the Diastat Label expressly disclosed that diazepam could be used to treat "bouts of increased seizure activity" in patients, including "intermittent and periodic episodes of markedly increased seizure activity" that "were not only stereotypic but were judged by those conducting and participating in these studies to be distinguishable from other seizures suffered by that patient." Diastat Label at 1.

Further, a POSA would have been motivated to combine the teachings of Cartt 2008 and the Diastat Label with Gwozdz, Meezan, and USP to develop an intranasal formulation of diazepam for that purpose. Finally, a POSA would have had a reasonable expectation of success in developing an intranasal diazepam formulation for the treatment of intermittent, stereotypic episodes of seizure activity in epilepsy patients in view of Cartt 2008 and the Diastat Label with Gwozdz, Meezan, and USP.

2. The Independent Claims of the '852 Patent

As explained above, the '852 patent contains four independent claims: claims 1, 6, 10, and 14. Independent claim 1 recites:

> 1. A method of treating bouts of intermittent and stereotypic episodes of increased seizure activity in an epilepsy patient that is distinguishable from other seizures suffered by the patient comprising:

[30] As discussed in detail below, the claim phrase "treating the bouts of intermittent and stereotypic episodes of increased seizure activity in the patient" is not defined by the specification, but apparently encompasses the treatment of acute seizure activity generally in view of Neurelis's arguments during prosecution of the '852 and '061 patents.

administering a single spray of 100 μL to one nasal mucosal membrane of the patient of a pharmaceutical solution consisting of:

56.47 mg of vitamin E USP +/−5%;
10 mg of diazepam;
0.25 mg of dodecyl maltoside;
10.50 mg of benzyl alcohol +/−5%, and a sufficient quantity of ethanol;

wherein administering the single spray of the pharmaceutical solution to the patient achieves 92.5% to 107.5% of the bioavailability of an equivalent dose of diazepam administered intravenously and is safe and effective in treating the bouts of intermittent and stereotypic episodes of increased seizure activity in the patient; and

wherein administering the single spray of the pharmaceutical solution to the one nasal mucosal membrane of the patient results in a treatment selected from the group consisting of a reduction in the severity of the seizure, a reduction in the probability that the patient will experience a repeat seizure, an increase in the interval between a current seizure and a next seizure in the patient, a reduction in the frequency of seizure in the patient and combinations thereof.

'852 patent at claim 1. Independent claims 6, 10, and 14 are similar to independent claim 1, except for differences in the amount of diazepam (claims 6 and 10) and/or the number of sprays to be administered to the patient (claims 6 and 14) (differences relative to independent claim 1 highlighted in yellow below):

6. A method of treating bouts of intermittent and stereotypic episodes of increased seizure activity in an epilepsy patient that is distinguishable from other seizures suffered by the patient comprising:

administering a single spray of 100 μL of a stable pharmaceutical solution to one nasal mucosal membrane of the patient **and administering a second single spray of 100 μL of the pharmaceutical solution to a second nasal mucosal membrane of the patient,** the 100 μL of the pharmaceutical solution consisting of:

56.47 mg of vitamin E USP +/−5%;
7.5 mg of diazepam;
0.25 mg of dodecyl maltoside;
10.50 mg of benzyl alcohol +/−5%, and a sufficient quantity of ethanol;

wherein administering the single spray **and the second single spray** of the pharmaceutical solution to the patient achieves 92.5% to 107.5% of the bioavailability of an equivalent dose of diazepam administered intravenously and

is safe and effective in treating the bouts of intermittent and stereotypic episodes of increased seizure activity in the patient; and

wherein administering the single spray **and the second single spray** of the pharmaceutical solution to the patient results in a treatment selected from the group consisting of a reduction in the severity of the seizure, a reduction in the probability that the patient will experience a repeat seizure, an increase in the interval between a current seizure and a next seizure in the patient, a reduction in the frequency of seizure in the patient and combinations thereof.

10. A method of treating bouts of intermittent and stereotypic episodes of increased seizure activity in an epilepsy patient that is distinguishable from other seizures suffered by the patient comprising:

administering as a single spray of 100 μL to one nasal mucosal membrane of the patient of a pharmaceutical solution consisting of:

56.47 mg of vitamin E USP +/−5%;
5 mg of diazepam;
0.25 mg of dodecyl maltoside;
10.50 mg of benzyl alcohol +/−5%, and a sufficient quantity of ethanol;

wherein administering the single spray of the pharmaceutical solution to the patient achieves 92.5% to 107.5% of the bioavailability of an equivalent dose of diazepam administered intravenously and is safe and effective in treating the bouts of intermittent and stereotypic episodes of increased seizure activity in the patient; and

wherein administering the single spray of the pharmaceutical solution to the patient achieves results in a treatment selected from the group consisting of a reduction in the severity of the seizure, a reduction in the probability that the patient will experience a repeat seizure, an increase in the interval between a current seizure and a next seizure in the patient, a reduction in the frequency of seizure in the patient and combinations thereof.

14. A method of treating bouts of intermittent and stereotypic episodes of increased seizure activity in an epilepsy patient that is distinguishable from other seizures suffered by the patient comprising:

administering a single spray of 100 μL of a stable pharmaceutical solution to one nasal mucosal membrane of the patient **and administering a second single spray of 100 μL of the pharmaceutical solution to a second nasal mucosal membrane of the patient**, the 100 μL of the pharmaceutical solution consisting of:

56.47 mg of vitamin E USP +/−5%;
10 mg of diazepam;

0.25 mg of dodecyl maltoside;
10.50 mg of benzyl alcohol +/−5%, and a sufficient quantity of ethanol;

wherein administering the single spray **and the second single spray** of the pharmaceutical solution to the patient achieves 92.5% to 107.5% of the bioavailability of an equivalent dose of diazepam administered intravenously and is safe and effective in treating the bouts of intermittent and stereotypic episodes of increased seizure activity in the patient;

wherein administering the single spray **and the second single spray** of the pharmaceutical solution to the patient results in a treatment selected from the group consisting of a reduction in the severity of the seizure, a reduction in the probability that the patient will experience a repeat seizure, an increase in the interval between a current seizure and a next seizure in the patient, a reduction in the frequency of seizure in the patient and combinations thereof.

'852 patent, claims 6, 10, 14 (emphasis added).

For the reasons set forth below, all independent claims of the '852 patent would have been obvious over Gwozdz in view of Meezan, further in view of Cartt 2008 and USP, optionally in view of the Diastat Label.

(a) The Treatment Elements of the Independent Claims of the '852 Patent

As an initial matter, the preamble of the independent claims recites "a method of treating bouts of intermittent and stereotypic episodes of increased seizure activity in an epilepsy patient that is distinguishable from other seizures suffered by the patient."[31] Similarly, the body of the independent claims of the '852 patent recites that administering the diazepam formulation is "safe and effective in treating the bouts of intermittent and stereotypic episodes of increased seizure activity in the patient." That treatment phrase is not defined by the '852 patent as requiring the treatment of any specific type of seizures, or any specific type of epilepsy, but is loosely associated with the treatment of acute seizures generally.

[31] Defendants take no position on whether the preamble of the claims of the '852 patent is limiting or non-limiting at this time. For purposes of these invalidity contentions only, Defendants address the preamble as if it is a limiting preamble.

For example, during the prosecution of the '852 patent, Neurelis amended the claims to recite the treatment of "bouts of intermittent and stereotypic episodes of increased seizure activity in an epilepsy patient that is distinguishable from other seizures suffered by the patient." Neurelis-02049980-50015. Neurelis stated that the claims "are directed to methods of administering a narrow range of formulations that encompass the first FDA approved diazepam nasal spray – Valtoco – a product approved for the acute treatment of intermittent, stereotypic episodes of frequent seizures activity (i.e., seizure clusters, acute repetitive seizures ('ARS')) that are distinct from a patient's usual seizure pattern in patients with epilepsy." *Id*. And Neurelis later argued that the claimed method of treating "bouts of intermittent and stereotypic episodes of increased seizure activity" was simply copied from the label of the prior art Diastat product (diazepam rectal gel):

> Diastat® was approved by the FDA when the instant application was filed, and its product label was publicly available. As of the filing date of the application, the Diastat product label states that Diastat is intended for "the management of selected, refractory, patients with ***epilepsy***...who require intermittent use of diazepam to control ***bouts of increased seizure activity***. [P]atients with partial onset or generalized convulsive seizures...***suffering intermittent and periodic episodes of markedly increased seizure activity***, sometimes heralded by nonconvulsive symptoms, that for the individual patient were characteristic.... Although these clusters or bouts of seizures differed among patients, for any individual patient ***the clusters of seizure activity were not only stereotypic*** but were judged by those conducting and participating in these studies to be ***distinguishable from other seizures suffered by that patient"*** (emphasis added). In other words, Diastat was known by skilled artisans to treat bouts of intermittent and stereotypic episodes of increased seizure activity in an epilepsy patient that is distinguishable from other seizures suffered by the patient. Over ten years later, this disorder is now described as "intermittent, stereotypic episodes of frequent seizure activity (i.e., seizure clusters, acute repetitive seizures) that are distinct from a patient's usual seizure pattern in patients with epilepsy" as recited in the Valtoco product label of 2020 and is presently recited in the claims.

Neurelis-02052485-2508. Thus, as Neurelis admitted during prosecution, the Diastat Label expressly disclosed that diazepam could be used for the claimed method of treating "bouts of intermittent and stereotypic episodes of increased seizure activity." A POSA would have been

motivated to use an intranasal formulation of diazepam for the same therapeutic endpoint as Diastat, and would have had a reasonable expectation of success, as explained above.

Further, as explained above, Cartt 2008 teaches administration of benzodiazepines (such as diazepam) for the treatment of seizure activity in epilepsy patients. *Supra* SectionV.D.3. For example, Cartt 2008 states:

> Known benzodiazepine compounds have anxiolytic, anticonvulsant, sedative and/or skeletal muscle relaxant effect. The term "anticonvulsant" includes treatment of seizures, protection against seizure, reduction or amelioration of the intensity of seizure, reduction or amelioration of the frequency of seizure, and/or prevention of the occurrence or re-occurrence of seizure. In this regard, treatment of seizure includes cessation of an ongoing seizure, reduction in the severity of an ongoing seizure, reduction in the duration of an ongoing seizure. Protection against seizure includes forestalling an oncoming seizure.

Cartt 2008 at ¶ [0136].

Cartt 2008 also explains that benzodiazepines are anticonvulsants that can be administered for the "treatment of seizures, protection against seizure, reduction or amelioration of the intensity of seizure, reduction or amelioration of the frequency of seizure, and/or prevention of the occurrence or re-occurrence of seizure." *Id*. at ¶ [0004]. In addition, Cartt 2008 teaches that diazepam is a known and preferred benzodiazepine compound. *Id*.

Further, Cartt 2008 explains that oral formulations of diazepam are "considered sub-optimal for acute treatment of seizures." *Id*.. "[I]ntravenous administration is generally limited to trained health care professionals (e.g. nurses)" and as a result "the intravenous administration of benzodiazepines for acute treatment of seizure is limited to tightly controlled clinical settings." *Id*. at ¶ [0005]. Finally, "[s]uppository formulations" are considered inconvenient and "unlikely to gain widespread acceptance as a means for acute treatment of seizure in adults outside controlled clinical environments." *Id*. at ¶ [0006]. Against that backdrop, Cartt 2008 explains that "[n]asal formulations of benzodiazepines have been suggested for the acute treatment of seizure." *Id*. at ¶

[0007]. Thus, a POSA would have been motivated to develop intranasal formulations of diazepam for the treatment of acute seizure activity in epilepsy patients (i.e., intermittent, stereotypic episodes of seizure activity in epilepsy patients) in view of Cartt 2008.

Accordingly, Cartt 2008 and the Diastat Label teach the preamble language reciting "a method of treating bouts of intermittent and stereotypic episodes of increased seizure activity in an epilepsy patient that is distinguishable from other seizures suffered by the patient" required by all independent claims of the '852 patent.

Further, all independent claims of the '852 patent require that the administration "of the pharmaceutical solution to the patient results in a treatment selected from the group consisting of a reduction in the severity of the seizure, a reduction in the probability that the patient will experience a repeat seizure, an increase in the interval between a current seizure and a next seizure in the patient, a reduction in the frequency of seizure in the patient and combinations thereof." '852 patent at claims 1, 6, 10, 14. For the reasons discussed above with respect to the preambles of the independent claims, the "treatment" clause of the independent claims also would have been obvious.

Specifically, the Diastat Label discloses that diazepam can be used for the claimed treatments. Diastat Label at 1. And Cartt 2008 teaches that benzodiazepines are anticonvulsants that can be administered for "treatment of seizures, protection against seizure, reduction or amelioration of the intensity of seizure, reduction or amelioration of the frequency of seizure, and/or prevention of the occurrence or re-occurrence of seizure." In addition, Cartt 2008 teaches that diazepam is a known and preferred benzodiazepine compound. Cartt 2008 at ¶ [0053] ("In some embodiments, the invention provides as a preferred embodiment, diazepam or a therapeutically acceptable salt thereof"). And Cartt 2008 teaches that diazepam can be

administered in "a first metered spray is applied to a first nostril and if necessary a second metered spray is applied to a second nostril." *Id*. at ¶ [0064].

Consequently, Cartt 2008's teaching that diazepam sprays can be administered for "reduction or amelioration of the intensity of seizure, reduction or amelioration of the frequency of seizure, and/or prevention of the occurrence or re-occurrence of seizure" meets the claimed requirement that administering a single spray of the claimed solution can result in "a reduction in the severity of the seizure, a reduction in the probability that the patient will experience a repeat seizure, an increase in the interval between a current seizure and a next seizure in the patient, a reduction in the frequency of seizure in the patient and combinations thereof."

(b) The Administration Limitations of the Independent Claims of the '852 Patent

As explained above, the independent claims of the '852 patent require "administering a single spray of 100 μL to one nasal mucosal membrane of the patient" (claims 1, 10) or "administering a single spray of 100 μL of a stable pharmaceutical solution to one nasal mucosal membrane of the patient and administering a second single spray of 100 μL of the pharmaceutical solution to a second nasal mucosal membrane of the patient" (claims 6, 14). '852 patent at claims 1, 6, 10, 14. These "administration" claim limitations would have been obvious in view of Gwozdz and/or Cartt 2008.

Gwozdz teaches pharmaceutical solutions for nasal administration. Gwozdz states that "the present invention relates to a pharmaceutical solution comprising a therapeutic agent dissolved in one or more natural or synthetic tocopherols or tocotrienols, or any combination thereof and one or more alcohols or glycols, or any combinations thereof." Gwozdz at 4:13-17; '281 provisional at 4:9-13. Additionally, Gwozdz states that the pharmaceutical solutions may be utilized for nasal administration:

> Pharmaceutical solutions of the instant invention are particularly useful in formulations to be administered to mucosal membranes, i.e. the nasal mucosa or lungs of a subject by any suitable means. For many therapeutic agents, administration via the nasal route provides for faster attainment of therapeutic levels of the therapeutic agent systemically. However, many therapeutic agents are so slightly soluble in water that a therapeutically effective amount cannot be dissolved in a volume of aqueous solvent that is amenable to application to a mucosal membrane. Use of a pharmaceutical solution of the present invention, however, provides for improved ability to dissolve lipophilic and lipophilic therapeutic agents, thus providing a useful delivery system for administration of such agents to one or more mucosal membranes, including the nasal mucosal membranes. Such solutions can be administered via, for example, a metered dose inhaler or nebulizer, or in a mist sprayer.

Gwozdz at 9:19-10:2; '281 provisional at 9:19-10:3.

Thus, Gwozdz states that the pharmaceutical solutions of the instant invention are preferably utilized to deliver drugs to the nasal mucosa via the nasal route, which provides faster achievement of systemic therapeutic agent concentrations. Gwozdz at 9:19-10:2; '281 provisional at 9:19-10:3. And Gwozdz explains that the therapeutic agent may be administered to the nasal mucosa utilizing known delivery mechanisms, such as metered dose inhalers, nebulizers, or nasal mist sprayers. Gwozdz at 9:19-10:2; '281 provisional at 9:19-10:3.

Further, Cartt 2008 discloses nasal formulations of diazepam and explains that "[n]asal preparations are generally administered in metered sprays having volumes of less than 250 µl, preferably less than 150 µl, and ideally from 25 to 100 µl, since administration of larger volumes usually exceeds the capacity of the nasal sinuses and results in volumes in excess of about 250 µl bypassing the sinuses and flowing down the back of the throat where it is swallowed." Cartt 2008 at ¶ [0007]. And Cartt 2008 discloses that the diazepam nasal formulations may be administered to one or both nostrils for the treatment of acute seizures. *Id*. at ¶¶ [0011]-[0014], [0033]. Finally, Cartt 2008 explains that:

> As a nasal formulation, diazepam may be administered in 25 to 250 µl metered sprays. In some preferred embodiments, diazepam is administered in 50 to 150 µl, especially about 100 µl, metered sprays. In some embodiments, a first metered

spray is applied to a first nostril and if necessary a second metered spray is applied to a second nostril.

Id. at ¶ [0064].

Finally, it was common knowledge for a POSA and well-known in the art that commercial nasal spray products typically deliver 100-200 µL (i.e., 0.1-0.2 mL) per spray, as the human nasal cavity can only receive and retain about 100-150 µL of liquid.[32] Consequently, by teaching that the pharmaceutical solution containing diazepam is preferably administered as a nasal spray, a POSA would have understood that Gwozdz and Cartt 2008 disclose that the pharmaceutical solution is administered in a spray volume of about 100 µL of liquid.

In view of these teachings, Gwozdz and Cartt 2008 render obvious the claimed requirements of "administering a single spray of 100 µL to one nasal mucosal membrane of the patient of a pharmaceutical solution," and "administering a single spray of 100 µL of a stable pharmaceutical solution to one nasal mucosal membrane of the patient and administering a second single spray of 100 µL of the pharmaceutical solution to a second nasal mucosal membrane of the patient, the 100 µL of the pharmaceutical solution."

(c) The Pharmaceutical Solution Formulation Limitations

As explained above, the independent claims of the '852 patent recite the administration of a "pharmaceutical solution consisting of" certain amounts of vitamin E, diazepam, DDM, benzyl alcohol and ethanol. For the reasons explained above with respect to the earlier-filed '664 patent,

[32] *See, e.g*., 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, at p. 357, Table 3 (teaching "100-200 µL delivery volume per spray for commercial products"); and Wermeling, D, Record K, Kelly T, et al*.,* Pharmacokinetics and pharmacodynamics of a new intranasal midazolam formulation in healthy volunteers. Anesth Analg 2006; 103: 344-349, 344 (teaching that "[t]he adult nasal cavity can only receive and retain about 100-150 µL of liquid, requiring the dose of midazolam be solubilized within this volume. A nasal formulation with a concentration of 2.5 mg per 100 µL is necessary to give a single spray per naris.").

a POSA would have been motivated to make a solution formulation of diazepam containing Vitamin E, benzyl alcohol and ethanol, and DDM, as required by the independent claims of the '852 patent. *Supra* Section VI.E.1. Further, as explained below, Gwozdz, Meezan, Cartt 2008, and USP disclosed, and would have motivated a POSA to use, the specific ingredients and amounts of each respective ingredient required by the claims, to make an intranasal diazepam solution with a reasonable expectation of success.

(i) The Vitamin E Limitations

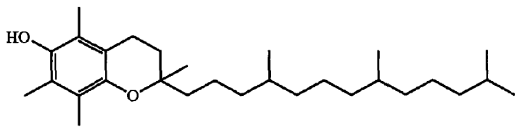
All independent claims of the '852 patent require the pharmaceutical solution to contain "56.47 mg of vitamin E USP +/-5%." '852 patent at claims 1, 6, 10, 14. The '852 patent states:

> Vitamin E is a class of fat soluble methylated phenols. There are at least eight naturally-occurring compounds that comprise this class: α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, α-tocotrienol, β-tocotrienol, γ-tocotrienol, and δ-tocotrienol, all of which may be used in the compositions and methods of the present invention.

'852 patent at 33:32-37. Thus, the claimed "Vitamin E" excipient refers to the tocopherols and tocotrienols referenced in the specification.

A POSA would have been motivated to use Vitamin E as an excipient in the claimed diazepam formulation, including in the claimed amount, in view of Gwozdz and USP. For example, Gwozdz states the following:

> The present invention is directed to the use of one or more tocopherols and/or tocotrienols and one or more alcohols and/or glycols as pharmaceutically acceptable solvents for solubilizing therapeutic agents, in particular hydrophobic or lipophilic therapeutic agents.
>
> …
>
> Tocopherols and/or tocotrienols for use in accordance with the present invention include a family of natural and synthetic compounds, also known by the generic names tocols or vitamin E. Alpha-tocopherol is the most abundant and active form of this family of compounds, and it has the following chemical structure:



> Other members of this family include beta-, gamma-, and delta-tocopherol, alpha-, beta-, gamma-, and delta-tocotrienols, tocopsoralen, alpha-tocopherol derivatives and/or analogs such as tocopherol acetate, phosphate, succinate, nicotinate and linoleate, as well as isomers thereof and esters thereof. Use of the phrase tocopherol (s) and/or tocotrienol (s) herein is meant to be inclusive of any member of this family alone or in combination. In one embodiment of the present invention the tocopherol (s) and/or tocotrienol (s) employed is alpha-tocopherol.

Gwozdz at 4:29-33, 5:26-6:15; '281 provisional at 4:25-29, 5:30-6:13. Further, Gwozdz states that "[i]n one embodiment of the present invention the tocopherol (s) and/or tocotrienol (s) employed is alpha-tocopherol." Gwozdz at 6:13-15. Gwozdz also discloses that "the tocopherol(s) and/or tocotrienol(s) is in an amount from about 30% to about 99% (w/w)." *Id*. at 4:17-19.

Additionally, the USP standard version of vitamin E was well-known in the art at the time of filing the '852 patent. Specifically, USP states:

> Vitamin E is a form of alpha tocopherol ($C_{29}H_{50}O_2$). It includes the following d- or dl-alpha tocopherol ($C_{29}H_{50}O_2$); d- or dl-alpha tocopheryl acetate ($C_{31}H_{52}O_3$); d- or dl-alpha tocopheryl acid succinate ($C_{33}H_{54}O_5$). It contains not less than 96.0 percent and not more than 102.00 percent of $C_{29}H_{50}O_2$, $C_{31}H_{52}O_3$, or $C_{33}H_{54}O_5$, respectively.

USP at 1631.

Further, a POSA would have been motivated to use vitamin E USP in the pharmaceutical solution rendered obvious by Gwozdz because USP was an internationally recognized standard for pharmaceutical grade compounds and ingredients. As such, a POSA would have been motivated to use vitamin E USP in the pharmaceutical solution rendered obvious by the prior art, and would have had at least a reasonable expectation that the USP grade vitamin E could be successfully incorporated into the formulation.

Similarly, a POSA would have been motivated to use the claimed amount of Vitamin E (i.e., 56.47 mg) in view of Gwozdz. While Gwozdz discloses a range of weight percentages that may be used (i.e., 30-99 % w/w), a POSA would have arrived at the amount recited by the independent claims of the '852 patent through routine optimization. *See Pfizer Inc. v. Sanofi Pasteur Inc.*, 94 F.4th 1341, 1348 (Fed. Cir. 2024); *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1367-68 (Fed. Cir. 2007); *DyStar Textilfarben GmbH v. C.H. Patrick Co.*, 464 F.3d 1356, 1371 (Fed. Cir. 2006); *see also In re Luck*, 476 F.2d 650, 652-53 (CCPA 1973) (stating use of routine testing to identify optimum amounts lies within the ambit of a POSA).

Accordingly, a POSA would have been motivated to use "56.47 mg of vitamin E USP +/- 5%" in an intranasal diazepam solution in view of Gwozdz and USP, and would have had a reasonable expectation of success.

(ii) The Diazepam Limitations

As explained above, the independent claims of the '852 patent require the intranasal solution formulations to contain 10 mg, 7.5 mg, or 5 mg of diazepam. '852 patent at claims 1, 6, 10, 14. A POSA would have been motivated to prepare intranasal solution formulations with the claimed amounts of diazepam in view of Gwozdz and Cartt 2008.

For example, Gwozdz states that the therapeutic agent may include various compounds, including diazepam:

> Exemplary hydrophobic or lipophilic therapeutic agents which can be solubilized in accordance with the present invention include, but are in no way limited to, steroids such as Dexamethasone, 17-beta-Estradiol; benzodiazepenes such as Diazepam, alprazolam, bromazepam, chlordiazepoxidem, clonazepam, estazolam, flunitrazepam, flurazepam, lorazepam, lormetazepam, mexazolam, nitrazepam, oxazepam, temazepam, and triazolam; Rapamycin and analogues; Taxol (paclitaxel) and analogues; Actinomycin D; Prostaglandins (PGEl) ; Vitamin A; Probucol; Batimastat; Statins (HMG-CoA Reductase Inhibitors; Trapidil (and other anti-proliferative Growth Factor Inhibitors); Cytochalasin B; and microtubule binding agents such as epothilones, elutherobin and discodermolide.

Gwozdz at 8:6-18; ’281 provisional at 8:5-17.

Further, Gwozdz identifies diazepam as a preferred therapeutic agent for use in the solubilizing solutions described therein, demonstrating that the solubility of diazepam can be increased from less than or equal to 6.67% (in ethanol) to “approaching the 10% level” (when incorporating tocopherol into the solution). Gwozdz at 7:12-16; ’281 provisional at 7:10-17. Diazepam is the only therapeutic agent/drug compound identified in the entirety of Gwozdz as an example of a drug compound that can achieve increased solubility when utilized in the pharmaceutical solutions described therein. Consequently, a POSA would recognize that Gwozdz teaches diazepam as a preferred therapeutic agent, and Gwozdz teaches and renders obvious the claimed requirement for the inclusion of diazepam in the pharmaceutical solution.

Regarding the specific amounts of diazepam required by the independent claims of the ’852 patent, Gwozdz states:

> [T]he solubility of Diazepam at room temperature is less than or equal to 6.67% in 190 proof ethanol. However, combining tocopherol and ethanol has been found to provide solubility of the Diazepam approaching the 10% level. By way of illustration, at 70% tocopherol : 30% ethanol (200 proof), Diazepam is soluble to greater than or equal to 8% and at 95% tocopherol : 5% ethanol (200 proof), Diazepam is soluble at greater than or equal to 9%.

Gwozdz at 7:12-19; ’281 provisional at 7:10-17. Consequently, Gwozdz teaches that diazepam can be solubilized at concentrations up to ~8-10% w/v. A POSA would have understood that ~8-10% w/v correlates to ~80-100 mg/mL (i.e., ~80-100 mg of diazepam per 1 mL of solution).

Further, the amount of diazepam present in the pharmaceutical solution of Gwozdz can be easily modified by increasing or decreasing the volume of the pharmaceutical solution present in the intranasal spray of Gwozdz. Specifically, Gwozdz teaches and renders obvious that the diazepam may be present in the solution in concentrations of ~8-10% w/v (i.e., ~80-100 mg of

diazepam/1 mL of solution). Consequently, the amount of diazepam in the pharmaceutical solution can be increased or decreased by increasing or decreasing the volume of the solution.

Further, Cartt 2008 discloses exemplary doses of diazepam to be delivered to patients per dose via nasal administration, stating "[d]iazepam is a benzodiazepine drug having sedative, tranquilizing and muscle relaxing properties. It is classified as an anxiolytic and skeletal muscle relaxant. It possesses anxiolytic, anticonvulsant, sedative, skeletal muscle relaxant and amnesic properties. The dosage of diazepam may vary by indication, however it is expected that a therapeutic dose will be in the range of about 1 to about 20, preferably about 2 to about 10 mg per dose…." Cartt 2008 at ¶ [0063]. Cartt 2008 explains that the administration of diazepam doses of about 1 mg to about 20 mg, and preferably about 2 mg to about 10 mg was found to be therapeutic. *Id*.

Accordingly, a POSA would have been motivated to use the amounts of diazepam recited in the independent claims of the '852 patent in view of Gwozdz and Cart 2008. Further, as explained above, the amount of diazepam present in the pharmaceutical solution of Gwozdz, read in view of Cartt 2008, is a result-effective variable, and a POSA would have found it to be a routine process to include differing amounts of diazepam, including doses of 10 mg, 7.5 mg, and 5 mg. *See Pfizer*, 94 F.4th at 1348; *Pfizer,* 480 F.3d at 1367-68; *DyStar*, 464 F.3d at 1371; *see also In re Luck*, 476 F.2d at 652-53.

(iii) The DDM Limitations

All independent claims of the '852 patent require the pharmaceutical solution to contain "0.25 mg of dodecyl maltoside." '852 patent at claims 1, 6, 10, 14. A POSA would have been motivated to use the claimed amount of DDM in an intranasal diazepam formulation in view of Gwozdz, Meezan, and Cartt 2008.

Gwozdz states that various excipients may be included in the benzodiazepine solution formulations it discloses:

> The instant pharmaceutical solutions comprising a therapeutic agent, one or more tocopherols and/or tocotrienols and one or more alcohols and/or glycols can also be formulated into a pharmaceutical composition for injection by combining the instant pharmaceutical solution with, e.g., saline solution or water and a Vitamin E solubilizing agent such as Cremophor. Such pharmaceutical compositions may further contain other pharmaceutically acceptable additives such as, but not limited to, acidifying, alkalizing, buffering, chelating, complexing and solubilizing agents, antioxidants and antimicrobial preservatives, penetration enhancers, humectants, suspending and/or viscosity modifying agents, tonicity and wetting or other biocompatible materials.
> …
>
> A carrier for topical application can also contain additional ingredients such as other carriers, moisturizers, penetration enhancers, humectants, emollients, dispersants, radiation blocking compounds, cleansing agents, anti-infective agents (e.g., antibiotics, fungicides, scabicides, or pediculicides), anti-inflammatory agents (e.g., corticosteroids), keratolytics (agents that soften, loosen, and facilitate exfoliation of the squamous cells of the epidermis), as well as other suitable materials that do not have a significant adverse effect on the activity of the topical composition.

Gwozdz at 10:3-16, 12:12-22; ’281 provisional at 10:4-17, 12:16-25.

Similarly, Cartt 2008 discloses that its benzodiazepine formulations may contain various excipients, including “n-dodecyl β-D-maltoside.” *See, e.g.*, Cartt 2008 at ¶¶ [0128]-[0129], [0168], [0183].

Further, Meezan teaches alkyl glycoside or saccharide alkyl ester compositions that provide enhanced bioavailability of therapeutic agents. In particular, Meezan states the following regarding the alkyl glycoside component:

> Alkyl glycosides of the present invention can include, but are not limited to: alkyl glycosides, such as octyl-, nonyl-, decyl-, undecyl-, dodecyl-, tridecyl-, tetradecyl-, pentadecyl-,hexadecyl-, heptadecyl-, and octadecyl-α- or β-D-maltoside, -glucoside or -sucroside….
>
> …

> Similarly, some preferred glycosides include maltose, sucrose, and glucose linked by glycosidic linkage to an alkyl chain of 9, 10, 12, 13, 14, 16, 18, 20, 22, or 24 carbon atoms, e.g., nonyl-, decyl-, dodecyl- and tetradecyl sucroside, glucoside, and maltoside, etc. These compositions are nontoxic, since they are degraded to an alcohol and an oligosaccharide, and amphipathic.

Meezan at ¶¶ [0056]-[0058].

Meezan explicitly identifies alkylmaltosides, including DDM, as a preferred alkyl glycoside compound. *Id*. at ¶¶ [0092]-[0156]. And Meezan identifies preferred alkyl glycoside concentrations, stating that intranasal delivery of a lipophilic therapeutic compound like diazepam "with 0.125% and 0.250% alkyl glycoside" resulted in "about 43% to about 90% bioavailability, respectively," as compared to only 3% bioavailability when the alkyl glycoside compound was not present. Meezan at ¶ [0150]. Consequently, Meezan teaches that the alkyl glycoside concentration of 0.25% was preferred, thereby providing a teaching and rendering obvious the claimed requirement for the inclusion of "0.25 mg of dodecyl maltoside."[33]

Accordingly, a POSA would have been motivated to incorporate 0.25 mg of DDM into an intranasal diazepam solution formulation with a reasonable expectation of success in view of Gwozdz, Cartt 2008, and Meezan.

(iv) The Alcohol Limitations

All independent claims of the '852 patent require the pharmaceutical solution to contain "10.50 mg of benzyl alcohol +/−5%, and a sufficient quantity of ethanol." '852 patent at claims 1, 6, 10, 14. A POSA would have been motivated to use the claimed amount of benzyl alcohol and ethanol in an intranasal diazepam formulation in view of Gwozdz and Cartt 2008, as well as Meezan.

[33] This assumes a solution density of approximately 1.0 g/ml.

With respect to the use of alcohols in its diazepam solution formulations, Gwozdz states the following:

> Examples of alcohol (s) for use in the present invention include, but are not limited to ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, and any isomers thereof, and any combinations thereof.

Gwozdz at 6:16 to 7:2. Thus, Gwozdz teaches a small number of exemplary alcohols for use in the pharmaceutical solutions, including ethanol and benzyl alcohol, as well as combinations thereof. Based on the small number of predictable exemplary alcohols taught by Gwozdz, a POSA would have found it to be common sense and prima facie obvious to utilize the combination of ethanol and benzyl alcohol in the Gwozdz pharmaceutical solution. *KSR*, 550 U.S. at 402 ("When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense.").

Further, Gwozdz explains that the pharmaceutical solutions should contain the alcohol excipient(s) "in an amount from about 1% to about 70% (w/w)." Gwozdz at 4:17-21. As explained above, the amount of benzyl alcohol (and ethanol) present in the pharmaceutical solution of Gwozdz is a result-effective variable, and a POSA would have arrived at the claimed "10.50 mg of benzyl alcohol +/−5%" requirement through routine optimization. *See Pfizer*, 94 F.4th at 1348; *Pfizer,* 480 F.3d at 1367-68; *DyStar*, 464 F.3d at 1371; *see also In re Luck*, 476 F.2d at 652-53.

In addition, Cartt 2008 identifies benzyl alcohol and ethanol as solvents that may be used to prepare intranasal diazepam formulations. Cartt 2008 at ¶ [0182]. Similarly, Meezan identifies benzyl alcohol as a potential "pharmaceutically acceptable carrier." Meezan at ¶ [0074]. Accordingly, a POSA would have been further motivated to use benzyl alcohol and ethanol in an intranasal diazepam solution formulation when Gwozdz is read in view of Cartt 2008 and Meezan.

Finally, there is nothing in the ’852 patent indicating that the specific combination of ethanol and benzyl alcohol provided any surprising or unexpected results over the other alcohols cited in the ’852 patent specification. Rather, the ’852 patent states:

> Lower alkyl alcohols are those with six or fewer carbon atoms. Thus, any of ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, any isomers thereof, or any combinations thereof can be used.

’852 patent at 34:20-23. A POSA would understand the ’852 patent as disclosing that ethanol, propyl alcohol, butyl alcohol, pentanol, and benzyl alcohol are all “lower alkyl alcohols,” and would be understood to have similar properties. Thus, the ’852 patent has not established any surprising and unexpected properties associated with the combination of ethanol and benzyl alcohol.

Accordingly, a POSA would have been motivated to incorporate “10.50 mg of benzyl alcohol +/−5%, and a sufficient quantity of ethanol” into an intranasal diazepam solution formulation with a reasonable expectation of success in view of Gwozdz, Cartt 2008, and Meezan.

(v) The “Stable” Limitations

Independent claims 6 and 14 of the ’852 patent (as well as all dependent claims that depend from independent claims 6 and 14 of the ’852 patent) require the claimed pharmaceutical solution to be “stable.” ’852 patent at claims 6, 14.[34] As explained below, the specification of the ’852 patent does not define the term “stable,” and does not require the claimed formulation to satisfy any specific stability requirements. *Infra* Section VI.J. Thus, to the extent the prior art discloses “stable” diazepam solution formulations, the claimed “stable” diazepam formulations would be obvious.

[34] As explained below, to the extent the prior art does not render the stability limitations obvious, Defendants contend that the stability limitations required by these claims of the ’852 patent renders them invalid under 35 U.S.C. § 112. *Infra* Section VI.J.

As a starting point, a POSA would have been motivated to ensure that an intranasal diazepam solution formulation was stable in view of Gwozdz, Cartt 2008, Meezan, and USP. Indeed, a POSA would have understood that any pharmaceutical formulation intended for administration to a patient must be "stable" to ensure it is safe and effective. *See, e.g.*, FDA, GUIDANCE FOR INDUSTRY: Q1A(R2) STABILITY TESTING OF NEW DRUG SUBSTANCES AND PRODUCTS (rev. 2, Nov. 2003); ICH, ICH HARMONISED TRIPARTITE GUIDELINE: EVALUATION FOR STABILITY DATA Q1E (Feb. 2003).

Regardless, the prior art discloses that the diazepam formulations are stable. For example, Meezan states "that therapeutic compositions comprising of least one drug and at least one surfactant, wherein the surfactant is comprised of at least one alkyl glycoside and/or at least one saccharide alkyl ester are ***stable***, non-toxic, non-irritating, anti-bacterial compositions that increase bioavailability of the drug and have no observable adverse effects when administered to a subject." Meezan at ¶ [0048] (emphasis added); *see also id.* at ¶ [0162].

Accordingly, a POSA would have been motivated to make a "stable" intranasal diazepam solution formulation with a reasonable expectation of success in view of Gwozdz, Cartt 2008, and Meezan.

(d) The Bioavailability Limitations

All independent claims of the '852 patent recite that administering the diazepam formulation to a patient "achieves 92.5% to 107.5% of the bioavailability of an equivalent dose of diazepam administered intravenously." '852 patent at claims 1, 6, 10, 14. This bioavailability requirement is obvious in view of Gwozdz, Meezan, Cartt 2008, and USP.

As a starting point, the mere recitation of an inherent or latent property of an otherwise obvious formulation will not render the formulation patentable. *See In re Kao*, 639 F.3d 1057, 1070 (Fed. Cir. 2011); *Santarus, Inc. v. Par Pharmaceutical, Inc.*, 694 F.3d 1344 (Fed. Cir. 2012);

Persion Pharms., 945 F.3d at 1191. Here, the bioavailability of the claimed diazepam formulation is an inherent property—upon administration of the formulation to a patient, it will inherently "achieve[] 92.5% to 107.5% of the bioavailability of an equivalent dose of diazepam administered intravenously." Thus, a POSA motivated to make and administer the claimed intranasal diazepam formulations would inherently achieve the claimed "bioavailability" element, thereby rendering it obvious in view of Gwozdz, Cartt 2008, Meezan, and USP even in the absence of an express disclosure of the bioavailability.

Further, the '852 patent does not provide any guidance or disclosure regarding specific components or characteristics of the pharmaceutical composition that must be present to achieve the claimed bioavailability. The only example provided in the '852 patent that addresses the bioavailability requirement is Example 11, where the formulation described in Table 11-1 purportedly resulted in the claimed bioavailability (i.e., "about 92.5 to 107.5% [of] that obtained with the same benzodiazepine administered intravenously"). '852 patent at 63:5-11.

Thus, the combination of Gwozdz and Meezan in view of Cartt 2008 and USP, optionally in view of the Diastat Label, render obvious the administration of a pharmaceutical solution meeting each and every limitation of the independent claims of the '852 patent. Such a formulation would inherently result in the bioavailability requirement: that "administering the single spray of the pharmaceutical solution to the patient achieves 92.5% to 107.5% of the bioavailability of an equivalent dose of diazepam administered intravenously and is safe and effective in treating the bouts of intermittent and stereotypic episodes of increased seizure activity in the patient." Thus, the bioavailability requirement of the independent claims of the '852 patent is rendered obvious by Gwozdz and Meezan in view of Cartt and USP as the inherent and latent properties of an otherwise obvious formulation and method of treatment.

(e) Motivation and Reasonable Expectation of Success

For the reasons discussed above, the combination of Gwozdz, Meezan, Cartt 2008, and USP render all independent claims of the ’852 patent obvious. Further, a POSA would have been motivated to combine the teachings of Gwozdz and Meezan in view of Cartt 2008 and USP, and would have had a reasonable expectation of success, as explained above. *Supra* Section VI.E.1.

3. Dependent Claims 2, 7, 11, 15, 18, and 19 of the ’852 Patent

Dependent claims 2, 7, 11, 15, 18, and 19 of the ’852 patent depend directly or indirectly from independent claims 1, 6, 10, or 14, respectively. Like the independent claims of the ’852 patent, dependent claims 2, 7, 11, 15, 18, and 19 of the ’852 patent recite specific bioavailability results for the claimed intranasal diazepam solution formulation. As explained above, because the bioavailability of the claimed intranasal diazepam solution formulation is an inherent property, dependent claims 2, 7, 11, 15, 18, and 19 of the ’852 are invalid as obvious over Gwozdz and Meezan in view of Cartt 2008 and USP. *Supra* Section VI.E.2(d).

4. Dependent Claims 3, 8, 12, 16, and 20-27 of the ’852 Patent

Dependent claims 3, 8, 12, 16, and 20-27 of the ’852 patent depend directly or indirectly from independent claims 1, 6, 10, or 14, respectively. Further, dependent claims 3, 8, 12, 16, and 20-27 of the ’852 patent require the claimed intranasal diazepam solution formulations to “achieve[] a T_{max} of about 1.5 hours” (claims 3, 8, 12, 16), “result[] in treatment in less than about 5 minutes and treatment over about 24 hours” (claims 20-23), or “exhibit[] a half-life ($t_{1/2}$) of about 49.2 hours” (claims 24-27). Because the properties recited in dependent claims 3, 8, 12, 16, and 20-27 of the ’852 patent are inherent properties, these claims are also invalid as obvious over Gwozdz and Meezan in view of Cartt 2008 and USP for the reasons discussed above. *Supra* Section VI.E.2.

5. Dependent Claims 4, 9, 13, and 17 of the ’852 Patent

Dependent claims 4, 9, 13, and 17 of the ’852 patent depend directly or indirectly from independent claims 1, 6, 10, or 14, respectively. Further, dependent claims 4, 9, 13, and 17 of the ’852 patent require the claimed intranasal diazepam solution formulations to be “substantially free of water.” ’852 patent at claims 4, 9, 13, 17. A POSA would have been motivated to make an intranasal diazepam solution formulation that is “substantially free of water” in view of Gwozdz and Meezan in view of Cartt 2008 and USP, and would have had a reasonable expectation of success. *Supra* Section VI.E.2.

Specifically, Gwozdz discloses that “[t]he present invention is directed to the use of one or more tocopherols and/or tocotrienols and one or more alcohols and/or glycols as pharmaceutically acceptable solvents for solubilizing therapeutic agents, in particular hydrophobic or lipophilic therapeutic agents.” Gwozdz at 4:29-33; ’281 provisional at 4:25-29. Thus, Gwozdz teaches that the solution for solubilizing the therapeutic agents (such as diazepam) includes only “one or more tocopherols and/or tocotrienols and one or more alcohols” as the solvents. Gwozdz does not discuss or teach the inclusion of water as a required additional component of the pharmaceutical solution.

Additionally, Meezan does not disclose or teach that DDM should be incorporated in combination with water. Thus, the pharmaceutical solution rendered obvious by Gwozdz and Meezan in view of Cartt 2008 and USP does not include water, and meets the claimed requirement that the pharmaceutical composition “is substantially free of water.”

Indeed, as explained above, Neurelis addressed a similar issue during the ’876 patent IPR. Specifically, Neurelis argued that “[b]ecause independent claim 1 of the ’876 patent excludes water from its benzodiazepine solution – through its ‘consisting of’ language – it does not provide a vehicle for which a surfactant such as alkyl glycoside could work to stabilize or act as a traditional

penetration enhancer in a solution." IPR2019-00451, Paper 16 at 38. Thus, according to Neurelis, "a POSA would have been discouraged from selecting the alkyl glycoside as disclosed and used in Meezan '962 to add to the non-aqueous formulations of Gwozdz." *Id.* The PTAB rejected Neurelis's arguments on this point, and found that "Meezan '962 is not limited to water soluble therapeutic drugs and discloses using alkyl glycosides in aqueous or non-aqueous systems." IPR2019-00451, Paper 44 at 45-46. Accordingly, consistent with the PTAB's final written decision on the '876 patent, a POSA would have been motivated to make the claimed intranasal diazepam formulation as a non-aqueous solution (i.e., such that it does not contain any water).

For at least these reasons, Gwozdz and Meezan in view of Cartt 2008 and USP teach each and every limitation of claims 4, 9, 13, and 17, a motivation existed to combine the teachings of the prior art with a reasonable expectation of success.

6. Dependent Claim 5 the '852 Patent

Dependent claim 5 of the '852 patent depends from independent claim 1 and further requires that "the single spray of 100 µL is administered to one nasal mucosal membrane of the patient as a single metered spray." '852 patent at claim 5. For the reasons set forth above with respect to independent claim 1, dependent claim 5 of the '852 patent would have been obvious in view of Gwozdz, Cartt 2008, Meezan, and USP.

To be sure, Cartt 2008 states that the methods described therein comprise "administering an effective amount of the composition to the nose by administering a therapeutically effective amount of the composition to at least one nostril." Cartt 2008 at ¶¶ [0011]-[0014]. Thus, Cartt 2008 discloses administering an intranasal diazepam solution formulation to "at least one nostril," as required by dependent claim 5 of the '852 patent. And Cartt 2008 teaches that diazepam can be administered in "in 50 to 150 µl, especially about 100 µl, metered sprays." *Id*. at ¶ [0064].

For at least these reasons, Gwozdz and Meezan in view of Cartt and USP teach each and every limitation of claim 5, a motivation existed to combine the teachings of the prior art, and a reasonable expectation of success existed.

7. Dependent claims 28-31 the ’852 Patent

Dependent claims 28-31 of the ’852 patent depend directly from independent claims 1, 6, 10, or 14, respectively. Further, dependent claims 28-31 of the ’852 patent require the claimed intranasal diazepam solution formulations to contain “n-dodecyl-β-D-maltoside” specifically. ’852 patent at claims 28-31. As already explained above, a POSA would have been motivated to make an intranasal diazepam solution formulation that contains DDM (i.e., n-dodecyl-β-D-maltoside) in view of Gwozdz and Meezan in view of Cartt 2008 and USP, and would have had a reasonable expectation of success. *Supra* Section VI.E.2.

8. The Independent Claims of the ’061 Patent

As explained above, the ’061 patent contains six independent claims: claims 1, 5, 21, 33, 43, and 53. The independent claims of the ’061 patent are similar to the independent claims of the ’852 patent and generally recite the same method of treatment, bioavailability, administration, and formulation limitations. Accordingly, for the reasons set forth above with respect to the independent claims of the ’852 patent, the independent claims of the ’061 patent would have been obvious in view of Gwozdz, Cartt 2008, Meezan, and USP. *Supra* Section VI.E.2.

The primary difference between the claims of the ’852 patent and the claims of the ’061 patent is that all claims of the ’061 patent require the claimed diazepam formulation to be “a stable pharmaceutical solution.”[35] As explained above with respect to certain claims of the ’852 patent, a POSA would have been motivated to ensure that an intranasal diazepam solution formulation

[35] As explained below, Defendants contend that the stability limitations of the ’061 patent render all claims of the ’061 patent invalid under 35 U.S.C. § 112. *Infra* SectionVI.J.

was stable in view of Gwozdz, Cartt 2008, Meezan, and USP. Indeed, a POSA would have understood that any pharmaceutical formulation intended for administration to a patient must be "stable" to ensure it is safe and effective. *See, e.g.*, FDA, GUIDANCE FOR INDUSTRY: Q1A(R2) STABILITY TESTING OF NEW DRUG SUBSTANCES AND PRODUCTS (rev. 2, Nov. 2003); ICH, ICH HARMONISED TRIPARTITE GUIDELINE: EVALUATION FOR STABILITY DATA Q1E (Feb. 2003).

Regardless, the prior art discloses that the diazepam formulations are stable. For example, Meezan states "that therapeutic compositions comprising of least one drug and at least one surfactant, wherein the surfactant is comprised of at least one alkyl glycoside and/or at least one saccharide alkyl ester are ***stable***, non-toxic, non-irritating, anti-bacterial compositions that increase bioavailability of the drug and have no observable adverse effects when administered to a subject." Meezan at ¶ [0048] (emphasis added); *see also id.* at ¶ [0162].

Accordingly, for at least these reasons, Gwozdz and Meezan in view of Cartt 2008 and USP teach each and every limitation of claims 1, 5, 21, 33, 43, and 53 of the '061 patent, a motivation existed to combine the teachings of the prior art, and a reasonable expectation of success existed. Thus, claims 1, 5, 21, 33, 43, and 53 of the '061 patent are invalid as obvious.

9. Dependent Claims 2, 6, 22, 34, 44, and 54 of the '061 Patent

Dependent claims 2, 6, 22, 34, 44, and 54 of the '061 patent depend directly or indirectly from independent claims 1, 5, 21, 33, 43, and 53, respectively. Dependent claims 2, 6, 22, 34, 44, and 54 of the '061 patent further specify that "the pharmaceutical solution is stable at 25° C and 60% relative humidity for at least 3 months." '061 patent at claims 2, 6, 22, 34, 44, and 54. For the reasons discussed above, a POSA would have been motivated to ensure that the claimed pharmaceutical solution was stable. *Supra* Sections VI.E.2.c.v; VI.E.8.

Further, the stability requirements recited in claims 2, 6, 22, 34, 44, and 54 of the '061 patent are standard stability requirements for pharmaceutical products. *See, e.g.*, FDA, GUIDANCE

FOR INDUSTRY: Q1A(R2) STABILITY TESTING OF NEW DRUG SUBSTANCES AND PRODUCTS (rev. 2, Nov. 2003); ICH, ICH HARMONISED TRIPARTITE GUIDELINE: EVALUATION FOR STABILITY DATA Q1E (Feb. 2003). Accordingly, a POSA would have had common knowledge of these requirements and would have understood that it would be necessary for a diazepam solution formulation to be "stable at 25° C and 60% relative humidity for at least 3 months," which is a well-understood expectation in the pharmaceutical field. Accordingly, a POSA would have been motivated by Gwozdz, Cartt 2008, Meezan, and USP to make an intranasal diazepam solution formulation that meets the claimed stability requirements and would have had a reasonable expectation of success.

Further, the claimed stability requirements are inherent properties, which are rendered obvious by Gwozdz, Cartt 2008, Meezan, and USP even in the absence of an express disclosure. *In re Kao*, 639 F.3d at 1070; *Santarus*, 694 F.3d at 1344; *Persion Pharms.*, 945 F.3d at 1191. Thus, a POSA motivated to make and administer the claimed intranasal diazepam solution formulations would inherently produce a formulation that meets the claimed stability requirements. For that additional reason, dependent claims 2, 6, 22, 34, 44, and 54 of the '061 patent are invalid as obvious.

10. Dependent Claims 3, 4, 7, 8, 23, 24, 35, 36, 45, 46, 55, and 56 of the '061 Patent

Dependent claims 3, 4, 7, 8, 23, 24, 35, 36, 45, 46, 55, and 56 of the '061 patent depend directly or indirectly from independent claims 1, 5, 21, 33, 43, and 53, respectively. Dependent claims 3, 4, 7, 8, 23, 24, 35, 36, 45, 46, 55, and 56 of the '061 patent further specify that the "single spray of the pharmaceutical solution results in treatment in less than about 5 minutes" (claims 3, 7, 23, 35, 45, 55) or "over about 24 hours" (claims 4, 8, 24, 36, 46, 58). '061 patent at claims 3, 4, 7, 8, 23, 24, 35, 36, 45, 46, 55, and 56. For the reasons discussed above, a POSA would have been

motivated to administer the claimed pharmaceutical solution to treat patients. *Supra* Sections VI.E.2.a-b; VI.E.8.

Further, a POSA motivated to administer the claimed diazepam formulation to a patient would inherently result in "treatment in less than about 5 minutes" and "treatment over about 24 hours." *In re Kao*, 639 F.3d at 1070; *Santarus*, 694 F.3d at 1344; *Persion Pharms.*, 945 F.3d at 1191. Thus, a POSA motivated to make and administer the claimed intranasal diazepam solution formulations would inherently produce a formulation that meets the claimed treatment requirements. For that additional reason, dependent claims 3, 4, 7, 8, 23, 24, 35, 36, 45, 46, 55, and 56 of the '061 patent are invalid as obvious.

11. Dependent Claims 9, 10, 25, 37, 47, and 57 of the '061 Patent

Dependent claims 9, 10, 25, 37, 47, and 57 of the '061 patent depend directly or indirectly from independent claims 1, 5, 21, 33, 43, and 53, respectively. Dependent claims 9, 10, 25, 37, 47, and 57 of the '061 patent further specify that the "single spray" of the claimed formulation is administered to the "nostril" of a patient "as a single metered spray." '061 patent at claims 9, 10, 25, 37, 47, and 57. For the reasons discussed above, a POSA would have been motivated to administer the claimed pharmaceutical solution to treat patients. *Supra* Sections VI.E.2.a-b; VI.E.8.

Further, as explained above, Cartt 2008 states that the methods described therein comprise "administering an effective amount of the composition to the nose by administering a therapeutically effective amount of the composition to at least one nostril." Cartt 2008 at ¶¶ [0011]-[0014]. And Cartt 2008 teaches that diazepam can be administered in "a first metered spray is applied to a first nostril and if necessary a second metered spray is applied to a second nostril." *Id.* at ¶ [0064]. Thus, Cartt 2008 discloses administering an intranasal diazepam solution formulation

to the "nostril" of a patient "as a single metered spray" as required by dependent claims 9, 10, 25, 37, 47, and 57 of the '061 patent.

For at least these reasons, Gwozdz and Meezan in view of Cartt 2008 and USP teach each and every limitation of claims 9, 10, 25, 37, 47, and 57 of the '061 patent, a motivation existed to combine the teachings of the prior art, and a reasonable expectation of success existed.

12. Dependent Claims 11, 12, 26, 38, 48, and 58 of the '061 Patent

Dependent claims 11, 12, 26, 38, 48, and 58 of the '061 patent depend directly or indirectly from independent claims 1, 5, 21, 33, 43, and 53, respectively. Dependent claims 11, 12, 26, 38, 48, and 58 of the '061 patent further specify that "the ethanol is dehydrated ethanol." '061 patent at claims 11, 12, 26, 38, 48, and 58. For the reasons discussed above, a POSA would have been motivated to include ethanol in an intranasal diazepam solution formulation. *Supra* Sections VI.E.2.c.iv; VI.E.8.

Further, a POSA would have been motivated to use dehydrated ethanol specifically. A POSA would understand that "dehydrated ethanol" contains "not less than 99.2 percent, by weight, corresponding to not less than 99.5 percent, by volume, at 15.56°, of C_2H_5OH." USP at 42-43. And a POSA would understand that the use of dehydrated ethanol was desirable in spray formulations. This is particularly the case when a poorly water-soluble drug, like diazepam, is being formulated, which Gwozdz and Cartt 2008 disclose. Gwozdz at 1:10-17; Cartt 2008 at ¶ [0007].

Accordingly, a POSA would have been motivated to use dehydrated ethanol in view of Gwozdz, Cartt 2008, Meezan, and USP, and would have had a reasonable expectation of success.

13. Dependent Claims 13, 14, 27, 39, 49, and 59 of the '061 Patent

Dependent claims 13, 14, 27, 39, 49, and 59 of the '061 patent depend directly or indirectly from independent claims 1, 5, 21, 33, 43, and 53, respectively. Dependent claims 13, 14, 27, 39,

49, and 59 of the ’061 patent further specify that “the dodecyl maltoside is n-dodecyl-β-D-maltoside” (i.e., DDM). ’061 patent at claims 13, 14, 27, 39, 49, and 59. For the reasons discussed above, a POSA would have been motivated to use DDM in an intranasal diazepam solution formulation with a reasonable expectation of success. *Supra* Sections VI.E.2(c)(iii); VI.E.7; VI.E.8.

14. Dependent Claims 15-20, 28-31, 40-41, 50-51, and 60-61 of the ’061 Patent

Dependent claims 15-20, 28-31, 40-41, 50-51, and 60-61 of the ’061 patent depend directly or indirectly from independent claims 1, 5, 21, 33, 43, and 53, respectively. Dependent claims 15-20, 28-31, 40-41, 50-51, and 60-61 of the ’061 patent further specify that the claimed formulation exhibits certain blood plasma concentrations, T_{max} values, C_{max} values, and half-lives. ’061 patent at claims 15-20, 28-31, 40-41, 50-51, and 60-61. For the reasons discussed above, a POSA would have been motivated to administer the claimed pharmaceutical solution to treat patients with a reasonable expectation of success. *Supra* Sections VI.E.2.a-b; VI.E.8.

Further, the claimed blood plasma concentrations, T_{max} values, C_{max} values, and half-lives are inherent properties, which are rendered obvious by Gwozdz, Cartt 2008, Meezan, and USP even in the absence of an express disclosure. *In re Kao*, 639 F.3d at 1070; *Santarus*, 694 F.3d at 1344; *Persion Pharms.*, 945 F.3d at 1191. Thus, a POSA motivated to make and administer the claimed intranasal diazepam solution formulations would inherently produce a formulation that results in the claimed blood plasma concentrations, T_{max} values, C_{max} values, and half-lives. For that additional reason, dependent claims 15-20, 28-31, 40-41, 50-51, and 60-61 of the ’061 patent are invalid as obvious.

15. Dependent Claims 32, 42, 52, and 62 of the ’061 Patent

Dependent claims 32, 42, 52, and 62 of the ’061 patent depend directly or indirectly from independent claims 1, 5, 21, 33, 43, and 53, respectively. Dependent claims 32, 42, 52, and 62 of the ’061 patent further specify that the claimed formulation exhibits an “absolute bioavailability” that “is 96% to 97%.” ’061 patent at claims 32, 42, 52, and 62. For the reasons discussed above, a POSA would have been motivated to administer the claimed pharmaceutical solution to treat patients with a reasonable expectation of success. *Supra* Sections VI.E.2.a-b; VI.E.8. And as discussed above, because the bioavailability of the claimed intranasal diazepam solution formulation is an inherent property, dependent claims 32, 42, 52, and 62 of the ’061 patent are invalid as obvious over Gwozdz and Meezan in view of Cartt 2008 and USP. *Supra* Sections VI.E.2(d); VI.E.3.

F. The Claims of the ’852 and ’061 Patents Are Invalid as Obvious Over Cartt 2009 in view of Meezan, further in view of NCT ’558, Agarwal, and/or the Neurelis Press Release

The disclosures and teachings that render the claims of the ’852 and ’061 patents obvious are discussed below and also identified in the claim charts attached hereto as Exhibits D and E. The claim charts provide an element-by-element disclosure of where specifically, in each prior art reference, the relevant claim elements, limitations, or rationale supporting the combination(s) are found. The identifications are not meant to be exhaustive, and the inclusion of certain exemplary combinations in the claim chart does not exclude other combinations. Defendants contend that it would have been obvious to a POSA to combine any of the prior art references to practice any of the claims of the ’852 and ’061 patents. The prior art references are analogous art as each reference is from the same field of endeavor and is reasonably pertinent to the particular problem with which the inventors were involved, or both. To the extent Neurelis contends that an embodiment within a particular prior art reference does not fully disclose all limitations of a claim, Defendants reserve

the right to rely on other embodiments in that prior art reference, or other information, to show obviousness.

As explained above, as of the priority date of the ’852 and ’061 patents, a POSA would have been aware of additional prior art and information related to intranasal diazepam solution formulations and their use for the treatment of patients. *Supra* Section VI.B. Specifically, a POSA would have been aware of Cartt 2009, which shares a specification with the ’664 patent and discloses intranasal diazepam solution formulations and methods of using the formulations for the treatment of epilepsy. *Supra* Section VI.D.3. Further, a POSA would have been aware of NCT ’558, Agarwal, and the Neurelis Press Release, which confirm that intranasal solution formulations of diazepam exhibit the pharmacokinetic and treatment properties recited in the claims of the ’852 and ’061 patents. *Supra* Section VI.D.4-6. Thus, for the reasons explained below and in the claim charts attached to these contentions as Exhibits D and E, all claims of the ’852 and ’061 patents would have been obvious to a POSA over Cartt 2009 in view of Meezan, further in view of NCT ’558, Agarwal, and/or the Neurelis Press Release.

1. A POSA Would Have Been Motivated to Develop Intranasal Formulations of Diazepam for the Treatment of Seizure Activity in Epilepsy Patients with a Reasonable Expectation of Success

As explained above, a POSA would have been motivated to make intranasal diazepam solution formulations for the treatment of seizures in epilepsy patients and would have had a reasonable expectation of success. *Supra* Section VI.E.1. The disclosures of Cartt 2009, NCT ’558, Agarwal, and the Neurelis Press Release would have provided a POSA with additional motivation and a reasonable expectation of success, as described above. *Supra* Section VI.B.

To be sure, by the priority date of the ’852 and ’061 patents, a POSA would have been aware of the clinical trial results reported in NCT ’558, Agarwal, and the Neurelis Press Release. These references explained that an intranasal “solution” formulation containing 10 mg of diazepam

was successful in a phase 1 clinical trial and outperformed its "suspension" formulation counterpart. *See, e.g.*, NCT '558 at 4-5 (explaining that "two nasal formulations," including a solution formulation "will be given as a 10 mg dose"); Agarwal at 220 ("Ten mg doses of two investigational [diazepam] formulations (solution, suspension) … were given" and "[t]he absolute bioavailability of the IN Solution was higher than that reported in prior intranasal diazepam and midazolam studies, while variability in exposure (AUC) for both the suspension and the solution was similar to the IV dose."); Neurelis Press Release ("[A] 10mg diazepam dose in the NRL-1 intranasal solution formulation" was successful in a clinical trial and "[t]he bioavailability and relatively low variability in exposure of the intranasal diazepam solution exceeded [] expectations."). Accordingly, a POSA would have been motivated by NCT '558, Agarwal, and the Neurelis Press Release to develop an intranasal diazepam solution formulation for the treatment of seizures in epilepsy patients and would have had a reasonable expectation of success.

Further, a POSA would have been motivated by Cartt 2009, which disclosed benzodiazepine-containing intranasal solution formulations that were "useful in preventing, treating, or ameliorating the symptoms of … seizures (such as those caused by epilepsy)." Cartt 2009 at ¶ [0003]; *see also, id.* at ¶ [0086]. And as explained below, Cartt 2009 disclosed specific intranasal formulations that were consistent with the diazepam dose and "solution" formulation reported in NCT '558, Agarwal, and the Neurelis Press Release. Thus, a POSA would have been motivated to combine the teachings of Cartt 2009, NCT '558, Agarwal, and the Neurelis Press Release and would have had a reasonable expectation of success.

2. The Formulation Elements of the Claims of the '852 and '061 Patents Would Have Been Obvious

As explained above, all independent claims of the '852 and '061 patents recite an intranasal spray composition formulated as a "pharmaceutical solution consisting of: 56.47 mg of vitamin E

USP +/−5%; 5 mg of diazepam; 0.25 mg of dodecyl maltoside; 10.50 mg of benzyl alcohol +/−5%, and a sufficient quantity of ethanol." '852 patent at claims 1, 6, 10, 14; '061 patent at claims 1, 5, 21, 33, 43, and 53. Dependent claims 28-31 of the '852 patent and dependent claims 13, 14, 27, 39, 49, and 59 of the '061 patent require the claimed intranasal diazepam solution formulations to contain "n-dodecyl-β-D-maltoside" specifically. '852 patent at claims 28-31; '061 patent at claims 13, 14, 27, 39, 49, and 59. Dependent claims 4, 9, 13, and 17 of the '852 patent require the claimed formulations to be "substantially free of water." '852 patent at claims 4, 9, 13, 17. And dependent claims 11, 12, 26, 38, 48, and 58 of the '061 patent further specify that "the ethanol is dehydrated ethanol." '061 patent at claims 11, 12, 26, 38, 48, and 58. A POSA motivated to develop an intranasal solution formulation of diazepam would have found the formulation limitations of the '852 and '061 patents obvious in view of Cartt 2009 and Meezan.

As a starting point, a POSA would have been motivated to develop an intranasal *solution* formulation of diazepam for the reasons discussed above. *Supra* Section VI.F.1. Specifically, while the prior art discussed both suspension and solution formulations of diazepam, NCT '558, Agarwal, and the Neurelis Press Release all indicated that a "solution" formulation of diazepam outperformed the related "suspension" formulation. *See, e.g.*, Agarwal at 220 ("Bioavailability of the IN solution approached 100% and was significantly ($p<0.05$) greater than the IN suspension, as was Cmax."); Neurelis Press Release (identifying the "NRL-1 intranasal solution formulation" as the "lead intranasal formulation."). Accordingly, a POSA would have been motivated to develop a solution formulation of diazepam specifically in view of NCT '558, Agarwal, and the Neurelis Press Release.

In view of this motivation, a POSA also would have been led to Cartt 2009, which disclosed intranasal diazepam solution formulations. Cartt 2009 at Abstract. Specifically, Cartt 2009

disclosed pharmaceutical compositions for nasal administration that contain "a benzodiazepine drug; one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); and one or more alcohols or glycols, or any combinations thereof, in an amount from about 5% to about 70% (w/w), preferably about 10% to about 70% (w/w) in a pharmaceutically-acceptable formulation for administration to one or more nasal mucosal membranes of the patient." *Id*. at ¶ [0010]. With respect to the alcohol component of the formulation, Cartt 2009 explained that the one or more alcohols may be chosen from benzyl alcohol and/or ethanol. *Id*. at ¶¶ [0013], [0136]. And the pharmaceutical compositions may also contain an alkyl glycoside, such as DDM. *Id*. at ¶¶ [0019], [0138], [0142]-[0143], [0210]. Finally, Cartt 2009 explained that the composition may be formulated such that diazepam is fully dissolved so that "the benzodiazepine drug is formulated as a solution." *Id*. at ¶ [0168].

Thus, Cartt 2009 disclosed intranasal diazepam solution formulations containing diazepam, Vitamin E, DDM, benzyl alcohol, and ethanol, like those recited in the claims of the '852 and '061 patents. Further, a POSA would have been motivated to select the specific ingredients and amounts of each ingredient recited in the claims of the '852 and '061 patents in view of Cartt 2009 and Meezan.

First, a POSA would have been motivated to use the claimed amounts of Vitamin E, benzyl alcohol, and ethanol in view of Cartt 2009. Cartt 2009 explained that "Vitamin E can provide an effective carrier for benzodiazepine drugs." Cartt 2009 at ¶ [0134]. However, because Vitamin E is hydrophobic, it was known to form emulsions, which "can have several drawbacks" such as being "unstable" and difficult to produce. *Id*. at ¶ [0135]. "[T]o avoid the drawbacks of emulsions," Cartt 2009 explained that the formulations should be "solutions of one or more benzodiazepine drugs in Vitamin E and one or more lower alkyl alcohols." *Id*. The "[l]ower alkyl alcohols" include

a limited number of alcohols, including benzyl alcohol and ethanol. *Id*. at ¶ [0136]. Thus, Cartt 2009 disclosed that diazepam solution formulations could be prepared using a carrier system containing Vitamin E and alcohols like benzyl alcohol and ethanol.

Further, Cartt 2009 explained that the carrier system may contain "about 50% to about 90% (w/w) Vitamin E and about 10% to about 50% (w/w) lower alcohol" or "about 65% to about 75% (w/w) Vitamin E and about 25% to about 35% (w/w) lower alkyl alcohol." *Id*. at ¶ [0162]. Thus, a POSA would have been motivated by Cartt 2009 to make a solution formulation containing diazepam in a carrier system containing Vitamin E, benzyl alcohol, and ethanol within the ranges discussed above. Because those ranges encompass the amounts of Vitamin E, benzyl alcohol, and ethanol (including dehydrated ethanol) recited in the claims of the '852 and '061 patent, a POSA would have considered those limitations obvious in view of Cartt 2009. Specifically, a POSA would have arrived at the claimed amounts of Vitamin E, benzyl alcohol, and ethanol through routine optimization. *See Pfizer*, 94 F.4th at 1348; *Pfizer,* 480 F.3d at 1367-68; *DyStar*, 464 F.3d at 1371; *see also In re Luck*, 476 F.2d at 652-53.

Cartt 2009 also disclosed that "[t]he dosage of diazepam may vary by indication, however it is expected that a therapeutic dose will be in the range of about 1 to about 20, preferably about 2 to about 10 mg per dose…" *Id*. at ¶ [0086]; *see also id.* at ¶ [0147]. And as explained above, NCT '558, Agarwal, and the Neurelis Press Release all disclosed the use of a 10 mg dose of diazepam. Thus, a POSA would have been motivated to formulate an intranasal diazepam solution formulation with the amounts of diazepam recited in the claims of the '852 and '061 patents (i.e., 5, 7.5, and 10 mg) using the claimed amounts of Vitamin E, benzyl alcohol, and ethanol in view of Cartt 2009. Further, a POSA would have arrived at the claimed amounts of diazepam, Vitamin

E, benzyl alcohol, and ethanol through routine optimization. *See Pfizer*, 94 F.4th at 1348; *Pfizer,* 480 F.3d at 1367-68; *DyStar*, 464 F.3d at 1371; *see also In re Luck*, 476 F.2d at 652-53.

Cartt 2009 and Meezan also would have motivated a POSA to use 0.25 mg of DDM, as required by the claims of the '852 and '061 patents. Indeed, Cartt 2009 explained that it would be beneficial to use a "penetration enhancer" like alkyl glycosides in intranasal diazepam solution formulations. Cartt 2009 at ¶ [0058]. Cartt 2009 explained that "[t]he term 'penetration enhancer', means any material which acts to increase absorption across the mucosa and/or increases bioavailability." *Id*. at ¶ [0139]. And Cartt 2009 explained that the penetration enhancer may be an alkyl glycoside, such as DDM specifically, where "the amount of alkyl glycoside in the composition is in a range of about 0.01% (w/v) to about 1% (w/v)." *Id*. at ¶ [0058].

Thus, a POSA would have been motivated to include 0.25 mg of DDM in an intranasal diazepam solution formulation in view of Cartt 2009, or would have arrived at that amount through routine optimization efforts. *See Pfizer*, 94 F.4th at 1348; *Pfizer,* 480 F.3d at 1367-68; *DyStar*, 464 F.3d at 1371; *see also In re Luck*, 476 F.2d at 652-53. Indeed, Cartt 2009 disclosed that the intranasal solution formulations could contain "a benzodiazepine drug," Vitamin E "in an amount from about 30% to about 95% (w/w); one or more alkyl glycosides; and one or more alcohols …in an amount from about 10% to about 70% (w/w)." Cartt 2009 at ¶ [0142]. Thus, a POSA would have been motivated to use DDM in the claimed amount and in combination with Vitamin E, benzyl alcohol, and ethanol to prepare a solution formulation of diazepam in view of Cartt 2009.

To be sure, for the reasons discussed above, a POSA would have been motivated to use 0.25 mg of DDM in view of Meezan. *Supra* Section V.D., V.E.; *see also* Meezan at ¶¶ [0056]-[0058]. To reiterate, Meezan explicitly identified alkylmaltosides, including DDM, as a preferred alkyl glycoside compound. *Id*. at ¶¶ [0092]-[0156]. And Meezan identified preferred alkyl

glycoside concentrations, stating that intranasal delivery of a lipophilic therapeutic compound similar to diazepam "with 0.125% and 0.250% alkyl glycoside" resulted in "about 43% to about 90% bioavailability, respectively," as compared to only 3% bioavailability when the alkyl glycoside compound was not present. *Id*. at ¶ [0150]. Thus, Meezan provided a POSA with an additional motivation and reasonable expectation of success to use the claimed "0.25 mg of dodecyl maltoside."

Finally, a POSA would have been motivated to ensure that the intranasal diazepam solution formulation was "substantially free of water"[36] for the reasons discussed above and in view of Cartt 2009. *Supra* Section V.D.3. Indeed, Cartt 2009 disclosed that "the solution is at least substantially free of water. (In some embodiments, 'substantially free of water' indicates that the solution contains less than about 1%, less than about 0.5%, less than about 0.25% or less than about 0.1% water.)." Cartt 2009 at ¶¶ [0046]-[0047].

Accordingly, a POSA would have been motivated to make an intranasal spray composition formulated as a "pharmaceutical solution consisting of: 56.47 mg of vitamin E USP +/−5%; 5 mg of diazepam; 0.25 mg of dodecyl maltoside; 10.50 mg of benzyl alcohol +/−5%, and a sufficient quantity of ethanol" based on the teachings of Cartt 2009, Meezan, NCT '558, Agarwal, and the Neurelis Press Release. A POSA would have arrived at the claimed amounts of these ingredients, as well as the additional limitations recited in certain dependent claims of the '852 and '061 patents, which are result-effective variables, through routine optimization of the ranges and amounts of each ingredient disclosed in Cartt 2009 and Meezan. *See Pfizer*, 94 F.4th at 1348; *Pfizer,* 480 F.3d at 1367-68; *DyStar*, 464 F.3d at 1371; *see also In re Luck*, 476 F.2d at 652-53.

[36] The specification of the '852 and '061 patents states that "[i]n some embodiments, 'substantially free of water' indicates that the solution contains less than about 1%, less than about 0.5%, less than about 0.25% or less than about 0.1% water." '852 patent at 11:65-12:2.

And a POSA would have had a reasonable expectation of success in making the claimed formulation in view of Cartt 2009, Meezan, NCT '558, Agarwal, and the Neurelis Press Release. For at least these reasons, the formulation limitations of the claims of the '852 and '061 patents would have been obvious.

3. The Method of Treatment Aspects of the Claims of the '852 and '061 Patents Would Have Been Obvious

As explained above, all independent claims of the '852 and '061 patents recite "[a] method of treating bouts of intermittent and stereotypic episodes of increased seizure activity in an epilepsy patient that is distinguishable from other seizures suffered by the patient." '852 patent at claims 1, 6, 10, 14; '061 patent at claims 1, 5, 21, 33, 43, and 53. The independent claims of the '852 and '061 patents also recite that administering the claimed intranasal diazepam solution formulation "results in a treatment selected from the group consisting of a reduction in the severity of the seizure, a reduction in the probability that the patient will experience a repeat seizure, an increase in the interval between a current seizure and a next seizure in the patient, a reduction in the frequency of seizure in the patient and combinations thereof." '852 patent at claims 1, 6, 10, 14; '061 patent at claims 1, 5, 21, 33, 43, and 53. The method of treatment aspects of the claims of the '852 and '061 patents would have been obvious over Cartt 2009 in view of Meezan, further in view of NCT '558, Agarwal, and the Neurelis Press Release.

As explained above, and as Neurelis discussed during prosecution of the '852 and '061 patents, the claimed method of treating "bouts of intermittent and stereotypic episodes of increased seizure activity" was simply copied from the label of the prior art Diastat product. *Supra* Section VI.E.2(a). And, as explained above, a POSA would have been motivated to use an intranasal formulation of diazepam for the same therapeutic purposes as Diastat, and would have had a reasonable expectation of success. Indeed, the purpose of the development of an intranasal

formulation of diazepam was to provide an alternative administration route (i.e., nasal instead of rectal) that could achieve the same treatment results. *Supra* Section VI.B.

Further, as explained above, NCT '558, Agarwal, and the Neurelis Press Release all reported that the intranasal diazepam solution formulation exhibited suitable bioavailability and pharmacokinetic properties. *Supra* Section VI.B. For example, NCT '558 described three arms and interventions, which sought to investigate "the absolute bioavailability of two intranasal diazepam formulations" for the treatment of "epilepsy." NCT '558 at 3-5. One intranasal diazepam formulation was described by NCT '558 as a "solution" while the other was referred to as a "suspension." *Id*. According to NCT '558, "[t]he two nasal formulations will be given as 10 mg doses." *Id*. Thus, NCT '558 itself demonstrates that POSAs were motivated to develop intranasal diazepam solution formulations for the treatment of epilepsy, and that they would have had a reasonable expectation of success.

Further, Agarwal expressly disclosed that the intranasal diazepam solution formulation was successful in a clinical trial. Agarwal at 220. Agarwal explained that the intranasal diazepam solution formulation was being investigated for the treatment of "acute repetitive seizures." *Id*. Agarwal reported that the 10 mg dose of the intranasal diazepam solution formulation resulted in a "[b]ioavailability" that "approached 100% and was significantly ($p<0.05$) greater than the IN suspension, as was Cmax." *Id*. Further, "[m]edian time to maximum concentration (Tmax) was 1hr and 1.5hr for suspension and formulation, respectively. The mean $T_{1/2}$ was similar for all three formulations. Both investigational intranasal formulations were well tolerated." *Id*. Agarwal concluded that:

> The absolute bioavailability of the IN Solution was higher than that reported in prior intranasal diazepam and midazolam studies, while variability in exposure (AUC) for both the suspension and the solution was similar to the IV dose. The results of this pilot study indicate that development of an intranasal diazepam

> formulation with high bioavailability, relatively low variability, and good tolerability is feasible.

Id. Thus, NCT '558 read in view of Agarwal would have further motivated a POSA to develop intranasal diazepam solution formulations for the treatment of epilepsy, and they would have had a reasonable expectation of success.

Additionally, the Neurelis Press Release reported that:

> Comparative analysis of the lead intranasal formulation, NRL-1, revealed promising pharmacokinetic results. In its evaluation of a 10 mg diazepam dose in the NRL-1 intranasal solution formulation, the study showed the following:
>
> - NRL-1 is well-tolerated, with only mild adverse events reported
> - Similar bioavailability to intravenous administration of diazepam (100% vs. 96%)
> - Tmax of 1.5 hours.
> - Cmax of approximately 272 ng/ml.
> - These values are comparable to those reported in the literature for Diastat® (rectal diazepam gel) at equivalent doses. Diastat is the only approved therapy for the at home treatment of acute repetitive seizures.

Neurelis, Inc., *Neurelis Announces Positive Results from Phase 1 Pharmacokinetic Study of NRL-01 (Intranasal Diazepam)* (June 14, 2011), press release.. The Neurelis Press Release continued by explaining that:

> "The results from this pilot study are very encouraging," commented Jim Cloyd, PharmD, University of Minnesota professor and principal investigator of the study, "The only approved drug to treat breakthrough seizures outside the hospital is diazepam rectal gel, a therapy that many older children and adults decline to use. The ability to quickly and efficiently deliver, via intranasal administration, clinically relevant diazepam levels offers a more acceptable method of rescue therapy. The bioavailability and relatively low variability in exposure of the intranasal diazepam solution exceeded our expectations. We look forward to further development of this important therapy."

Id. Finally, Neurelis explained that:

> NRL-01 (intranasal diazepam) is a proprietary formulation of diazepam delivered via a commercially available nasal sprayer. It is being developed for the management of patients who require intermittent use of diazepam to control bouts of acute repetitive seizure activity. There are over 2.7 million people with epilepsy

> in the United States with approximately 200,000 new patients diagnosed each year. It is estimated that between 30% to 40% of these patients are uncontrolled on oral therapy and are at-risk for acute repetitive seizures. Studies have shown that prolonged or repetitive seizures can cause neurological damage and dramatically increase the risk of changes in neuropsychological function or even death.

Id. Thus, the Neurelis Press Release provides an additional motivation and reasonable expectation of success for the development and use of an intranasal diazepam solution formulation for the treatment of seizures in epilepsy patients.

Finally, Cartt 2009 disclosed that the intranasal diazepam solution formulations were developed, in large part, to overcome the drawbacks known to affect oral, intravenous, and suppository formulations that were on the market. Cartt 2009 at ¶¶ [0006]-[0009]. Indeed, Cartt 2009 explained that the intranasal diazepam solution formulations would be useful for the treatment of seizures. *Id*. at ¶ [0077]-[0078], [0086]-[0090]. Cartt 2009 defined the term "seizure" to broadly include "commonly recognized types of seizures, including absence seizures, myoclonic seizures, clonic seizures, tonic seizures, tonic-clonic seizures, and atonic seizures." *Id*. at ¶ [0066]. Thus, Cartt 2009 explained that "treatment of seizure" using the intranasal diazepam solution formulations "includes cessation of an ongoing seizure, reduction in the severity of an ongoing seizure, reduction in the duration of an ongoing seizure." *Id*. at ¶ [0131].

Accordingly, a POSA would have been motivated to use the intranasal diazepam solution formulations rendered obvious by Cartt 2009, Meezan, NCT '558, Agarwal, and the Neurelis Press Release for "treating the bouts of intermittent and stereotypic episodes of increased seizure activity in the patient," including for "a reduction in the severity of the seizure, a reduction in the probability that the patient will experience a repeat seizure, an increase in the interval between a current seizure and a next seizure in the patient, a reduction in the frequency of seizure in the patient and combinations thereof." In view of Cartt 2009, Meezan, NCT '558, Agarwal, and the

Neurelis Press Release, a POSA also would have had a reasonable expectation of success for at least the reasons discussed above.

4. The Administration Aspects of the Claims of the '852 and '061 Patents Would Have Been Obvious

As explained above, all independent claims of the '852 and '061 patents require "administering a single spray of 100 μL to one nasal mucosal membrane of the patient" or "administering a single spray of 100 μL of a stable pharmaceutical solution to one nasal mucosal membrane of the patient and administering a second single spray of 100 μL of the pharmaceutical solution to a second nasal mucosal membrane of the patient." '852 patent at claims 1, 6, 10, 14; '061 patent at claims 1, 5, 21, 33, 43, and 53. Dependent claim 5 of the '852 patent depends from independent claim 1 and requires that "the single spray of 100 μL is administered to one nasal mucosal membrane of the patient as a single metered spray." '852 patent at claim 5. Dependent claims 9, 10, 25, 37, 47, and 57 of the '061 patent further specify that the "single spray" of the claimed formulation is administered to the "nostril" of a patient "as a single metered spray." '061 patent at claims 9, 10, 25, 37, 47, and 57. The "administration" claim limitations of the '852 and '061 patents would have been obvious in view of Cartt 2009, Meezan, NCT '558, Agarwal, and the Neurelis Press Release.

First, as explained above, a POSA would have understood that administering intranasal drug formulations typically involved administering a single spray to one or both nostrils in 100 μL sprays. *Supra* Section VI.E.2(b). Indeed, it was well-accepted and common in the art to follow these administration parameters, as the '852 and '061 patents acknowledge. *See, e.g.*, '852 patent at 36:38-42 ("The dosage volume of preparations, in particular nasal preparations, preferably ranges from 25 to 100 μL. Volumes in excess of the aforementioned ranges may bypass the sinuses and flow down the back of the throat where the excess is swallowed."). Thus, a POSA motivated

to make and administer the intranasal diazepam solution formulations would have understood that it should be administered to one or both nostrils in 100 μL sprays, and would have had a reasonable expectation of success in doing so.

Second, Cartt 2009 expressly taught that the intranasal diazepam solution formulations could be administered in one or both nostrils, preferably in "about 100 μL metered sprays." Cartt 2009 at ¶¶ [0029], [0060]; *see also id.* at ¶ [0181] ("In some embodiments, a first metered spray is applied to a first nostril and if necessary a second metered spray is applied to a second nostril."). And like the '852 and '061 patents, Cartt 2009 explained that this administration protocol was well-understood to POSAs and common in the art. *See, e.g.*, *id*. at ¶ [0144] ("Mucosal membrane preparations are generally administered in metered sprays having volumes of … ideally from 25 to 100 μL. Although not prohibited in this invention, administration of volumes larger than about 300 μL per dose usually exceeds the absorption capacity of the membranes. This results in a large portion of the pharmaceutically-active ingredient being lost. The dosage volume of preparations, in particular nasal preparations, preferably ranges from 25 to 100 μL. Volumes in excess of the aforementioned ranges may bypass the sinuses and flow down the back of the throat where the excess is swallowed."). Accordingly, Cartt 2009 expressly disclosed the administration limitations of the claims of the '852 and '061 patents, and renders them obvious for that additional reason.

Third, NCT '558, Agarwal, and the Neurelis Press Release provide further confirmation that the intranasal diazepam solution formulations should be administered as claimed by the '852 and '061 patents. *See, e.g.*, NCT '558 at 5 (confirming that the diazepam solution was administered as a "nasal spray"); Agarwal at 220 (confirming the diazepam solution was administered intranasally); Neurelis Press Release ("NRL-01 (intranasal diazepam) is a proprietary formulation of diazepam delivered via a commercially available nasal sprayer"). Accordingly, a POSA would

have been motivated to administer the intranasal diazepam solution formulations via common intranasal delivery devices and procedures in view of Cartt 2009, NCT ’558, Agarwal, and the Neurelis Press Release and would have had a reasonable expectation of success.

Accordingly, a POSA would have been motivated to administer the intranasal diazepam solution formulations rendered obvious over Cartt 2009 and Meezan, in view of NCT ’558, Agarwal, and the Neurelis Press Release into one or both nostrils of a patient via metered doses of 100 μL sprays. In view of the teachings of Cartt 2009, Meezan, NCT ’558, Agarwal, and the Neurelis Press Release, a POSA also would have had a reasonable expectation of success for at least the reasons discussed above.

5. The Bioavailability and Pharmacokinetic Properties Recited in the Claims of the ’852 and ’061 Patents Would Have Been Obvious

As explained above, the claims of the ’852 and ’061 patents recite various bioavailability, pharmacokinetic, and other related properties in relation to the administration of the claimed intranasal diazepam solution formulations. As explained above, those properties are inherent to the intranasal diazepam solution formulation upon its administration to patients. *Supra* Section VI.E.2(d). Thus, because a POSA would have been motivated to make and administer the claimed intranasal diazepam solution formulations with a reasonable expectation of success in view of Cartt 2009, Meezan, NCT ’558, Agarwal, and the Neurelis Press Release, the bioavailability and pharmacokinetic properties recited in the claims of the ’852 and ’061 patents are inherent properties of an otherwise obvious formulation. *In re Kao*, 639 F.3d at 1070; *Santarus*, 694 F.3d at 1344; *Persion Pharms.*, 945 F.3d at 1191.

Additionally, the bioavailability and pharmacokinetic properties recited in the claims of the ’852 and ’061 patents also would have been obvious to achieve because NCT ’558, Agarwal, and the Neurelis Press Release expressly disclosed that such functional properties were achieved

with diazepam intranasal solutions. Thus, as explained below, the bioavailability and pharmacokinetic properties required by the claims of the ’852 and ’061 patents are invalid as obvious.

(a) The Bioavailability Claim Limitations

As explained above, certain claims of the ’852 and ’061 patents recite that administering the diazepam formulation to a patient “achieves 92.5% to 107.5% of the bioavailability of an equivalent dose of diazepam administered intravenously” (’852 patent at claims 1, 6, 10, 14), “96% of the bioavailability of an equivalent dose of diazepam administered intravenously” (’852 patent at claims 2, 7, 11, 15, 18, 19), or “96% to 97% of the bioavailability of an equivalent dose of diazepam administered intravenously” (’061 patent at claims 1, 5, 21, 32, 33, 42, 43, 52, 53, and 62). The Neurelis Press Release and Agarwal expressly disclosed that the intranasal diazepam solution formulation reported in the prior art clinical trial achieved the claimed bioavailability.

For example, Agarwal explained that the 10 mg dose of diazepam administered as an intranasal solution “approached 100%” and that “[t]he absolute bioavailability of the IN solution was higher than that reported in prior intranasal diazepam and midazolam studies.” Agarwal at 220. The Neurelis Press Release similarly reported that “the NRL-1 intranasal solution formulation” achieved “[s]imilar bioavailability to intravenous administration of diazepam (100% vs. 96%).” Neurelis Press Release. Accordingly, Agarwal and the Neurelis Press Release expressly disclosed that the intranasal diazepam solution formulation subject to the NCT ’558 clinical trial resulted in the bioavailability claimed in the ’852 and ’061 patents.

For that additional reason, a POSA motivated to administer the claimed intranasal diazepam solution formulation in view of Cartt 2009, Meezan, NCT ’558, and the Neurelis Press Release would have had a reasonable expectation of success in achieving the bioavailability limitations claimed in the ’852 and ’061 patents. Thus, the bioavailability limitations of the ’852

and ’061 patents are invalid as obvious in view of Cartt 2009, Meezan, NCT ’558, Agarwal, and the Neurelis Press Release.

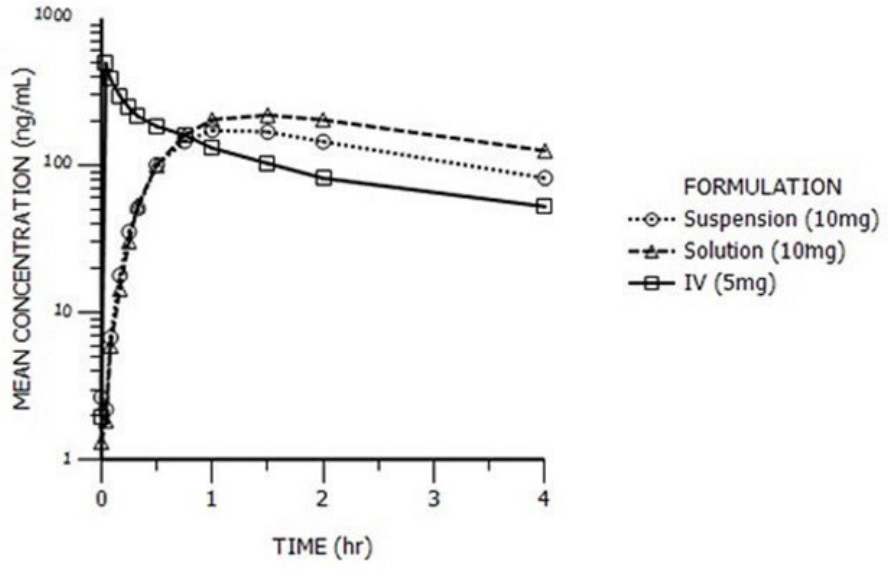
(b) The T_{max} and C_{max} Claim Limitations

As explained above, certain claims of the ’852 and ’061 patents recite that administering the diazepam formulation to a patient results in “a Tmax of about 1.5 hours” (’852 patent at claims 3, 8, 12, 16; ’061 patent at claims 19-20, 30, 40, 50, 60) or “an approximate C_{max} of 272 ng/mL” (’061 patent at 17-18, 29). The Neurelis Press Release and Agarwal expressly disclosed that the intranasal diazepam solution formulation reported in the prior art clinical trial achieved the claimed T_{max} and C_{max} values.

For example, Agarwal explained that for the 10 mg dose of diazepam administered as an intranasal solution “[m]edian time to maximum concentration (Tmax) was … 1.5hr for … solution formulation.” Agarwal at 220. And Agarwal disclosed that the Cmax for the solution formulation was “significantly ($p<0.05$) greater than the IN suspension” at approximately 270 ng/mL[37]:

[37] *See, e.g.*, https://aesnet.org/abstractslisting/a-pilot-study-assessing-the-bioavailability-and-pharmacokinetics-of-diazepam-after-intranasal-and-intravenous-administration-in-healthy-volunteers

Mean plasma diazepam concentration-time profiles after intravenous and intranasal administration in 24 healthy volunteers (0-4h)



The Neurelis Press Release similarly reported that "the NRL-1 intranasal solution formulation" achieved a "Tmax of 1.5 hours" and a "Cmax of approximately 272 ng/ml." Neurelis Press Release.

Accordingly, Agarwal and the Neurelis Press Release expressly disclosed that the intranasal diazepam solution formulation subject to the NCT '558 clinical trial resulted in the T_{max} and C_{max} values claimed in the '852 and '061 patents. For that additional reason, a POSA motivated to administer the claimed intranasal diazepam solution formulation based on the teachings of Cartt 2009 and Meezan, in view of NCT '558, Agarwal, and the Neurelis Press Release would have had a reasonable expectation of success in achieving the T_{max} and C_{max} values claimed in the '852 and '061 patents. Thus, the T_{max} and C_{max} values recited by the claims of the '852 and '061 patents are invalid as obvious over Cartt 2009 and Meezan, in view of NCT '558, Agarwal, and the Neurelis Press Release.

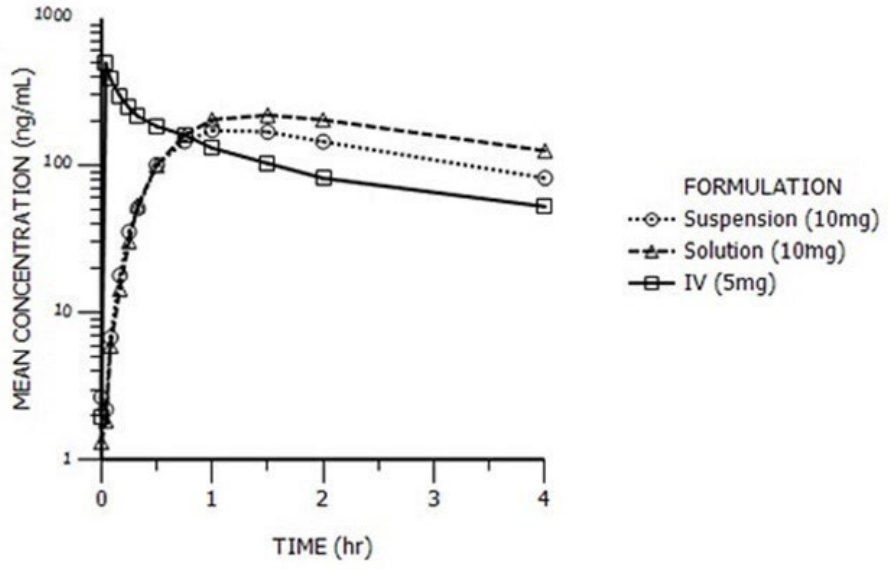
(c) The Treatment-Time, AUC, and Half-Life Claim Limitations

As explained above, certain claims of the ’852 and ’061 patents recite that administering the diazepam formulation “to the one nasal mucosal membrane of the patient results in treatment in less than about 5 minutes and treatment over about 24 hours” (’852 patent at claims 20-23; ’061 patent at claims 3-4, 7-8, 23-24, 35-36, 45-46, 55-56) or “a half-life of about 49.2 hours” (’852 patent at claims 24-27; ’061 patent at claims 31, 41, 51, 61). Certain claims of the ’061 patent also recite that “the pharmaceutical solution exhibits an approximate area under a blood plasma concentration curve measuring total drug exposure across time ($AUC_{0-\infty}$) of 7338 hours*ng/ml.” ’061 patent at claims 15-16, 28. The Neurelis Press Release and Agarwal expressly disclosed that the intranasal diazepam solution formulation reported in the prior art clinical trial achieved the claimed treatment-time, half-life, and AUC properties.

For example, Agarwal disclosed that the diazepam solution formulation exhibited a similar half-life as the comparator IV formulation, and provided data that a POSA could use to extrapolate a half-life, treatment-time, AUC value that renders the claims obvious[38]:

[38] *See, e.g.*, https://aesnet.org/abstractslisting/a-pilot-study-assessing-the-bioavailability-and-pharmacokinetics-of-diazepam-after-intranasal-and-intravenous-administration-in-healthy-volunteers

Mean plasma diazepam concentration-time profiles after intravenous and intranasal administration in 24 healthy volunteers (0-4h)



Similarly, the Neurelis Press Release reported that to be able to "to quickly and efficiently deliver, via intranasal administration, clinically relevant diazepam levels offers a more acceptable method of rescue therapy" based on the pharmacokinetic data. Neurelis Press Release.

Accordingly, Agarwal and the Neurelis Press Release disclosed that the intranasal diazepam solution formulation subject to the NCT '558 clinical trial resulted in the half-life, treatment-time, and AUC properties claimed in the '852 and '061 patents. For that additional reason, a POSA motivated to administer the claimed intranasal diazepam solution formulation in view of Cartt 2009, Meezan, NCT '558, Agarwal, and the Neurelis Press Release would have had a reasonable expectation of success in achieving the half-life, treatment-time, and AUC properties claimed in the '852 and '061 patents. Thus, the half-life, treatment-time, and AUC properties recited by the claims of the '852 and '061 patents are invalid as obvious in view of Cartt 2009, Meezan, NCT '558, Agarwal, and the Neurelis Press Release.

6. The Stability Requirements Recited in the Claims of the ’061 Patent Would Have Been Inherently Obvious

As explained above, all independent claims of the ’061 patent recite a “stable” intranasal diazepam solution formulation. ’061 patent at claims 1, 5, 21, 33, 43, and 53. And certain dependent claims of the ’061 patent recite that “the pharmaceutical solution is stable at 25° C and 60% relative humidity for at least 3 months.” ’061 patent at claims 2, 6, 22, 34, 44, and 54. For the reasons discussed above, a POSA would have been motivated to ensure that the claimed pharmaceutical solution was stable, including at 25° C and 60% relative humidity for at least 3 months. *Supra* Sections VI.E.8, VI.E.8, VI.E.9.

Further, the claimed stability requirements are inherent properties, which are rendered obvious by Cartt 2009 and Meezan, in view of NCT ’558, Agarwal, and the Neurelis Press Release even in the absence of an express disclosure. *In re Kao*, 639 F.3d at 1070; *Santarus*, 694 F.3d at 1344; *Persion Pharms.*, 945 F.3d at 1191. Thus, a POSA motivated to make and administer the claimed intranasal diazepam solution formulations would inherently produce a formulation that meets the claimed stability requirements. For that additional reason, the stability limitations of the claims of the ’061 patent are invalid as obvious.

However, the stability properties recited in the claims of the ’061 patents also would have been obvious in view of Cartt 2009’s express disclosure of stability testing on similar diazepam solution formulations. For example, Cartt 2009 explained that solution formulations containing diazepam, Vitamin E USP, and dehydrated ethanol “were setup on stability at 25° C./60% RH, 30° C./65% RH and 40° C./75% RH.” Cartt 2009 at ¶¶ [0200], [0204]. Cartt 2009 also reported the results of those stability tests, and showed that the solution formulations were “stable,” including at “25° C and 60% relative humidity for at least 3 months.” *Id*. at ¶¶ [0204]-[0210]. Thus, a POSA would have understood that Cartt 2009’s solution formulations were stable.

Accordingly, a POSA would have been motivated to prepare a "stable" intranasal diazepam solution formulation in view of Cartt 2009, and would have had a reasonable expectation of success in doing so in view of the stability test results disclosed in Cartt 2009. For that additional reason, the stability limitations recited in the claims of the '061 patent would have been obvious.

G. The Claims of the '852 and '061 Patents Are Invalid as Obvious Over Cartt 2009 and Meezan, in view of the Diastat Label, NCT '558, Gwozdz, and USP

The disclosures and teachings that render the claims of the '852 and '061 patents obvious are discussed below and also identified in the claim charts attached hereto as Exhibits D and E. The claim charts provide an element-by-element disclosure of where specifically, in each prior art reference, the relevant claim elements, limitations, or rationale supporting the combination(s) are found. The identifications are not meant to be exhaustive, and the inclusion of certain exemplary combinations in the claim chart does not exclude other combinations. Defendants contend that it would have been obvious to a POSA to combine any of the prior art references to practice any of the claims of the '852 and '061 patents. The prior art references are analogous art as each reference is from the same field of endeavor and is reasonably pertinent to the particular problem with which the inventors were involved, or both. To the extent Neurelis contends that an embodiment within a particular prior art reference does not fully disclose all limitations of a claim, Defendants reserve the right to rely on other embodiments in that prior art reference, or other information, to show obviousness.

All claims of the '852 and '061 patents also would have been obvious in view of Cartt 2009 and Meezan, optionally in view of the Diastat Label, NCT '558, Gwozdz, and USP. Each of these references is discussed in detail above. *Supra* Sections VI.D-F. Further, for the reasons discussed above, the claims of the '852 and '061 patents would have been obvious in view of Cartt 2009 and Meezan, optionally in view of the Diastat Label, NCT '558, Gwozdz, and USP. *Supra* Sections

VI.D-F. Accordingly, in view of this additional and alternative combination of the prior art references addressed above, a POSA would have been motivated to make and administer the claimed intranasal diazepam solution formulations to treat seizures in epilepsy patients, and would have had a reasonable expectation of success.

Without restating all of the arguments described in detail above, but incorporating them by reference here, the combination of the references listed above renders all limitations of the claims of the ’852 and ’061 patents obvious. For example, the claimed diazepam solution formulations containing specific amounts of Vitamin E, diazepam, benzyl alcohol and ethanol, and DDM are obvious in view of the disclosures of Cartt 2009 and Meezan, optionally in view of Gwozdz and USP. *Supra* Sections VI.D-F. Further, NCT ’558 disclosed that Neurelis was conducting a clinical trial on a “solution” formation of diazepam that contained a 10 mg dose for the treatment of seizures. NCT ’558 at 1. And to the extent these references do not expressly disclose any specific amounts of the claimed ingredients, which they do, a POSA would have arrived at said amounts via routine optimization. *See Pfizer*, 94 F.4th at 1348; *Pfizer,* 480 F.3d at 1367-68; *DyStar*, 464 F.3d at 1371; *see also In re Luck*, 476 F.2d at 652-53.

In addition, the treatment elements of the claims of the ’852 and ’061 patents would have been obvious in view of Cartt 2009’s express disclosure of the use of intranasal diazepam formulations for the treatment of seizures, including those recited in the claims of the ’852 and ’061 patents. Cartt 2009 at ¶¶ [0066], [0077]-[0078], [0086]-[0090]. And as explained above, the Diastat Label expressly disclosed that diazepam could be used for the claimed methods of treatment, which Neurelis acknowledged is where the claim language was taken from in the first place. Diastat Label at 1. Finally, NCT ’558 disclosed that Neurelis was investigating an intranasal solution formulation of diazepam for the treatment of seizures. NCT ’558 at 1.

Further, the administration elements of the claims of the ’852 and ’061 patents would have been obvious in view of Cartt 2009’s express disclosure of the claimed volumes and parameters. *Supra* Section VI.F.4.

Finally, the bioavailability, pharmacokinetic, and stability properties recited in the claims of the ’852 and ’061 patents would have been inherently obvious in view of Cartt 2009 and Meezan, optionally in view of the Diastat Label, NCT ’558, Gwozdz, and USP. *Supra* Sections VI.E-F; *see also In re Kao*, 639 F.3d at 1070; *Santarus*, 694 F.3d at 1344; *Persion Pharms.*, 945 F.3d at 1191.

Accordingly, all claims of the ’852 and ’061 patents are invalid as obvious in view of Cartt 2009 and Meezan, optionally in view of the Diastat Label, NCT ’558, Gwozdz, and USP.

H. The Claims of the ’852 and ’061 Patents Are Invalid as Obvious Over Cartt 2009 in view of Gwozdz, Meezan, and/or Bream

In addition to the disclosures and teachings above, the claims of the ’852 and ’061 patents are further shown below to be obvious and as shown in the claim charts attached hereto as Exhibits D and E. *See Sections* VI.A-G. The claim charts provide an element-by-element disclosure of where specifically, in each prior art reference, the relevant claim elements, limitations, or rationale supporting the combination(s) are found. The identifications are not meant to be exhaustive, and the inclusion of certain exemplary combinations in the claim chart does not exclude other combinations. Defendants contend that it would have been obvious to a POSA to combine any of the prior art references to practice any of the claims of the ’852 and ’061 patents. The prior art references are analogous art as each reference is from the same field of endeavor and is reasonably pertinent to the particular problem with which the inventors were involved, or both. To the extent Neurelis contends that an embodiment within a particular prior art reference does not fully disclose

all limitations of a claim, Defendants reserve the right to rely on other embodiments in that prior art reference, or other information, to show obviousness.

For the reasons explained below and in the claim charts attached to these contentions as Exhibits D and E, all the claims of the ’852 and ’061 patents would have been obvious to a POSA over Cartt 2009 in view of Gwozdz, Meezan, and/or Bream. Each of these references is discussed in detail above. *Supra* Sections VI.D-G.

First, Cartt 2009 teaches nasal administration of intranasal diazepam solution, containing diazepam in the claimed dosage amounts, for treatment of seizures associated with epilepsy, that includes vitamin E, ethanol and dodecyl maltoside. Cartt 2009 at Example 1. Cartt 2009 also teaches that solutions are administered in about 100 μL as a first metered spray applied to a first nostril and, if necessary, a second metered spray applied to a second nostril. Cartt 2009 at Abstract, ¶¶ [0029], [0060], [0135], [0144]. The compositions can be used to treat seizure, protect against seizure, reduce or ameliorate the intensity of seizure, reduce or ameliorate the frequency of seizure, and/or prevent occurrence or re-occurrence of seizure. Cartt 2009 also discloses ethanol as a preferred solvent. Cartt 2009 at ¶¶ [0013], [0136]. Specific amounts of vitamin E as claimed significantly overlaps with the ranges mentioned in Cartt 2009. Cartt 2009 at [0135]-[0136], [0162]. Thus, Cartt 2009 renders obvious a substantial portion of the claimed formulation and treatment limitations of the ’852 and ’061 patents.

Second, a POSA would also be motivated from the teachings of Gwozdz to select and optimize the specific combination and amounts of ethanol and benzyl alcohol necessary for preparation of diazepam solution as claimed, as a matter of routine experimentation. *See* Gwozdz at 6:16-7:2, 7:3-8. For benzyl alcohol amount, POSA would easily experiment with various amounts of ethanol (for example, 10% to 30% of ethanol), and arrive at the benzyl alcohol amount

of 1% to 40% so as to make up remainder of the disclosed total alcohol amount of 1% to about 70%.

Third, a POSA would also optimize the specific amount of dodecyl maltoside as claimed, from teachings of Meezan. *See* Meezan at ¶¶ [0056], [0058], [0150]-[0151], [0158]-[0159]. Lastly, treatment of bouts of intermittent and stereotypic episodes of increased seizure activity is taught by Bream, which provides methods for treating and/or preventing seizures, including ARS, which is defined as a cluster or number of primary generalized and/or partial seizures that occur over a short period of time. Bream at ¶¶ [008], [0091].

A POSA would also be motivated from the teachings of *Gwozdz* to select and optimize the specific combination and amounts of ethanol and benzyl alcohol for preparation of diazepam solution as claimed, as a matter of routine experimentation. For benzyl alcohol amount, POSA would easily experiment with various amounts of ethanol (for example, 10% to 30% of ethanol), and arrive at the benzyl alcohol amount of 1% to 40% so as to make up remainder of the disclosed total alcohol amount of 1% to about 70%. Furthermore, POSA would also optimize the specific amount of dodecyl maltoside as claimed, from teachings of *Meezan.* Lastly, treatment of bouts of intermittent and stereotypic episodes of increased seizure activity is taught by *Bream,* which provides methods for treating and/or preventing seizures, including ARS, which is defined as a cluster or number of primary generalized and/or partial seizures that occur over a short period of time.

Accordingly, all the claims of the ’852 and ’061 patents would have been obvious to a POSA over Cartt 2009 in view of Gwozdz, Meezan, and/or Bream.

I. The Claims of the ’852 and ’061 Patents Are Invalid for Obviousness Type Double Patenting

The claims of the ’852 and ’061 patents are invalid for non-statutory double patenting as being unpatentable over claims 18 and 19 of the ’546 patent in view of Cartt 2009 and Bream. Cartt 2009 and Bream are discussed in detail above. *Supra* Sections VI.D-G; *see also* Exhibits G-H. Although the claims of the ’852 and ’061 patents are not identical to the claims of the ’546 patent, they are not patentably distinct.

The ’546 patent was filed on June 13, 2012, and issued on November 25, 2014. The ’546 patent will expire on March 27, 2029. The ’852 patent, which is a continuation of the application that stems from the ’546 patent, is a later-filed, later-issued and later-expiring patent, as compared to the ’546 patent. The ’546 patent is listed in the Orange Book for Valtoco® and is a family equivalent (commonly owned) of the ’852 patent. Additionally, the ’061 patent is a later-filed, later-issued, and later-expiring patent compared to the ’546 patent.

Claims 1, 14, 17 , 18 and 19 of the ’546 patent read as below:

1. A pharmaceutical solution for nasal administration consisting of: (a) a benzodiazepine drug; (b) one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); (c) ethanol and benzyl alcohol in a combined amount from about 10% to about 70% (w/w); and (d) an alkyl glycoside.

14. The pharmaceutical solution of claim 1, consisting of 5-15% (w/v) diazepam, 0.01-1% (w/v) alkyl glycoside, 45-65% (w/v) vitamin E, 10-25% (w/v) ethanol and 5-15% (w/v) benzyl alcohol.

17. The solution of claim 1, consisting of diazepam, vitamin E, ethanol, benzyl alcohol and dodecyl maltoside.

18. The solution of claim 17, consisting of about 56.47% (w/v) vitamin E, about 10.5% (w/v) benzyl alcohol, about 10% (w/v) diazepam, about 0.25% (w/v) dodecyl maltoside, q.s. dehydrated ethanol.

19. The pharmaceutical solution of claim 14, consisting of 5-15% (w/v) diazepam, 0.01-1% (w/v) dodecyl maltoside, 45-65% (w/v) vitamin E, 10-25% (w/v) ethanol and 5-15% (w/v) benzyl alcohol.

Thus, it is evident that claim 18 of the ’546 patent broadly covers a pharmaceutical solution for nasal administration consisting of about 56.47% (w/v) vitamin E, about 10.5% (w/v) benzyl alcohol, about 10% (w/v) diazepam, about 0.25% (w/v) dodecyl maltoside, and sufficient quantity of dehydrated ethanol. It is also evident that claim 19 of the ‘546 patent broadly covers a pharmaceutical solution for nasal administration consisting of 5–15% (w/v) diazepam, 0.01–1% (w/v) dodecyl maltoside, 45–65% (w/v) vitamin E, 10–25% (w/v) ethanol, and 5–15% (w/v) benzyl alcohol. A POSA would understand that claim 18 of the ’546 patent covers diazepam formulation containing 10 mg/spray, whereas claim 19 of the ’546 patent covers diazepam formulations containing 5–15 mg/spray.

Claims of the ’546 patent do not address a method of treating bouts of intermittent and stereotypic episodes of increased seizure activity in an epilepsy patient that is distinguishable from other seizures by administering 100 μL of the intranasal solution to nasal mucosal membrane of the patient. The claims also do not address certain bioavailability and pharmacokinetic properties as claimed in the independent and dependent claims of the ’852 and ’061 patents.

It would have been *prima facie* obvious to to administer the claimed composition of the ’546 patent for the treatment of ARS, given that U.S. Publication No. 2012/0252793 A1 (“Bream”), discussed in detail above, teaches treatment of ARS. Moreover, a POSA would have

been motivated to administer the claimed composition of the ’546 Patent as a single spray of about 100 μL to the first and/or second nostril, consistent with achieving a fast onset of therapeutic benefit (e.g., less than about 5 minutes), and to administer therapeutic doses of diazepam (about 2 to about 10 mg per dose, given 1 to 8 times per day) as taught in U.S. Publication No. 2009/0258865 A1 (“Cartt 2009”), discussed in detail above. The compositions taught by Cartt 2009 are stable. Additionally, bioavailability and pharmacokinetic properties (e.g., AUC0-∞, C_{max}, T_{max} and half-life) are inherent properties of the composition. Thus, a POSA would understand that the formulations of Claims 18 and 19 of the ’546 patent inherently provide the bioavailability and pharmacokinetic properties.

Accordingly, for at least these reasons, the claims of the ’852 and ’061 patents are invalid for non-statutory double patenting as being unpatentable over claims 18 and 19 of the ’546 patent in view of Cartt 2009 and Bream.

J. Secondary Considerations

Defendants contend that no secondary considerations weigh in favor of non-obviousness with respect to any of the claims of the ’852 and ’061 patents. Any secondary considerations that Neurelis may assert would be insufficient to overcome the strong showing of obviousness in this case with respect to the claims of the ’852 and ’061 patents. *See DyStar Textilfarben GmbH v. C.H. Patrick Co.*, 464 F.3d 1356, 1371 (Fed. Cir. 2006) (patent found obvious despite commercial success); *In re GPAC Inc.*, 57 F.3d 1573, 1580-81 (Fed. Cir. 1995) (same); *Pentec, Inc. v. Graphic Controls Corp.*, 776 F.2d 309, 315-17 (Fed. Cir. 1985) (same); *Pfizer*, 480 F.3d at 1371-72 (finding secondary considerations insufficient where the record establishes a strong case of obviousness); *Leapfrog Enters., Inc. v. Fisher-Price, Inc.*, 485 F.3d 1157, 1162 (Fed. Cir. 2007) (“[G]iven the strength of the prima facie obviousness showing, the evidence on secondary considerations was inadequate.”); *W. Union Co. v. MoneyGram Payment Sys., Inc.*, 626 F.3d 1361, 1373 (Fed. Cir.

2010) ("[W]eak secondary considerations generally do not overcome a strong prima facie case of obviousness.").

Further, Defendants are presently unaware of any secondary considerations that are relevant to any of the claims of any of the '852 and '061 patents. Secondary considerations do not form a part of the *prima facie* case of obviousness. Rather, a patentee may try to rebut a *prima facie* case of obviousness by coming forth with purported evidence of secondary considerations. Defendants therefore have no burden at this stage to address any secondary considerations, or to come forward with any evidence rebutting such considerations. To the contrary, it is Neurelis's obligation and burden to produce evidence of so-called secondary considerations, if any, on which it intends to rely. Defendants expect that additional discovery directed to any secondary considerations Neurelis may allege will take place in accordance with the case schedule, and that the evidence will rebut any alleged or claimed secondary considerations in full. As such, if and in the event Neurelis cites to any alleged secondary considerations, Defendants reserve the right to supplement these contentions.

K. The Claims of the '852 and '061 Patents Contain New Matter Not Included in the Priority '546 Patent and Are Either Invalid as Anticipated by the Valtoco Label or Invalid Under §112 for Lack of Written Description Support

As explained above, the earliest priority date to which the claims of the '852 and '061 patents are entitled is June 13, 2012. *Supra* Section VI.A. However, certain claim elements and phrases were not supported by the original specification of the '852 and '061 patents, or the '546 patent from which Neurelis claims priority. To claim priority based on an earlier application, "each previous application in the chain must comply with the written description requirement of 35 U.S.C. § 112(a)." *L.A. Biomedical Rsch. Int. v. Eli Lilly & Co.*, 849 F.3d 1049, 1057 (Fed. Cir. 2017). "Patent claims are awarded priority on a claim-by-claim basis based on the disclosure in the priority applications." *Lucent Techs., Inc. v. Gateway, Inc.*, 543 F.3d 710, 718 (Fed. Cir. 2008).

Here, as noted above, Neurelis amended the specification of the ’852 and ’061 patents during prosecution as follows:

Please replace paragraph [0237] with the following amended paragraph:

[0237] The solution of Table 11-1 and the suspension of Table 11-2 were found to be well-tolerated with only mild adverse events reported. The solution of Table 11-1 was further found to have similar bioavailability to intravenous administration of diazepam (96% to 97% of i.v.) The intranasal formulation of Table 11-1 exhibited a Tmax of 1.5 hours, a Cmax of approximately 272 ng/mL. These results are comparable to those reported in the literature for commercially available diazepam gel (Diastat®).

Please replace paragraph [0239] with the following amended paragraph:

[0239] Solutions similar to those set forth in Table 11-1 achieve bioavailability that is from about 80-125% of that achieved with the same benzodiazepine administered intravenously, e.g. bioavailability that is from about 90-110% of that achieved with the same benzodiazepine administered intravenously or about 92.5 to 107.5% that obtained with the same benzodiazepine administered intravenously. Such solutions may be used in methods of treating a patient with a disorder which may be treatable with a benzodiazepine drug, such as seizure, epileptic seizure and/or breakthrough seizure. In some embodiments, solutions described herein may be used to treat a disorder such as is treated with Diastat® diazepam gel. Diazepam rectal gel is approved by the FDA to treat selected, refractory, patients with epilepsy who require intermittent use of diazepam to control bouts of increased seizure activity or intermittent and periodic episodes of markedly increased seizure activity that for any individual patient, the clusters of seizure activity were not only stereotypic but were judged by those conducting and participating in these studies to be distinguishable from other seizures suffered by that patient. Accordingly, in some embodiments, solutions described herein may be used to treat bouts of intermittent and stereotypic episodes of increased seizure activity in an epilepsy patient that is distinguishable from other seizures suffered by the patient.

See, e.g., Neurelis-02058156-175; Neurelis-02052485-2508. Thus, it was not until the above specification amendments were filed on December 13, 2023 and March 14, 2024 that the ’061 and

’852 patents, respectively, contained written description support for the claimed methods of treating “bouts of intermittent and stereotypic episodes of increased seizure activity,” including “in an epilepsy patient that is distinguishable from other seizures suffered by the patient,” as required by all claims of the ’852 and ’061 patents. Accordingly, the claims of the ’852 and ’061 patents first find support as of the date the amendments were filed on December 13, 2023 and March 14, 2024, and have earliest possible priority dates of the same.

Further, certain claims of the ’852 and ’061 patents expressly recite bioavailability values of “96% to 97%.” ’852 patent at claims 18-19; ’061 patent at claims 1-20, 32, 42, 52, 62. As shown above, it was not until the specification of the ’852 and ’061 patents were amended on December 13, 2023 that the claimed bioavailability values of “96% to 97%” contained adequate written description support. Thus, for that additional reason, claims 18 and 19 of the ’852 patent, and claims 1-20, 32, 42, 52, 62 of the ’061 patent are entitled to a priority date of no earlier than March 14, 2024 and December 13, 2023, respectively.

Because the ’852 and ’061 patents are only entitled to a priority date of March 14, 2024 and December 13, 2023, respectively, the Valtoco label is prior art against the claims of the ’852 and ’061 patents under 35 U.S.C. § 102. Specifically, the Valtoco label was initially approved and publicly available in January 2020, with subsequent supplemental labels published in February 2021 and February 2022. Further, the prior art versions of the Valtoco label disclosed all limitations of the claims of the ’852 and ’061 patents, consistent with Neurelis’s representations that Valtoco is an embodiment of the claims of the ’852 and ’061 patents.

Indeed, during prosecution of the ’852 patent, Neurelis submitted the declaration of Dr. Stuart Madden, the Chief Scientific Officer for Neurelis. Within that declaration, Dr. Madden stated that “Valtoco® is currently indicated for the acute treatment of intermittent, stereotypic

episodes of frequent seizures activity (i.e., seizure clusters, acute repetitive seizures ("ARS")) that are distinct from a patient's usual seizure pattern in patients with epilepsy 6 years of age or older." Neurelis-02049865-881 (Decl. of Dr. Madden in Support of Patentability, ¶ 4). Dr. Madden also stated "[p]rior to the development of the clinically superior Valtoco® product ***covered in the claimed invention***, a diazepam rectal gel (Diastat®) was the only available FDA-approved treatment for ARS, which was inconvenient to administer and not readily accepted by patients compared to Valtoco®." *Id*. at ¶ 7 (emphasis added). Further, Dr. Madden explained that the claimed solutions, which he alleged cover Valtoco, included the following:

> 26. Each of the solutions recited in the claims of the '398 Application utilizes a solvent system and the specific formulation amounts of each ingredient of the solvent system are set forth in Table 2 below:

Table 2: Unit Dose Content per 100 µL

Ingredient	**5 mg**	**7.5 mg**	**10 mg**	**15 mg**	**20 mg**
Vitamin E (mg)	56.47	56.47	56.47	46.52	41.68
Benzyl Alcohol (mg)	10.5	10.5	10.5	39.5	39.5
Diazepam (mg)	5.0	7.5	10.0	15.0	20.0
Dodecyl maltoside (mg)	0.25	0.25	0.25	0.50	0.50
Ethanol (mg)	21.08	19.51	18.0	2.0	2.0
TOTAL (mg)	93.30	94.23	95.22	103.52	103.68

Id. at ¶ 26. Moreover, Dr. Madden included Table 4 in his declaration, shown below:

Table 4: Nasal Discomfort Comparison of Diazepam Formulations

Group Title	**Single Dose (10 mg or 0.16 mg/kg) of Valtoco®**	**Single Dose (0.2 mg/kg) of Diazepam Nasal Spray (Plumiaz®)**	**Single Dose (0.2 mg/kg) of Diazepam Rectal Gel (Diastat®)**
AUC Mean (Standard Deviation)	7338 ng*h/mL (2072)	1357.7 ng*h/mL (802.78)	2117.9 ng*h/mL (996.27)
Cmax Mean (Standard Deviation)	272 ng/mL (100)	157 ng/mL (120.15)	309 ng/mL (137.95)
Adverse Event			
Nasal Discomfort†	**6.1%**	**38.46%**	N/A

† Indicates events were collected by systematic assessment; *Specific values not available

Id. at ¶ 31-32. Dr. Madden explained that "[a]s can be seen from Table 4, ***the formulation of the claimed invention*** is less irritating within the nose, nasal cavity, mouth and throat than Plumiaz despite containing benzyl alcohol and a significantly higher amount of total alcohols." *Id*. at ¶ 32 (emphasis added). Again, Dr. Madden alleged that Valtoco® is "the formulation of the claimed invention. Thus, all claims of the '852 and '061 patents are invalid as anticipated by the Valtoco label under 35 U.S.C. § 102.

Alternatively, to the extent that it is asserted by Neurelis that the priority date of the '852 and '061 patent claims is not December 13, 2023 or March 14, 2024 (corresponding to the filing of the amendments to the specification noted above), the claims of the '852 and '061 patents are invalid under §112 for lacking written description support. As noted above, the only support and disclosure for the claimed preamble directed to a "method of treating bouts of intermittent and stereotypic episodes of increased seizure activity in an epilepsy patient that is distinguishable from other seizures suffered by the patient" (as found in all claims of both the '852 and '061 patents) is in the language of the specification added via the amendments dated December 13, 2023 and March 14, 2024.

Absent the additional disclosure provided by these amendments, the specification of the '852 and '061 patents fails to demonstrate that the inventors possessed the full scope of the claims. *Juno*, 10 F.4th at 1335 (quoting *Ariad*, 598 F.3d at 1351). Accordingly, to the extent that the '061 and '852 patent claims are not deemed to have an earliest priority date of December 13, 2023 and March 14, 2024, respectively, all claims of the '061 and '852 patent are invalid for lack of written description under 35 U.S.C. § 112.

L. The Claims of the '852 and '061 Patents Are Invalid 35 U.S.C. § 112

As explained above, "a patent is invalid for indefiniteness if its claims, read in light of the specification delineating the patent, and the prosecution history, fail to inform, with reasonable

certainty, those skilled in the art about the scope of the invention." *Nautilus,* 134 S. Ct. at 2124. For the reasons discussed below, to the extent the claims of the '852 and '061 patents are not obvious, they are invalid as indefinite because a POSA would lack reasonable certainty about the scope of certain claim terms and phrases.[39]

1. The Phrase "Pharmaceutical Solution Consisting Of" Is Indefinite

As Padagis explained in its preliminary invalidity contentions with respect to the '546, '414, and '786 patents, to the extent the claims of the '546, '414, and '786 patents allow for the presence of water, the phrase "pharmaceutical solution consisting of" is indefinite because a POSA would lack reasonable certainty about whether the claimed "pharmaceutical solution" can contain water. *See* Padagis's Initial Inv. Contentions at 33-36. For the same reasons discussed in Padagis's preliminary invalidity contentions with respect to the '546, '414, and '786 patents, the phrase "pharmaceutical solution consisting of" recited in the claims of the '852 patent is indefinite.[40] *Id*.

Indeed, like the claims of the '546, '414, and '786 patents, all claims of the '852 patent recite either a "pharmaceutical solution consisting of" specific amounts of Vitamin E, diazepam, DDM, benzyl alcohol, and ethanol. *Supra* Sections II.E.1. To reiterate, the transitional phrase "consisting of" is a term of patent convention meaning that the claimed invention contains only what is expressly set forth in the claim." *Multilayer Stretch Cling Film Holdings, Inc. v. Berry*

[39] As explained here, Defendants' indefiniteness positions are in the alternative to the obviousness positions discussed above. Defendants maintain that all claims of the '852 and '061 patents would have been obvious in view of the prior art, but to the extent Neurelis disputes those obviousness positions, certain phrases and limitations in the claims of the '852 and '061 patents are indefinite, as described below.

[40] Defendants note that dependent claims 4, 9, 13, and 17 of the '852 patent recite that "the pharmaceutical solution is substantially free of water." '852 patent at claims 4, 9, 13, 17. Thus, the indefiniteness positions discussed here do not apply to claims 4, 9, 13, and 17 of the '852 patent. However, Defendants reserve the right to assert that these claims are indefinite for the reasons discussed in this section upon receiving Neurelis's validity contentions and upon the completion of claim construction proceedings in this case.

Plastics Corp., 831 F.3d 1350, 1358 (Fed. Cir. 2016) (quoting *Norian Corp. v. Stryker Corp.*, 363 F.3d 1321, 1331 (Fed. Cir. 2004)). Due to the "consisting of" transitional phrase, a pharmaceutical solution within the scope of the claims may not contain any additional unrecited ingredients.

However, the claims of the '852 patent fail to inform a POSA with reasonable certainty the extent to which they include water, if at all. Indeed, for the reasons explained in Padagis's preliminary invalidity contentions, the specification of the Asserted Patents acknowledges that the claimed excipients may also include water. *See* Padagis's Initial Inv. Contentions at 33-36. The same is true with respect to the specification of the '852 patent, and thus for the same reasons discussed in Padagis's preliminary invalidity contentions, to the extent the claims of the '852 patent allow for the presence of water, the claims of the '852 patent are invalid as indefinite because a POSA would not have reasonable certainty as to whether the claims allow for the inclusion of water, and, if so, what amount of water may be included, while still falling within the scope of the claims.

Therefore, the claims of the '852 patent are invalid as indefinite.

2. The Bioavailability Claim Phrases Are Indefinite

All claims of the '852 and '061 patents recite that "administering the single spray of the pharmaceutical solution to the patient achieves" a specific "bioavailability of an equivalent dose of diazepam administered intravenously." *Supra* Sections II.E.1, II.F.1. Because a POSA would lack reasonable certainty about what "an equivalent dose of diazepam administered intravenously" would be or how the "bioavailability" values should be measured, all claims of the '852 and '061 patents are invalid as indefinite.

First, the claims do not include any additional limitations or guidance about what "an equivalent dose of diazepam administered intravenously" would be or how the "bioavailability" values should be measured." *Id*. Thus, the claims do not offer a POSA any further context or

guidance for determining what "an equivalent dose of diazepam administered intravenously" would be or how the "bioavailability" values should be measured.

Second, the specification of the '852 and '061 patents do not define or offer sufficient guidance to a POSA for determining what "an equivalent dose of diazepam administered intravenously" would be or how the "bioavailability" values should be measured. As explained above, the specification of the '852 and '061 patents generally explains that the claimed diazepam solutions may exhibit the claimed bioavailability values relative IV injections of diazepam. *Supra* Section II.E.2. However, the specification explains that different amounts of intravenous diazepam may be used for the bioavailability testing depending on the type of study (i.e., animal model vs. human), and that ranges of intravenous diazepam may be used within each type of study. *See, e.g.*, '852 patent at 59:32-60:33, 63:5-29. Further, the specification generally discloses the bioavailability of the intranasal diazepam solutions, but does not explain how those values were calculated. *Id*. Thus, the specification does not offer a POSA sufficient context or guidance for determining what "an equivalent dose of diazepam administered intravenously" would be or how the "bioavailability" values should be measured.

Third, as explained above, the prosecution histories of the '852 and '061 patents do not clarify what "an equivalent dose of diazepam administered intravenously" would be or how the "bioavailability" values should be measured. *Supra* Sections II.E.3, II.F.3. Thus, a POSA would lack reasonable certainty about the scope of the bioavailability claim phrase in view of the claims, specification, and prosecution histories of the '852 and '061 patents.

In addition, a POSA would understand that the "bioavailability" of a drug can be tested, measured, and calculated using different methodologies. For example, the specification of the '852 and '061 patents explains that bioavailability may "be determined by a suitable pharmacodynamic

method, such as comparison of area under the blood plasma concentration curve (AUC) for the nasally and intravenously administered drug. It is further understood that the percent bioavailability of the nasally administered benzodiazepine may be determined by comparing the area under the blood plasma concentration curve obtained with one dose of the benzodiazepine (e.g. 10 mg of nasal diazepam) with another dose of the same benzodiazepine administered intravenously (e.g. 5 mg of i.v. diazepam), taking into consideration the difference in dose." '852 patent at 4:54-65. A POSA would understand that the various parameters referenced by the specification of the '852 and '061 patents (e.g., different pharmacodynamic methods, calculating the AUC, using different doses of IV diazepam, etc.) could result in different bioavailability results.

Indeed, a POSA would understand that bioavailability may be measured by reference to AUC values. And a POSA would understand that there are different methods and techniques that may be used to measure AUC values, where those different techniques and methodologies can result in different numerical AUC values. Further, a POSA would understand that different patient populations, the number of patients involved in bioavailability studies, and other related parameters can have a significant impact on the final bioavailability and AUC results.

The Federal Circuit has long held that claims are indefinite, for instance, where there are multiple methods of defining or measuring a claimed parameter that yield materially different results without guidance in the patent or prosecution history as to which method should be used. *Dow Chem. Co. v. Nova Chems. Corp.*, 803 F.3d 620, 634 (Fed. Cir. 2015); *Teva Pharms. USA, Inc. v. Sandoz, Inc.*, 789 F.3d 1335, 1345 (Fed. Cir. 2015); *Pac. Coast Bldg. Pods., Inc. v. CertainTeed Gypsum, Inc.*, 816 F. App'x 454, 460 (Fed. Cir. 2020). Thus, for this additional reason, all claims of the '852 and '061 patents are invalid as indefinite because the claimed

bioavailability values and "equivalent dose of diazepam administered intravenously" can be measured using different methods to obtain materially different results, and the '852 and '061 patents do not offer guidance as to which method should be used.

3. The Treatment Claim Phrases Are Indefinite

All claims of the '852 and '061 patents require that administering the claimed diazepam formulation "is safe and effective in treating the bouts of intermittent and stereotypic episodes of increased seizure activity in the patient" and "results in a treatment selected from the group consisting of a reduction in the severity of the seizure, a reduction in the probability that the patient will experience a repeat seizure, an increase in the interval between a current seizure and a next seizure in the patient, a reduction in the frequency of seizure in the patient and combinations thereof." *Supra* Sections II.E.1, II.F.1. Because a POSA would lack reasonable certainty about the scope and meaning of these treatment claim terms, all claims of the '852 and '061 patents are invalid as indefinite.

For example, a POSA would lack reasonable certainty about the scope of the phrase "safe and effective." The specification does not define that phrase, nor does it use the word "safe" at all. *See generally* '852 patent and '061 patent specification. Further, the specification does not define the term "effective," other than explaining that "the phrase 'therapeutically effective amount' (or more simply 'effective amount') includes an amount sufficient to provide a specific therapeutic response for which the drug is administered to a patient in need of particular treatment. The skilled clinician will recognize that the therapeutically effective amount of drug will depend upon the patient, the indication and the particular drug administered." '852 patent at 17:52-59. While that definition vaguely indicates that different amounts of different drugs may be effective when they provide a specific therapeutic response, it offers no clarity about what it means for a 10 mg dose

of diazepam to be "effective" for the claimed treatments, let alone what would be both "safe and effective."

Likewise, the prosecution histories of the '852 and '061 patents do not offer any guidance or information about what the phrase "safe and effective" means in the context of the claimed methods of treatment. *Supra* Sections II.E.3, II.F.3. While Neurelis argued that the prior art did not disclose a safe and effective intranasal diazepam solution formulation, as purportedly claimed and disclosed by the '852 and '061 patents, no clarity was provided about what the phrase "safe and effective" means or requires. *Id*. For example, Neurelis argued that the FDA approved Valtoco product is "safe and effective," and that the claims of the '852 and '061 patents encompass the Valtoco product, but also argued that certain unapproved Valtoco formulations (referred to as the Valtoco Product Candidates) encompassed by the claims were safe and effective. *See, e.g.*, Neurelis-02049980-50015. A POSA would understand that establishing that a drug is "safe and effective" for purposes of full FDA approval (i.e., the FDA approved Valtoco product that Neurelis referred to during prosecution of the '852 patent) requires complete phase three clinical trial data, whereas unapproved and developmental drugs may be informally characterized as safe and effective with a lower level of safety and efficacy data. Thus, Neurelis's arguments during prosecution of the '852 and '061 patents offer no clarity on what it means for the claimed diazepam formulations to be "safe and effective" and only inject further ambiguity into the scope of the claims.

Because the specification of the '852 and '061 patents does not provide any guidance to a POSA about what "safe and effective" means in relation to the claimed treatments (i.e., "treating the bouts of intermittent and stereotypic episodes of increased seizure activity in the patient" and "a treatment selected from the group consisting of a reduction in the severity of the seizure, a

reduction in the probability that the patient will experience a repeat seizure, an increase in the interval between a current seizure and a next seizure in the patient, a reduction in the frequency of seizure in the patient and combinations thereof"), a POSA would lack reasonable certainty about the scope of the claims. But a POSA would also lack reasonable certainty about the scope of the claims in view of the vague treatment conditions recited by the claims.

For example, the claims require the intranasal diazepam solution formulation to be "safe and effective" for "treating the bouts of intermittent and stereotypic episodes of increased seizure activity in the patient" but also for "a treatment selected from the group consisting of a reduction in the severity of the seizure, a reduction in the probability that the patient will experience a repeat seizure, an increase in the interval between a current seizure and a next seizure in the patient, a reduction in the frequency of seizure in the patient and combinations thereof." Thus, as an initial point, a POSA would lack reasonable certainty about whether "treating the bouts of intermittent and stereotypic episodes of increased seizure activity in the patient" would also result in "a treatment selected from the group consisting of a reduction in the severity of the seizure, a reduction in the probability that the patient will experience a repeat seizure, an increase in the interval between a current seizure and a next seizure in the patient, a reduction in the frequency of seizure in the patient and combinations thereof."

Indeed, the specification does not define any of these phrases or terms, and separately discusses the two different treatment limitations. In reference to the prior art Diastat product, the specification states that:

> Diazepam rectal gel is approved by the FDA to treat selected, refractory, patients with epilepsy who require ***intermittent use of diazepam to control bouts of increased seizure activity or intermittent and periodic episodes of markedly increased seizure activity*** that for any individual patient, the clusters of seizure activity were not only stereotypic but were judged by those conducting and participating in these studies to be distinguishable from other seizures suffered by

> that patient. Accordingly, in some embodiments, ***solutions described herein may be used to treat bouts of intermittent and stereotypic episodes of increased seizure activity in an epilepsy patient*** that is distinguishable from other seizures suffered by the patient.

'852 patent at 63:17-29 (emphasis added). Thus, the specification (in reference to Diastat) states that "treating the bouts of intermittent and stereotypic episodes of increased seizure activity in the patient" excludes the treatment of "other seizures suffered by the patient." *Id*. That description is consistent with the positions Neurelis took during prosecution of the '852 and '061 patents, as explained above. *Supra* Section VI.E.2(a).

However, more generally, the specification explains that diazepam may be used for a "reduction in the severity of the seizure (e.g. general relaxation of the muscles, reduction in seizure-induced anxiety experienced by the patient and a general impartation of a feeling of well-being to the patient), reduction in the duration of the seizure, reduction in the probability that the patient will experience a repeat seizure, an increase in the interval between the current seizure and the next seizure." *Id*. at 22:31-38. In other words, the specification recognizes that diazepam may be used to treat various types of seizures in epilepsy patients, not just the narrower types of seizure activity that Diastat was used to treat.

Further, as discussed above, the prosecution histories of the '852 and '061 patents offer no clarity on this issue, other than reiterating that Diastat's treatment indications cover a narrower set of seizure treatments than diazepam's broader known uses for the treatment of seizures generally. Thus, a POSA would lack reasonable certainty about whether the claimed diazepam solution formulations must be used to treat the specific type of seizure activity that Diastat was used to treat, or if the claims also encompass the broader treatment of seizures, consistent with the more general statements in the specification of the '852 and '061 patents.

Finally, a POSA would lack reasonable certainty about the scope of when a treatment satisfies the treatment conditions recited in the claims of the ’852 and ’061 patents. Specifically, the claims require “a reduction in the severity of the seizure, a reduction in the probability that the patient will experience a repeat seizure, an increase in the interval between a current seizure and a next seizure in the patient, a reduction in the frequency of seizure in the patient and combinations thereof.” Each of these treatment conditions includes subjective requirements, but the specification and file histories do not offer a POSA any guidance about when or how they can be satisfied.

For example, a POSA would be uncertain about when a treatment results in a “reduction in the severity of a seizure,” which the specification states might refer to “e.g. general relaxation of the muscles, reduction in seizure-induced anxiety experienced by the patient and a general impartation of a feeling of well-being to the patient.” ’852 patent at 22:31-38. Whether a treatment reduces the severity of a seizure, or achieves “general relaxation of the muscles, reduction in seizure-induced anxiety experienced by the patient and a general impartation of a feeling of well-being to the patient” is a purely subjective endeavor and thus renders the claims invalid as indefinite. *See, e.g.*, *Dow Chem.*, 803 F.3d at 634; *Teva Pharms.*, 789 F.3d at 1345; *Pac. Coast. Bldg. Pods.*, 816 F. App’x at 460.

The same is true for the remaining treatment limitations recited by the claims of the ’852 and ’061 patents (i.e., “a reduction in the probability that the patient will experience a repeat seizure, an increase in the interval between a current seizure and a next seizure in the patient, a reduction in the frequency of seizure in the patient and combinations thereof”). The specification and file histories of the ’852 and ’061 patents offer no guidance on how these treatment conditions can be objectively measured or satisfied, and thus these treatment limitations encompass subjective

requirements and are therefore invalid as indefinite. *See, e.g.*, *Dow Chem.*, 803 F.3d at 634; *Teva Pharms.*, 789 F.3d at 1345; *Pac. Coast. Bldg. Pods.*, 816 F. App'x at 460.

Accordingly, for at least the reasons discussed above, a POSA would lack reasonable certainty about the scope of the claims of the '852 and '061 patents in view of the claimed treatment limitations. Thus, all claims of the '852 and '061 patents are invalid as indefinite.

4. The Term "Stable" in the Claims of the '852 and '061 Patents is Indefinite

All claims of the '061 patent, and certain claims of the '852 patent, require "a stable pharmaceutical solution." '061 patent at all claims; '852 patent at claims 6-9, 14-17, 19, 21, 23, 25, 27, 29, 31. Because a POSA would lack reasonable certainty about the scope and meaning of the term "stable," all claims of the '061 patent and claims 6-9, 14-17, 19, 21, 23, 25, 27, 29, 31 of the '852 patent are invalid as indefinite.

A POSA would understand that the stability of pharmaceutical formulations can be measured in many different ways by many different methods. For example, stability testing of pharmaceutical formulations generally includes chemical, physical, biological and microbiological attributes, including preservative content and the testing of those attributes, of a drug product that is susceptible to changes during storage as they could influence quality, safety and/or efficacy of a formulated drug. Indeed, the FDA has long-recognized that a variety of factors, include humidity, solvent, oxidation, photostability, pH, temperature, and storage conditions, can affect drug stability. *See, e.g.*, FDA, GUIDANCE FOR INDUSTRY: Q1A(R2) STABILITY TESTING OF NEW DRUG SUBSTANCES AND PRODUCTS (rev. 2, Nov. 2003); *see also, e.g.*, ICH, ICH HARMONISED TRIPARTITE GUIDELINE: EVALUATION FOR STABILITY DATA Q1E (Feb. 2003).

Further, stability testing of pharmaceutical formulations can be done via many different methodologies, depending on the attribute that is being tested. *See generally, e.g.*, FDA, GUIDANCE

FOR INDUSTRY: Q1A(R2) STABILITY TESTING OF NEW DRUG SUBSTANCES AND PRODUCTS (rev. 2, Nov. 2003); *see also, e.g.*, ICH, ICH HARMONISED TRIPARTITE GUIDELINE: EVALUATION FOR STABILITY DATA Q1E (Feb. 2003). Those methodologies include various types of chromatography, light-based characterization techniques, pH testing, and spectrometry and spectroscopy techniques, just to name a few. Each of those methods can be performed in many different ways, with different levels of sensitivity and for either qualitative or quantitative purposes.

In addition, each individual drug product typically requires an assessment of specific impurities or other stability issues. Because a drug compound (e.g., diazepam) may degrade to form specific impurities related to that drug compound, stability testing typically involves tests aimed at detecting drug-specific impurities. The same is true with respect to excipients.

Thus, the term "stable" as recited in the claims of the '061 patent and certain claims of the '852 patent, is vague and could encompass any number of possible stability tests or results. Because the specification and file histories of the '852 and '061 patents do not define or clarify what constitutes a "stable" diazepam solution, a POSA would lack reasonable certainty about the scope of the claims.

Indeed, neither the specification nor the file histories of the '852 and '061 patents define the term "stable." Further, while the specification purportedly includes an example of stability tests conducted on the claimed formulations (Example 11), it does not explain whether those tests indicate that the claimed formulation is "stable." '852 patent at 60:52-61:38. In fact, Example 11 involves stability tests conducted at different temperatures, relative humidities, and timepoints to assess the formulations for their "appearance" and "diazepam % label claim." *Id*. But the specification never explains what test results would be considered "stable" (or what would be

considered not stable), or what timepoint or test condition is encompassed by the term "stable" (i.e., which temperature, relative humidity, timepoint, etc.). *Id*.

Further, earlier stability tests conducted on other diazepam solution formulations (i.e., those described in the prior art specification of the '664 patent, e.g. Cartt 2009) encompassed many additional tests. *See, e.g.*, *id*. at 49:25-59:17 (Example 5). Thus, the specification also would have indicated to a POSA that a diazepam solution formulation may need to meet those additional test specifications to be considered "stable." Indeed, the specification provides a prophetic example in which it states that the claimed diazepam solution formulations "may be put up on stability as described in Example 5, mutatis mutandis," but those tests are not reported in the specification of the '852 and '061 patents for the claimed diazepam solution formulations.

Accordingly, a POSA would lack reasonable certainty about which stability tests described in the specification of the '852 and '061 patents are necessary to ensure the claimed diazepam solution formulations are "stable." For that additional reason, all claims of the '061 patent and claims 6-9, 14-17, 19, 21, 23, 25, 27, 29, 31 of the '852 patent are invalid as indefinite

5. The Phrase "A Sufficient Quantity of Ethanol" is Indefinite

All claims of the '852 and '061 patents require the claimed diazepam solution formulations to contain "a sufficient quantity of ethanol." *Supra* Sections II.E.1; II.F.1. Because a POSA would lack reasonable certainty about the scope and meaning of the phrase "a sufficient quantity of ethanol," all claims of the '852 and '061 patents are invalid as indefinite.

First, the claims of the '852 and '061 patents do not provide any additional limitations, or offer any other guidance, related to what amount of "ethanol" would be considered a "sufficient

quantity."[41] While the claims recite specific amounts of Vitamin E, diazepam, benzyl alcohol, and DDM, they vaguely require the formulation to contain "a sufficient quantity of ethanol." And while the claims recite that the claimed pharmaceutical solution must be administered as "a single spray of 100 μL" (i.e., in a fixed volume), it recites the claimed ingredients by weight (i.e., in "mg"). Thus, a POSA would lack reasonable certainty about what volume relative to the claimed "100 μL" volume is accounted for by the weights of Vitamin E, diazepam, benzyl alcohol, and DDM. And a POSA would likewise lack reasonable certainty about how much ethanol constitutes a "sufficient quantity" relative to the claimed "100 μL" volume and the other ingredients.

Second, the specification does not define the phrase "a sufficient quantity of ethanol," and provides sparse references to what amount of ethanol would be "sufficient." For example, the specification states that the solutions may contain "two or more alcohols, such as ethanol (1-25% (w/v)) and benzyl alcohol (1-25% (w/v)), or ethanol (10-22.5% (w/v)) and benzyl alcohol (7.5-12.5% (w/v))," "ethanol (10-25% (w/v)) and benzyl alcohol (5-15% (w/v))," or "ethanol (17-20% (w/v)) and benzyl alcohol (10-12% (w/v))." '852 patent at 2:58-3:22. And the specification states that "the carrier system comprises one or more alcohols or glycols, or any combinations thereof, in an amount from about 10% to about 55%," where the "alcohol is ethanol or contains ethanol." *Id*. at 11:3-25. Finally, the specification includes certain examples in which "q.s." amounts of ethanol (i.e., as much as needed) were used. *Id*. at 39:1-37, 48:1-10, 60:52-61:7.

Thus, the specification describes general amounts and ranges of ethanol that may be used, but never explains what amount of ethanol would be sufficient, particularly in reference to the narrow formulation otherwise recited in the claims. And while one of the examples (Example 11)

[41] Dependent claims 11, 12, 26, 38, 48, and 58 of the '061 patent require the ethanol to be "dehydrated ethanol," but do not explain or otherwise specify what "quantity" of ethanol to include in the claimed diazepam solution formulations.

purportedly contains the ingredients and amounts of each ingredient recited in the claims of the ’852 and ’061 patents, it does not include any language that would indicate to a POSA that the amount of ethanol listed in that example is the only amount that may be considered a “sufficient quantity.” Thus, the specification does not offer objective guidance for a POSA to understand the scope of the phrase “a sufficient quantity of ethanol.”

Third, as described above, the prosecution histories do not offer any objective guidance that would allow a POSA to understand the scope of the phrase “a sufficient quantity of ethanol.” Consistent with the specification, Neurelis discussed and relied on certain examples that purportedly contain the ingredients and amounts of each ingredient recited in the claims of the ’852 and ’061 patents, including specific amounts of ethanol. *See, e.g.*, Neurelis-02049865-881. But Neurelis did not expressly state that those amounts of ethanol are the only amounts that may be considered a “sufficient quantity.”

Accordingly, all claims of the ’852 and ’061 patents are invalid as indefinite because the claims phrase “a sufficient quantity of ethanol” is indefinite.

6. The Phrase “Distinguishable From Other Seizures” Is Indefinite

All claims of the ’061 and ’852 patent are invalid as indefinite under 35 U.S.C. § 112. A claim is indefinite if it fails to “inform those skilled in the art about the scope of the invention with reasonable certainty.” *Nautilus, Inc*., 134 S. Ct. at 2129. “[T]he claims, when read in light of the specification and the prosecution history, must provide *objective* boundaries.” *Interval Licensing LLC v. AOL, Inc*., 766 F.3d 1364, 1371 (Fed. Cir. 2014) (emphasis added).

All claims cover a method of treating episodes of increased seizure activity that are “distinguishable from other seizures” suffered by the patient. The scope of the claims that includes this language cannot be reasonably determined by a POSA because the term “distinguishable” includes necessarily subjective elements. There are multiple types of seizures and some types, as

the specification states, are preceded by "auras" that are "unique" to each individual patient. *See* '061 patent at 18:32-47; '852 patent at 18:23-26. Moreover, the remainder of the specification, the claims, and the file history do not shed any further light on just how to "distinguish" each type of unique seizure experienced by a patient.

Thus, all claims of the '061 and '852 patents, read in light of the specification of the patents and the prosecution histories, fail to inform with reasonable certainty those skilled in the art the scope of the claimed invention. Therefore, the claims are indefinite. *Nautilus*, 134 S. Ct. at 2124.

M. The Claims of the '852 and '061 Patents Are Invalid under 35 U.S.C. § 112 for Lack of Enablement

To the extent the claims of the '852 and '061 patents are not invalid as obvious, which they are, they are invalid for non-enablement as discussed below. Each claim of the '852 and '061 patents requires "an increase in the interval between a current seizure and a next seizure." *See, e.g.*, '852 patent at claim 1, 6, 10, and 14; '061 patent at claim 1, 5, 21, 33, 43, and 53. By the plain text, the claims cover an infinite amount of intervals between one seizure and the next – as examples: 1 day, 1 week, 1 year, 1 decade, etc. Indeed, if a patient experiences a seizure on day 1, is administered the claimed formulation(s), and then does not experience another seizure for decades, then that would be covered by the claims of the '852 and '061 patents. This is precisely the type of "open-ended" claim language found invalid for lack of enablement in *MagSil Corp. v. Hitachi Glob. Storage Techs., Inc.*, 687 F.3d 1377 (Fed. Cir. 2012).

The specifications of the '852 and '061 patents fail to enable the full scope of the claims. As discussed, the exceptionally broad language covers seizure intervals up through the potential lifespan of a patient. The extent of this "interval" is not at all addressed – or even mentioned – in the specification of the patent. Indeed, such "efficacy" may even approach a "cure" for seizures,

something that does not exist today much less at the time of the invention. As such, the full scope of the claims is not enabled without undue experimentation. *See id.* at 1381-82.

Given the dependent claims all depend from the independent claims and each requires "an increase in the interval between a current seizure and a next seizure," each of the claims of the '852 and '061 patents are invalid for lack of enablement.

VII. PRODUCTION OF PRIOR ART

To the extent not already produced, Defendants will produce herewith prior art documents on which they intend to rely to prove the invalidity of the Asserted Patents. Defendants expressly reserve the right to rely on additional documents in furtherance of establishing the invalidity of the Asserted Patents, and to the extent not previously produced, will timely produce such documents to Neurelis.

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that on May 8, 2026, a copy of the foregoing document was served on the counsel listed below in the manner indicated:

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Exhibits A-E

Exhibit A: Invalidity of U.S. Patent No. 12,268,664

WIPO Publication No. WO 2009/120933 to Gwozdz et al. (hereinafter "Gwozdz") is titled "Pharmaceutical Solutions and Method for Solubilizing Therapeutic Agents," and was published October 1, 2009. Gwozdz claims priority to U.S. Prov. App. No. 61/040,281 ("the '281 provisional"), filed March 28, 2008. All of the teachings and disclosure provided herein are supported in the specification of the '281 Provisional. Based on the filing date of the '281 Provisional, Gwozdz constitutes prior art under § 102(e)(1).

U.S. Patent Application Publication No. 2008/0279784 to Cartt et al. (hereinafter "Cartt 2008") is titled "Nasal Administration of Benzodiazepines," was published on November 13, 2008, and constitutes prior art under § 102(a) and/or § 102(e)(1).

U.S. Pat. 6,193,985 to Sonne (hereinafter "Sonne") is titled "Tocopherol Composition for Delivery of Biologically Active Agents," is dated February 27, 2001, and constitutes prior art under § 102(b).

U.S. Patent Application Publication No. 2008/0070904 to Jamieson et al. (hereinafter "Jamieson") is titled "Pharmaceutical Compositions of Benzodiazepines and Method of Use thereof," was published on March 20, 2008, and constitutes prior art under at least § 102(a).

Li et al., *Rapid-onset intranasal delivery of anticonvulsants: pharmacokinetic and pharmacodynamic evaluation in rabbits*, INTERNATIONAL JOURNAL OF PHARMACEUTICS 199:65-76 (2000) (hereinafter "Li") published in 2000 and constitutes prior art under § 102(b).

U.S. Patent Application Publication No. 2006/0046962 to Meezan et al. (hereinafter "Meezan") is titled "Absorption Enhancers for Drug Administration," and was published on March 2, 2006, and constitutes prior art under § 102(b).

U.S. Patent Application Publication No. 2004/0176359 to Wermeling (hereinafter "Wermeling V") is titled "Intranasal Benzodiazepine Compositions," and was published on September 9, 2004, and constitutes prior art under § 102(b).

USP 23/NF 18, Ed., "United States Pharmacopeia. The National Formulary," The United States Pharmacopoeial Convention Inc., Rockville (hereinafter "USP") was published in 1995, and constitutes prior art under § 102(b).

The "Florida EMS Manual" was published in 2005 and constitutes prior art under § 102(b).

Physician's Desk Reference (hereinafter "PDR") was published in 2000 and constitutes prior art under § 102(b).

U.S. Patent Application Publication No. 2007/0208011 to Cloyd et al. (hereinafter "Cloyd") was published on September 6, 2007, and constitutes prior art under § 102(b).

The Pharmacopeial Forum Jan.-Feb. 2004, 30(1) (hereinafter "Pharmacopeial Forum for Diazepam") was published in January-February 2004 and constitutes prior art under § 102(b).

Exhibit A: Invalidity of U.S. Patent No. 12,268,664

As set forth in the chart below, all elements of the claims of the '664 patent are disclosed, taught, suggested, and rendered obvious by the following combinations of prior art: (i) Gwozdz in view of Meezan; (ii) Gwozdz in view of Meezan and Cartt 2008; (iii) Sonne in view of Meezan, optionally further in view of Cartt 2008, Cloyd, Florida EMS Manual, and/or USP; (iv) Li in view of Sonne and Meezan, optionally further in view of Cartt 2008, Florida EMS Manual, and/or USP; (v) Sonne in view of Jamieson, Li, Meezan, and/or Wermeling V; and (v) Gwozdz, Meezan, and Cartt 2008, in view of Pharmacopeial Forum for Diazepam.

The excerpts cited herein are exemplary. For any claim limitation, Defendants may rely on excerpts cited for any other limitation or additional excerpts not set forth fully herein to the extent necessary to provide a more comprehensive explanation for a reference's disclosure of a limitation. Where an excerpt refers to or discusses a figure or figure items, that figure and any additional descriptions of that figure should be understood to be incorporated by reference as if set forth fully therein. As set forth in the Preliminary Invalidity Contentions (incorporated herein in their entirety), to which this exhibit has been attached, a POSA at the time would have been motivated to combine the teachings of any groupings of the foregoing prior art references with his knowledge of the art. Such combinations would provide a reasonable expectation of success to arrive at the claimed invention(s), and thus each claim of this patent is invalid.

Claim Language	Exemplary Prior Art Citations
1. A pharmaceutical composition for intranasal administration comprising:	Gwozdz discloses pharmaceutical solutions that "are particularly useful in formulations to be administered to mucosal membranes, i.e. the nasal mucosa or lungs of a subject by any suitable means." Gwozdz at 9:19-22. Sonne discloses that "[t]he present invention provides the use of a tocopherol or a derivative thereof as a solvent and/or emulsifier for substantially insoluble and sparingly soluble biologically active agents, especially in the manufacture of pharmaceutical compositions. Such compositions are particularly suitable for transmucosal, and especially intranasal… administration…" Sonne at Abstract. Sonne further discloses that "[t]ransmucosal delivery is preferred however, and compositions according to the invention may be administered to mucosal membranes… [n]asal, rectal and oral cavity administrations are particularly preferred." *Id*. at 3:54-59.

Claim Language	Exemplary Prior Art Citations
	Li discloses experiments using intranasal delivery of anticonvulsants such as diazepam. *See* Li at Abstract, 67. Jamieson discloses benzodiazepine pharmaceutical formulations for transmucosal administration and, more specifically, for intranasal administration comprising multiple solvents. *See, e.g.*, Jamieson at [Claim 1], [Claim 13], [Claim 34]. Meezan discloses "a method of increasing absorption of a low molecular weight compound into the circulatory system of a subject by administering the compound via the... nasal,... delivery route..." Meezan at ¶ [0008]. Meezan also discloses that "[a] 'therapeutic composition'... can be compounded... with the usual non-toxic, pharmaceutically acceptable carriers for... solutions,... The carriers,... can include... other carriers suitable for use in manufacturing preparations, in solid, semisolid, or liquid form." *Id*. at ¶ [0049]. Wermeling V discloses pharmaceutical compositions for intranasal administration of effective amounts of benzodiazepines and specifically highlights the use of diazepam. Wermeling V at Abstract, ¶ [0026]. Wermeling V further discloses that the "principal advantages of intranasal route are non-invasive delivery, rapid drug absorption, and convenience." *Id*. at ¶ [0008] Cartt 2008 discloses nasal formulations for the administration of benzodiazepine drug compounds, including diazepam. Cartt 2008 at ¶ [0028].
about 1 to about 20 mg of diazepam	Gwozdz discloses that "[e]xemplary hydrophobic or lipophilic therapeutic agents which can be solubilized in accordance with

Claim Language	Exemplary Prior Art Citations
	the present invention include, but are in no way limited to,… benzodiazepenes such as Diazepam,…" Gwozdz at 8:6-18. Gwozdz also discloses that "…the solubility of Diazepam at room temperature is less than or equal to 6.67% in 190 proof ethanol. However, combining tocopherol and ethanol has been found to provide solubility of the Diazepam approaching the 10% level. By way of illustration, at 70% tocopherol:30% ethanol (200 proof), Diazepam is soluble to greater than or equal to 8% and at 95% tocopherol:5% ethanol (200 proof), Diazepam is soluble at greater than or equal to 9%." *Id*. at 7:12-19. Sonne discloses that diazepam was one preferred drug compound, with low water solubility, that could be developed in the tocopherol-based formulations, including exemplary solution formulations. *See* Sonne at 7:32 to 8:10 (Example 1, diazepam "nosedrop"); 8:11-27 (Example 1, diazepam nosedrop); and 11:1-13 (Example 11, solution containing diazepam and approximately 40% alpha-tocopherol, e.g. as a nosedrop). Sonne also discloses the intranasal administration of 2 mg, 2.5 mg, and 10 mg of diazepam. *See* Sonne at Fig. 1; Examples 1, 22, and 23; 7:32-58; 13:56 to 14:13; and 14:63-67. Sonne further discloses that "[t]he active substance may be present in an amount of from about 0.0001% to 50% of the total composition, preferably 0.001% to 40% (w/w)." Sonne at 5:52-54; *see also* Examples 1-3, 7-10, 19, 22-23. Li discloses experiments using intranasal delivery of anticonvulsants such as diazepam. *See* Li at Abstract, 67. Li further discloses 20 mg of diazepam dissolved in 1 ml of the carrier and that the

Claim Language	Exemplary Prior Art Citations
	resulting intranasal solutions provided a diazepam concentration of 20 mg/ml. *Id*. at 67, 70 (Table 1, reporting the 2% diazepam solution). Jamieson discloses compositions that include a therapeutically effective amount of a benzodiazepine, including specifically diazepam. *See, e.g.*, Jamieson at [Claim 8], [Claim 17]. [Claim 40]. Jamieson also discloses intranasal diazepam formulations where the amount is "typically present at a weight percent of between about 0.1% to about 20% and often between 0.1% and 10% often 0.25% to 6%." *Id*. at ¶ [0102]. Jamieson further discloses "[a] therapeutically effective amount of diazepam in the compositions of the present invention may be, for example between about 1.0 mg and about 40.0 mg per unit dose, more preferably between about 2.0 mg and about 10.0 mg per unit dose." *Id*. at ¶ [0118]. Jamieson also discloses that "[t]ypical unit doses delivered by these spray devices for intranasal delivery are between about 50 uL to about 300 uL, often 25 uL to about 150 uL, preferably a volume of about 100 uL…" *Id*. at ¶ [0127]. Cloyd discloses solution formulations containing "at least about 10 mg/ml of the benzodiazepine" where "the intranasal volume delivered to an individual in need of a benzodiazepine is… between about 50 µl to about 150 µl per nostril." Cloyd at ¶¶ [0055]-[0056]. Wermeling V discloses pharmaceutical compositions for intranasal administration of effective amounts of benzodiazepines and

Claim Language	Exemplary Prior Art Citations
	specifically highlights the use of diazepam. Wermeling V at Abstract, ¶ [0026]. Cartt 2008 discloses exemplary doses of diazepam to be delivered to patients per dose via nasal administration: "The dosage of Diazepam may vary by indication, however it is expected that a therapeutic dose will be in the range of about 1 to about 20, preferably about 2 to about 10 mg per dose…." Cartt 2008 at ¶ [0063].
dissolved in about 45% to about 85% (w/w) of one or more natural or synthetic tocopherols or tocotrienols selected from the group consisting of: α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, α-tocotrienol, β-tocotrienol, γ-tocotrienol, δ-tocotrienol, tocophersolan, any esters thereof and any combinations thereof,	Gwozdz discloses that "[t]ocopherols and/or tocotrienols for use in accordance with the present invention include a family of natural and synthetic compounds, also known by the generic names tocols or vitamin E. Alpha-tocopherol is the most abundant and active form of this family of compounds… Other members of this family include beta-, gamma-, and delta-tocopherol, alpha-, beta-, gamma-, and delta-tocotrienols, tocopsoralen, alpha-tocopherol derivatives and/or analogs such as tocopherol acetate, phosphate, succinate, nicotinate and linoleate, as well as isomers thereof and esters thereof … In one embodiment of the present invention the tocopherol(s) and/or tocotrienol(s) employed is alpha-tocopherol." Gwozdz at 5:26-6:15. Gwozdz also discloses that "[i]n accordance with the present invention, solutions of one or more tocopherols and/or tocotrienols and one or more alcohols and/or glycols are used in the solubilization of hydrophobic or lipophilic therapeutic agents thereby providing increased bioavailability of the therapeutic agent." *Id*. at 7:3-8. Gwozdz further discloses that "…preferred for some embodiments is that alpha-tocopherol and ethanol constitute 60% to 99% and 1% to 40%, respectively, of the pharmaceutical solution. In other embodiments, the alpha-tocopherol and ethanol constitute

Claim Language	Exemplary Prior Art Citations
	approximately 70% to 90% and 10% to 30%, respectively, of the pharmaceutical solution. In still other embodiments, the tocopherol and ethanol are used at ratios of approximately 95:5, 90:10, 85:15, 80-20, 75:25, 70:30, 65:35, or 60:40, respectively." *Id*. at 7:20-28. Gwozdz also discloses that "[p]harmaceutical solutions of the present invention can be produced by dissolving any difficult to solubilize therapeutic agent (i.e., hydrophobic or lipophilic therapeutic agents) in one or more tocopherols and/or tocotrienols and one or more alcohols and/or glycols as pharmaceutically acceptable solvents." *Id*. at 7:29-34. Sonne discloses that "[t]he present invention is based on the surprising observation that tocopherols and derivatives thereof are excellent solvents for drugs which are substantially insoluble or sparingly soluble in water, whilst at the same time having a very low irritative potential for mucosal tissues." Sonne at 2:54-58. Sonne also discloses that "[i]n one aspect, the present invention thus provides the use of a tocopherol or a derivative thereof as a solvent and/or emulsifier for substantially insoluble and sparingly soluble biologically active agents, especially in the manufacture of pharmaceutical compositions." *Id*. at 2:63-67. Sonne further discloses that diazepam was one preferred drug compound, with low water solubility, that could be developed in the tocopherol-based formulations, including exemplary solution formulations. *See id*. at 7:32 to 8:10 (Example 1, diazepam "nosedrop"); 8:11-27 (Example 1, diazepam nosedrop); and 11:1-13 (Example 11, solution containing diazepam and approximately 40% alpha-tocopherol, e.g. as a nosedrop).

Claim Language	Exemplary Prior Art Citations
	Sonne also discloses formulations containing "1 to 95% (w/w) of the tocopherol or derivative thereof, preferably 20 to 95% (w/w), most preferably 35 to 80% (w/w)." *Id*. at 5:58-61. Sonne further discloses at least one exemplary solution formulation containing 10 g of α-tocopherol in a total solution weight of 25 g, equating to an α-tocopherol concentration of 40% w/w. *Id*. at 11:1-13 (Example 11). Sonne also discloses that: "Generally Speaking compositions of the invention may contain from 1 to 99.99% (w/w), preferably 20 to 99.99%, most preferably 40 to 99.99% (w/w) of the tocopherol or tocopherol derivative Solvent." *Id*. at 5:55-58. Jamieson discloses benzodiazepine compositions that include tocopherols. *See, e.g.*, Jamieson at [Claim 24], [Claim 49]. *See also id.* at ¶ [0209] ("Addition of an anti-oxidant to the formulations of the present invention used for intranasal delivery of benzodiazepines may provide desirable protective benefits to such formulations. Examples include, but are not limited to, tocopherol and derivatives thereof…"). USP discloses that vitamin E was well-known in the art at the time: "Vitamin E is a form of alpha tocopherol ($C_{29}H_{50}O_2$). It includes the following d- or dl-alpha tocopherol ($C_{29}H_{50}O_2$); d- or dl-alpha tocopheryl acetate ($C_{31}H_{52}O_3$); d- or dl-alpha tocopheryl acid succinate ($C_{33}H_{54}O_5$)." USP at 1631.
and about 25% to about 40% (w/w) of one or more alcohols selected from the group consisting of ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, and any combinations thereof,	Gwozdz discloses that "[i]n accordance with the present invention, solutions of one or more tocopherols and/or tocotrienols and one or more alcohols and/or glycols are used in the solubilization of hydrophobic or lipophilic therapeutic agents thereby providing increased

Claim Language	Exemplary Prior Art Citations
	bioavailability of the therapeutic agent." Gwozdz at 7:3-8. Gwozdz also discloses that "[e]xamples of alcohol(s) for use in the present invention include, but are not limited to ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, and any isomers thereof, and any combinations thereof." *Id*. at 6:16-19. Gwozdz further discloses that "[i]n some embodiments, the tocopherol(s) and/or tocotrienol(s) is in an amount from about 30% to about 99% (w/w) and the alcohol (s) and/or glycol (s) is in an amount from about 1% to about 70% (w/w)." *Id*. at 4:17-21. Gwozdz also discloses that "[p]harmaceutical solutions of the present invention can be produced by dissolving any difficult to solubilize therapeutic agent (i.e., hydrophobic or lipophilic therapeutic agents) in one or more tocopherols and/or tocotrienols and one or more alcohols and/or glycols as pharmaceutically acceptable solvents." *Id*. at 7:29-34. Li discloses use of ethanol in diazepam intranasal delivery systems at about 20%-60% concentrations. Li at 71-72 ("The peak DZ plasma concentration, observed within 2–3 min after [intranasal] administration, increased significantly with increasing EtOH concentrations in the IN formulations (20–60%)…"). Sonne discloses that "[t]he formulations according to the invention may be optimized with respect to bioadhesion, sprayability and viscosity, as desired" by incorporating "co-solvents" like "alcohols such as ethanol … or benzyl alcohol." Sonne at 6:47-53.

Claim Language	Exemplary Prior Art Citations
	Sonne also discloses that "[v]iscosity can be reduced by addition of co-solvents such as ethanol…" *Id*. at 3:60-67. Sonne further discloses a solution of diazepam, incorporated 55% w/w of a co-solvent, namely triacetin (13.75 g of triacetin within a total solution weight of 25 g). *Id*. at 11:1-13 (Example 11). Jamieson discloses benzodiazepine formulations containing 20% ethanol. *See* Jamieson at Table 12A. Wermeling V discloses that "[s]uitable preservatives for use in some embodiments include, but is not limited to, …benzyl alcohol… Typically, the preservative is added to the composition quantities of from about 0.01% to about 0.5% by weight." Wermeling V at ¶ [0033].
and about 0.01% to about 1% (w/v) of dodecyl β-D-maltoside,	Meezan discloses that "[a]lkyl glycosides of the present invention can include, but are not limited to: alkyl glycosides, such as octyl-, nonyl-, decyl-, undecyl-, dodecyl-, tridecyl-, tetradecyl-, pentadecyl-, hexadecyl-, heptadecyl-, and octadecyl-α- or β-D-maltoside,…" Meezan at ¶ [0056]. * * * "Similarly, some preferred glycosides include maltose, sucrose, and glucose linked by glycosidic linkage to an alkyl chain of 9, 10, 12, 13, 14, 16, 18, 20, 22, or 24 carbon atoms, e.g., nonyl-, decyl-, dodecyl- and tetradecyl sucroside, glucoside, and maltoside, etc. These compositions are nontoxic, since they are degraded to an alcohol and an oligosaccharide, and amphipathic." *Id*. at ¶ [0058]. *See also id*. at ¶ [0061]. Meezan also discloses adding alkyl glycosides to formulations in amounts of "about 0.01-20%, preferably about 0.01-5%, more preferably about 0.01-2%, even more

Claim Language	Exemplary Prior Art Citations
	preferably 0.01-1%, and most preferably 0.01-0.125% by weight" while testing the effects of dodecyl maltoside as an absorption enhancer in amounts of 0.125%, 0.25%, 0.375%, and 0.50%. *Id*. at ¶ [0070]. Meezan also discloses that alkyl glycosides will increase the bioavailability of small molecules, and identifies molecules having molecular weight below 1.5 k Daltons as candidates for improved bioavailability. *Id*. at ¶ [0130]. Meezan further discloses alkylmaltosides, including dodecyl-beta-D-maltoside as a preferred alkyl glycoside compound. *Id*. at ¶¶ [0092], [0156] ("[A]t least two alkylmaltosides [including dodecyl-beta-D-maltoside] are effective in achieving sufficient absorption" of the drug substance studied), Table 1. Meezan specifically discloses compositions having an alkyl glycoside (such as dodecyl-beta-D-maltoside) in an amount of about 0.25%. *See, e.g., id*. at ¶¶ [0150]-[0151]. *See also id.* at Fig. 1, ¶¶ [0158]-[0159], Table I, and Example 6. Jamieson discloses the use of penetration enhancers in diazepam for intranasal spray formulations. *See* Jamieson at ¶ [0104] ("pharmaceutical compositions comprising the benzodiazepine (e.g., clonazepam, diazepam or lorazepam) of the present invention, for example, for intranasal administration… may further comprise one or more components including… mucosa penetration enhancing agent"), ¶ [0105] ("In preferred embodiments of the present invention, the pharmaceutical compositions… are formulation to be sprayable."). Cartt 2008 discloses that its benzodiazepine formulations may contain various excipients

Claim Language	Exemplary Prior Art Citations
	including "n-dodecyl β-D-maltoside." *See, e.g.*, Cartt 2008 at ¶¶ [0128]-[0129], [0168], [0183]. A POSA would have expected surfactants, such as alkyl glycosides to increase the bioavailability of intranasal formulations. *See e.g.* Sharma at 500-01, Ahsan at 27.
wherein the pharmaceutical composition is a solution and contains less than 1% water,	Gwozdz discloses that "[t]he present invention is directed to the use of one or more tocopherols and/or tocotrienols and one or more alcohols and/or glycols as pharmaceutically acceptable solvents for solubilizing therapeutic agents, in particular hydrophobic or lipophilic therapeutic agents." Gwozdz at 4:29-33. Gwozdz does not discuss or teach the inclusion of water as an additional component of its pharmaceutical solutions. Gwozdz also discloses that "[i]n accordance with the present invention, solutions of one or more tocopherols and/or tocotrienols and one or more alcohols and/or glycols are used in the solubilization of hydrophobic or lipophilic therapeutic agents thereby providing increased bioavailability of the therapeutic agent." *Id*. at 7:3-8. Gwozdz further discloses that "many therapeutic agents are so slightly soluble in water that a therapeutically effective amount cannot be dissolved in a volume of aqueous solvent that is amenable to application to a mucosal membrane. Use of a pharmaceutical solution of the present invention, however, provides for improved ability to dissolve lipophilic and lipophilic therapeutic agents, thus providing a useful delivery system for administration of such agents to one or more mucosal membranes, including the nasal mucosal membranes." *Id*. at 9:25-34; *see also id*. at 4:29-33.

Claim Language	Exemplary Prior Art Citations
	Sonne discloses that diazepam was one preferred drug compound, with low water solubility, that could be developed in the tocopherol-based formulations, including exemplary solution formulations. *See* Sonne at 7:32 to 8:10 (Example 1, diazepam "nosedrop"); 8:11-27 (Example 1, diazepam nosedrop); and 11:1-13 (Example 11, solution containing diazepam and approximately 40% alpha-tocopherol, e.g. as a nosedrop). Sonne also discloses that "[t]he compositions of the invention may be used directly as solutions of the bioactive agent in the tocopherol solvent." *Id*. at 3:60-61. Li discloses intranasal diazepam solutions, stating that that "[f]or [intranasal] application, the test formulations were prepared in 30% EtOH—60% PG—10% water, plus or minus 1% SGC. All the nasal formulations were prepared just prior to the experiment by dissolving [diazepam] (20 mg), CZ (4.2 mg), or MCA (100 mg) in 1 ml of the aforementioned vehicles." Li at 67. *See also id.* at 70 (Table 1, reporting the 2% diazepam solution). A POSA would have understood at the time that it would be desirable to make a solution formulation of diazepam that does not contain water but, instead, utilizes a non-aqueous solvent system to overcome diazepam's known solubility challenges. *See e.g.* '664 patent at 1:52-56 ("Current formulations of benzodiazepine drugs can be administered orally, rectally, or parenterally. The ability to utilize these and other types of formulations has been significantly limited due, in many cases, to solubility challenges."). In view of Meezan, a POSA would have known to make the claimed intranasal diazepam formulation as a non-aqueous solution: "Meezan '962 is not limited to water

Claim Language	Exemplary Prior Art Citations
	soluble therapeutic drugs and discloses using alkyl glycosides in aqueous or non-aqueous systems." IPR2019-00451, Paper 44 at 45-46.
wherein the pharmaceutical composition is in a pharmaceutically-acceptable spray formulation.	Gwozdz discloses that its "solutions can be administered via, for example, a metered dose inhaler or nebulizer, or in a mist sprayer" "for administration" "to one or more mucosal membranes, including the nasal mucosal membranes." Gwozdz at 9:28-10:2. Cartt 2008 discloses nasal formulations of diazepam and that "[n]asal preparations are generally administered in metered sprays…" Cartt 2008 at ¶ [0007]. Cartt 2008 specifically discloses that "[a]s a nasal formulation, diazepam may be administered in 25 to 250 µl metered sprays. In some preferred embodiments, diazepam is administered in 50 to 150 µl, especially about 100 µl, metered sprays. In some embodiments, a first metered spray is applied to a first nostril and if necessary a second metered spray is applied to a second nostril." *Id*. at ¶ [0064]. Sonne discloses that "[t]he compositions of the invention may take any of the conventional pharmaceutical forms known in the art, and may be formulated in conventional manner, optionally with one or more pharmaceutically acceptable carriers or excipients. Thus for example the compositions may take the form of… sprays,…" Sonne at 6:29-35. "The formulations according to the invention may be optimized with respect to bioadhesion, sprayability and viscosity, as desired." *Id.* at 6:36-49; *see also id*. at 3:58-59, 6:34-35. Li discloses that, for intranasal administration, "100 µl of the IN formulations [was administered] into each nostril within 5 s by means of a Pfeiffer spray device." Li at 67.

Claim Language	Exemplary Prior Art Citations
	Jamieson discloses the use of penetration enhancers in diazepam for intranasal spray formulations. Jamieson at ¶ [0104] ("pharmaceutical compositions comprising the benzodiazepine (e.g., clonazepam, diazepam or lorazepam) of the present invention, for example, for intranasal administration… may further comprise one or more components including… mucosa penetration enhancing agent"), ¶ [0105] ("In preferred embodiments of the present invention, the pharmaceutical compositions… are formulation to be sprayable.")..
2. The pharmaceutical composition of claim 1, wherein the one or more natural or synthetic tocopherols or tocotrienols is α-tocopherol.	*See* claim 1. Gwozdz discloses that "[i]n one embodiment of the present invention the tocopherol(s) and/or tocotrienol(s) employed is alpha-tocopherol." Gwozdz at 5:26-6:15. *See also id*. at 7:20-28 (providing alpha-tocopheral solution ratios). Sonne discloses that "α-Tocopherol… is the most active and widely distributed in nature, and has been the most widely studied. Other members of the class include beta, gamma, and delta tocopherols…" Sonne at 3:7-12. *See also id.* at Examples 3, 7-10, 17-19, 22-23. Sonne also discloses that diazepam was shown to have a solubility of 12% w/w in 100 grams of α-tocopherol. *Id*. at 9:35-60 (Table 1). Sonne further discloses at least one exemplary solution formulation containing 10 g of α-tocopherol in a total solution weight of 25 g, equating to an α-tocopherol concentration of 40% w/w. *Id*. at 11:1-13 (Example 11).
3. The pharmaceutical composition of claim 1, wherein the therapeutically effective amount of the diazepam is present in the	*See* claim 1.

Claim Language	Exemplary Prior Art Citations
pharmaceutical solution at a concentration of about 10 mg/mL to about 250 mg/mL.	
4. The pharmaceutical composition of claim 1, wherein the diazepam is present in the pharmaceutical solution at a concentration of about 20 mg/mL to about 50 mg/mL.	*See* claim 1.
5. The pharmaceutical composition of claim 1, wherein the diazepam is about 2 mg to about 10 mg.	*See* claim 1.
6. The pharmaceutical composition of claim 1, wherein the pharmaceutical solution comprises one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof in an amount from about 60% to about 75% (w/w).	*See* claim 1.
7. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition further comprises at least one additional ingredient selected from the group consisting of stabilizers, coloring agents, pH adjusters, buffering agents, preservatives, wetting agents, flavoring agents and combinations thereof.	*See* claim 1. Sonne discloses that "[t]he compositions of the invention may take any of the conventional pharmaceutical forms known in the art, and may be formulated in conventional manner, optionally with one or more pharmaceutically acceptable carriers or excipients. Thus for example the compositions may take the form of… sprays,…" Sonne at 6:29-35. "The formulations according to the invention may be optimized with respect to bioadhesion, sprayability and viscosity, as desired." *Id.* at 6:36-49. Sonne also discloses the use of excipients in such compositions: "To ensure that the formulations have a reasonable shelf-life it may be desirable to include preservatives Such as benzalkonium chloride, Sodium edetate, Sorbic acid, potassium Sorbate, phenoxyethanol, phenetanol, parabens or others known in the art. Addition of odour- or taste-masking compounds can also be desirable." *Id*. at 7:4-9; *see also id*. at claim 10.

Claim Language	Exemplary Prior Art Citations
	Meezan discloses a range of excipients including "…a Surfactant, emollient, lubricant, Stabilizer, dye, perfume, preservative, acid or base for adjustment of pH, a Solvent, emulsifier, gelling agent, moisturizer, Stabilizer, wetting agent, time release agent, humectant, or other component…" among others. Meezan at ¶ [0074]. Li discloses intranasal formulations that include propylene glycol and ethanol, as well as sodium glycocholate as it was "known to enhance intranasal absorption while producing minimal irritation and morphological alteration in the nasal mucosa." Li at 70-71. Jamieson discloses the use of penetration enhancers in diazepam for intranasal spray formulations. Jamieson at ¶ [0104] ("pharmaceutical compositions comprising the benzodiazepine (e.g., …diazepam…) of the present invention, for example, for intranasal administration… may further comprise one or more components including… mucosa penetration enhancing agent"). Jamieson further discloses that, due to the "highly lipophilic nature of lipophilic nature of the benzodiazepines a combination of surfactants, strong solubilizing solvents, and carrier solutions are often used." *Id*. at ¶ [0142].
8. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition is about 25 μL to about 250 μL.	*See* claim 1. Sonne discloses that the "administration of drugs with very low water solubility to the nose is difficult, because of the limited volume which is acceptable for the nose (about 100 μL)." Sonne at 7:25-28. Cloyd discloses solution formulations containing "at least about 10 mg/ml of the benzodiazepine" where "the intranasal volume

Claim Language	Exemplary Prior Art Citations
	delivered to an individual in need of a benzodiazepine is… between about 50 µl to about 150 µl per nostril." Cloyd at ¶¶ [0055]-[0056]. Li discloses that a "constraint concerning nasal administration is that a small administration volume is required; it is not generally possible to administer more than approximately 150 µl per nostril." Li at 66. Cartt 2008 discloses nasal formulations of diazepam and that "[n]asal preparations are generally administered in metered sprays having volumes of less than 250 µl, preferably less than 150 µl, and ideally from 25 to 100 µl, since administration of larger volumes usually exceeds the capacity of the nasal sinuses and results in volumes in excess of about 250 µl bypassing the sinuses and flowing down the back of the throat where it is swallowed." Cartt 2008 at ¶ [0007]. Cartt 2008 specifically discloses that "[a]s a nasal formulation, diazepam may be administered in 25 to 250 µl metered sprays. In some preferred embodiments, diazepam is administered in 50 to 150 µl, especially about 100 µl, metered sprays. In some embodiments, a first metered spray is applied to a first nostril and if necessary a second metered spray is applied to a second nostril." *Id*. at ¶ [0064]. A POSA at the time would know that commercial nasal spray products typically deliver 100-200 µL (i.e., 0.1-0.2 mL) per spray, as the human nasal cavity can only receive and retain about 100-150 µL of liquid. *See*, *e.g.*, Wermeling, D. et al., "Pharmacokinetics and pharmacodynamics of a new intranasal midazolam formulation in healthy volunteers." Anesth Analg 2006; 103:344-349, 344 (teaching that "[t]he adult nasal cavity can only receive and retain about 100-150 µL of liquid, requiring the dose of

Claim Language	Exemplary Prior Art Citations
	midazolam be solubilized within this volume. A nasal formulation with a concentration of 2.5 mg per 100 μL is necessary to give a single spray per naris.").
9. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition is about 50 μL to about 150 μL.	*See* claims 1 and 8.
10. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition is about 100 μL.	*See* claims 1 and 8.
11. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition contains less than 0.5% water.	*See* claim 1.
12. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition contains less than 0.25% water.	*See* claim 1.
13. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition contains less than 0.1% water.	*See* claim 1.
14. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition contains no water.	*See* claim 1.
15. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition contains no more than 0.01% of a diazepam impurity.	*See* claim 1. The mere recitation of an inherent or latent property of an otherwise obvious formulation will not render the formulation patentable. *In re Kao*, 639 F.3d 1057, 1070 (Fed. Cir. 2011); *Santarus, Inc. v. Par Pharmaceutical, Inc.*, 694 F.3d 1344 (Fed. Cir. 2012). The Pharmacopeial Forum for Diazepam discloses that pharmaceutical compositions should not contain more than 0.01% of diazepam related compound A. A POSA at the time would know that the claimed pharmaceutical composition should maintain impurity levels of diazepam solution—

Claim Language	Exemplary Prior Art Citations
	particularly compound A (NMT 0.01%)—within the limits specified in the Pharmacopeial Forum under various storage conditions in order to meet product standards and obtain regulatory approval.
16. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition contains no more than 0.01% of a diazepam impurity at 25° C. and 60% relative humidity, 30° C. and 65% relative humidity and 40° C. and 75% relative humidity.	*See* claims 1 and 15.
17. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition maintains a similar average spray content at 25° C. and 60% relative humidity, 30° C. and 65% relative humidity and 40° C. and 75% relative humidity each measured at one month, three months and six months.	*See* claims 1 and 15.
18. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition maintains a similar average spray content uniformity at 25° C. and 60% relative humidity and 40° C. and 75% relative humidity.	*See* claims 1 and 15.

Exhibit B: Invalidity of U.S. Patent No. 11,241,414

WIPO Publication No. WO 2009/120933 to Gwozdz et al. (hereinafter "Gwozdz") is titled "Pharmaceutical Solutions and Method for Solubilizing Therapeutic Agents," and was published October 1, 2009. Gwozdz claims priority to U.S. Prov. App. No. 61/040,281 ("the '281 provisional"), filed March 28, 2008. All of the teachings and disclosure provided herein are supported in the specification of the '281 Provisional. Based on the filing date of the '281 Provisional, Gwozdz constitutes prior art under § 102(e)(1).

U.S. Patent Application Publication No. 2008/0279784 to Cartt et al. (hereinafter "Cartt 2008") is titled "Nasal Administration of Benzodiazepines," was published on November 13, 2008, and constitutes prior art under § 102(a) and/or § 102(e)(1).

U.S. Pat. 6,193,985 to Sonne (hereinafter "Sonne") is titled "Tocopherol Composition for Delivery of Biologically Active Agents," is dated February 27, 2001, and constitutes prior art under § 102(b).

U.S. Patent Application Publication No. 2008/0070904 to Jamieson et al. (hereinafter "Jamieson") is titled "Pharmaceutical Compositions of Benzodiazepines and Method of Use thereof," was published on March 20, 2008, and constitutes prior art under at least § 102(a).

Li et al., *Rapid-onset intranasal delivery of anticonvulsants: pharmacokinetic and pharmacodynamic evaluation in rabbits*, INTERNATIONAL JOURNAL OF PHARMACEUTICS 199:65-76 (2000) (hereinafter "Li") published in 2000 and constitutes prior art under § 102(b).

U.S. Patent Application Publication No. 2006/0046962 to Meezan et al. (hereinafter "Meezan") is titled "Absorption Enhancers for Drug Administration," and was published on March 2, 2006, and constitutes prior art under § 102(b).

U.S. Patent Application Publication No. 2004/0176359 to Wermeling (hereinafter "Wermeling V") is titled "Intranasal Benzodiazepine Compositions," and was published on September 9, 2004, and constitutes prior art under § 102(b).

USP 23/NF 18, Ed., "United States Pharmacopeia. The National Formulary," The United States Pharmacopoeial Convention Inc., Rockville (hereinafter "USP") was published in 1995, and constitutes prior art under § 102(b).

The "Florida EMS Manual" was published in 2005 and constitutes prior art under § 102(b).

Physician's Desk Reference (hereinafter "PDR") was published in 2000 and constitutes prior art under § 102(b).

U.S. Patent Application Publication No. 2007/0208011 to Cloyd et al. (hereinafter "Cloyd") was published on September 6, 2007, and constitutes prior art under § 102(b).

As set forth in the chart below, certain elements of the Asserted Claims of the '414 patent are disclosed, taught, suggested, and rendered obvious by the following combinations of prior art: (i) Gwozdz in view of Meezan; (ii) Gwozdz in view of Meezan and Cartt 2008; (iii) Sonne in view

of Meezan, optionally further in view of Cartt 2008, Cloyd, Florida EMS Manual, and/or USP; (iv) Li in view of Sonne and Meezan, optionally further in view of Cartt 2008, Florida EMS Manual, and/or USP; and (v) Sonne in view of Jamieson, Li, Meezan, and/or Wermeling V. The excerpts cited herein are exemplary. For any claim limitation, Defendants may rely on excerpts cited for any other limitation or additional excerpts not set forth fully herein to the extent necessary to provide a more comprehensive explanation for a reference's disclosure of a limitation. Where an excerpt refers to or discusses a figure or figure items, that figure and any additional descriptions of that figure should be understood to be incorporated by reference as if set forth fully therein. As set forth in the Preliminary Invalidity Contentions (incorporated herein in their entirety), to which this exhibit has been attached, a POSA at the time would have been motivated to combine the teachings of any groupings of the foregoing prior art references with his knowledge of the art. Such combinations would provide a reasonable expectation of success to arrive at the claimed invention(s), and thus each claim of this patent is invalid.

Claim Language	Exemplary Prior Art Citations
1. A pharmaceutical solution for nasal administration consisting of:	Gwozdz discloses pharmaceutical solutions that "are particularly useful in formulations to be administered to mucosal membranes, i.e. the nasal mucosa or lungs of a subject by any suitable means." Gwozdz at 9:19-22. Sonne discloses that "[t]he present invention provides the use of a tocopherol or a derivative thereof as a solvent and/or emulsifier for substantially insoluble and sparingly soluble biologically active agents, especially in the manufacture of pharmaceutical compositions. Such compositions are particularly suitable for transmucosal, and especially intranasal… administration…" Sonne at Abstract. Sonne further discloses that "[t]ransmucosal delivery is preferred however, and compositions according to the invention may be administered to mucosal membranes… [n]asal, rectal and oral cavity administrations are particularly preferred." *Id*. at 3:54-59. Li discloses experiments using intranasal delivery of anticonvulsants such as diazepam. *See* Li at Abstract, 67. Jamieson discloses benzodiazepine pharmaceutical formulations for transmucosal administration and, more specifically, for intranasal administration comprising multiple

Claim Language	Exemplary Prior Art Citations
	solvents. *See, e.g.*, Jamieson at [Claim 1], [Claim 13], [Claim 34]. Meezan discloses "a method of increasing absorption of a low molecular weight compound into the circulatory system of a subject by administering the compound via the... nasal,... delivery route..." Meezan at ¶ [0008]. Meezan also discloses that "[a] 'therapeutic composition'... can be compounded... with the usual non-toxic, pharmaceutically acceptable carriers for... solutions,... The carriers,... can include... other carriers suitable for use in manufacturing preparations, in solid, semisolid, or liquid form." *Id*. at ¶ [0049]. Wermeling V discloses pharmaceutical compositions for intranasal administration of effective amounts of benzodiazepines and specifically highlights the use of diazepam. Wermeling V at Abstract, ¶ [0026]. Wermeling V further discloses that the "principal advantages of intranasal route are non-invasive delivery, rapid drug absorption, and convenience." *Id*. at ¶ [0008] Cartt 2008 discloses nasal formulations for the administration of benzodiazepine drug compounds, including diazepam. Cartt 2008 at ¶ [0028].
diazepam or a pharmaceutically acceptable salt thereof;	Gwozdz discloses that "[e]xemplary hydrophobic or lipophilic therapeutic agents which can be solubilized in accordance with the present invention include, but are in no way limited to,… benzodiazepenes such as Diazepam,…" Gwozdz at 8:6-18. Gwozdz also discloses that "…the solubility of Diazepam at room temperature is less than or equal to 6.67% in 190 proof ethanol. However, combining tocopherol and ethanol has been

Claim Language	Exemplary Prior Art Citations
	found to provide solubility of the Diazepam approaching the 10% level. By way of illustration, at 70% tocopherol:30% ethanol (200 proof), Diazepam is soluble to greater than or equal to 8% and at 95% tocopherol:5% ethanol (200 proof), Diazepam is soluble at greater than or equal to 9%." *Id*. at 7:12-19. Sonne discloses that diazepam was one preferred drug compound, with low water solubility, that could be developed in the tocopherol-based formulations, including exemplary solution formulations. *See* Sonne at 7:32 to 8:10 (Example 1, diazepam "nosedrop"); 8:11-27 (Example 1, diazepam nosedrop); and 11:1-13 (Example 11, solution containing diazepam and approximately 40% alpha-tocopherol, e.g. as a nosedrop). Sonne also discloses the intranasal administration of 2 mg, 2.5 mg, and 10 mg of diazepam. *See* Sonne at Fig. 1; Examples 1, 22, and 23; 7:32-58; 13:56 to 14:13; and 14:63-67. Sonne further discloses that "[t]he active substance may be present in an amount of from about 0.0001% to 50% of the total composition, preferably 0.001% to 40% (w/w)." Sonne at 5:52-54. *See also* Examples 1-3, 7-10, 19, 22-23. Li discloses experiments using intranasal delivery of anticonvulsants such as diazepam. *See* Li at Abstract, 67. Li further discloses 20 mg of diazepam dissolved in 1 ml of the carrier and that the resulting intranasal solutions provided a diazepam concentration of 20 mg/ml. *Id*. at 67, 70 (Table 1, reporting the 2% diazepam solution). Jamieson discloses compositions that include a therapeutically effective amount of a benzodiazepine, including specifically

Claim Language	Exemplary Prior Art Citations
	diazepam. *See, e.g.*, Jamieson at [Claim 8], [Claim 17]. [Claim 40]. Jamieson also discloses intranasal diazepam formulations where the amount is "typically present at a weight percent of between about 0.1% to about 20% and often between 0.1% and 10% often 0.25% to 6%." *Id*. at ¶ [0102]. Jamieson further discloses "[a] therapeutically effective amount of diazepam in the compositions of the present invention may be, for example between about 1.0 mg and about 40.0 mg per unit dose, more preferably between about 2.0 mg and about 10.0 mg per unit dose." *Id*. at ¶ [0118]. Jamieson also discloses that "[t]ypical unit doses delivered by these spray devices for intranasal delivery are between about 50 uL to about 300 uL, often 25 uL to about 150 uL, preferably a volume of about 100 uL…" *Id*. at ¶ [0127]. Cloyd discloses solution formulations containing "at least about 10 mg/ml of the benzodiazepine" where "the intranasal volume delivered to an individual in need of a benzodiazepine is… between about 50 µl to about 150 µl per nostril." Cloyd at ¶¶ [0055]-[0056]. Wermeling V discloses pharmaceutical compositions for intranasal administration of effective amounts of benzodiazepines and specifically highlights the use of diazepam. Wermeling V at Abstract, ¶ [0026]. Cartt 2008 discloses exemplary doses of diazepam to be delivered to patients per dose via nasal administration: "The dosage of Diazepam may vary by indication, however it is expected that a therapeutic dose will be in the range of about 1 to about 20, preferably

Claim Language	Exemplary Prior Art Citations
	about 2 to about 10 mg per dose….” Cartt 2008 at ¶ [0063]. Cartt 2008 also discloses that “[i]n some embodiments, the benzodiazepine or pharmaceutically acceptable salt thereof is present in a concentration of from about 0.05 mg/mL up to about 600 mg/mL.” *Id*. at ¶ [0034].
one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from 30% to 95% (w/w);	Gwozdz discloses that “[t]ocopherols and/or tocotrienols for use in accordance with the present invention include a family of natural and synthetic compounds, also known by the generic names tocols or vitamin E. Alpha-tocopherol is the most abundant and active form of this family of compounds… Other members of this family include beta-, gamma-, and delta-tocopherol, alpha-, beta-, gamma-, and delta-tocotrienols, tocopsoralen, alpha-tocopherol derivatives and/or analogs such as tocopherol acetate, phosphate, succinate, nicotinate and linoleate, as well as isomers thereof and esters thereof. …In one embodiment of the present invention the tocopherol(s) and/or tocotrienol(s) employed is alpha-tocopherol.” Gwozdz at 5:26-6:15. *See also id*. at 7:20-28 (providing alpha-tocopheral solution ratios). Gwozdz also discloses that “[i]n accordance with the present invention, solutions of one or more tocopherols and/or tocotrienols and one or more alcohols and/or glycols are used in the solubilization of hydrophobic or lipophilic therapeutic agents thereby providing increased bioavailability of the therapeutic agent.” *Id*. at 7:3-8. Gwozdz further discloses that “…preferred for some embodiments is that alpha-tocopherol and ethanol constitute 60% to 99% and 1% to 40%, respectively, of the pharmaceutical solution. In other embodiments, the alpha-tocopherol and ethanol constitute

Claim Language	Exemplary Prior Art Citations
	approximately 70% to 90% and 10% to 30%, respectively, of the pharmaceutical solution. In still other embodiments, the tocopherol and ethanol are used at ratios of approximately 95:5, 90:10, 85:15, 80-20, 75:25, 70:30, 65:35, or 60:40, respectively." *Id*. at 7:20-28. Gwozdz also discloses that "[p]harmaceutical solutions of the present invention can be produced by dissolving any difficult to solubilize therapeutic agent (i.e., hydrophobic or lipophilic therapeutic agents) in one or more tocopherols and/or tocotrienols and one or more alcohols and/or glycols as pharmaceutically acceptable solvents." *Id*. at 7:29-34. Sonne discloses that "[t]he present invention is based on the surprising observation that tocopherols and derivatives thereof are excellent solvents for drugs which are substantially insoluble or sparingly soluble in water, whilst at the same time having a very low irritative potential for mucosal tissues." *Id*. at 2:54-58. Sonne also discloses that "[i]n one aspect, the present invention thus provides the use of a tocopherol or a derivative thereof as a solvent and/or emulsifier for substantially insoluble and sparingly soluble biologically active agents, especially in the manufacture of pharmaceutical compositions." *Id*. at 2:63-67. Sonne specifically discloses that: "Tocopherols are a range of natural and synthetic compounds, also known by the generic term Vitamin E. α-Tocopherol… is the most active and widely distributed in nature, and has been the most widely studied." Sonne at 3:4-10. Sonne further discloses that diazepam was one preferred drug compound, with low water solubility, that could be developed in the

Claim Language	Exemplary Prior Art Citations
	tocopherol-based formulations, including exemplary solution formulations. *See id*. at 7:32 to 8:10 (Example 1, diazepam "nosedrop"); 8:11-27 (Example 1, diazepam nosedrop); and 11:1-13 (Example 11, solution containing diazepam and approximately 40% alpha-tocopherol, e.g. as a nosedrop). Sonne also discloses formulations containing "1 to 95% (w/w) of the tocopherol or derivative thereof, preferably 20 to 95% (w/w), most preferably 35 to 80% (w/w)." *Id*. at 5:58-61. Sonne further discloses at least one exemplary solution formulation containing 10 g of α-tocopherol in a total solution weight of 25 g, equating to an α-tocopherol concentration of 40% w/w. *Id*. at 11:1-13 (Example 11). Sonne specifically discloses that "α-Tocopherol… is the most active and widely distributed in nature, and has been the most widely studied. Other members of the class include beta, gamma, and delta tocopherols…" Sonne at 3:7-12. *See also id.* at Examples 3, 7-10, 17-19, 22-23. Sonne further discloses that diazepam was shown to have a solubility of 12% w/w in 100 grams of α-tocopherol. *Id*. at 9:35-60 (Table 1). Sonne also discloses that: "Generally Speaking compositions of the invention may contain from 1 to 99.99% (w/w), preferably 20 to 99.99%, most preferably 40 to 99.99% (w/w) of the tocopherol or tocopherol derivative Solvent." *Id*. at 5:55-58. Jamieson discloses benzodiazepine compositions that include tocopherols. *See, e.g.*, Jamieson at [Claim 24], [Claim 49]. *See also id.* at ¶ [0209] ("Addition of an anti-oxidant to the formulations of the present

Claim Language	Exemplary Prior Art Citations
	invention used for intranasal delivery of benzodiazepines may provide desirable protective benefits to such formulations. Examples include, but are not limited to, tocopherol and derivatives thereof…"). USP discloses that vitamin E was well-known in the art at the time: "Vitamin E is a form of alpha tocopherol ($C_{29}H_{50}O_2$). It includes the following d- or dl-alpha tocopherol ($C_{29}H_{50}O_2$); d- or dl-alpha tocopheryl acetate ($C_{31}H_{52}O_3$); d- or dl-alpha tocopheryl acid succinate ($C_{33}H_{54}O_5$)." USP at 1631.
ethanol and benzyl alcohol in a combined amount from 10% to 70% (w/w); and	Gwozdz discloses that "[i]n accordance with the present invention, solutions of one or more tocopherols and/or tocotrienols and one or more alcohols and/or glycols are used in the solubilization of hydrophobic or lipophilic therapeutic agents thereby providing increased bioavailability of the therapeutic agent." Gwozdz at 7:3-8. Gwozdz also discloses that "[e]xamples of alcohol(s) for use in the present invention include, but are not limited to ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, and any isomers thereof, and any combinations thereof." *Id*. at 6:16-19. Gwozdz further discloses that "[i]n some embodiments, the tocopherol(s) and/or tocotrienol(s) is in an amount from about 30% to about 99% (w/w) and the alcohol (s) and/or glycol (s) is in an amount from about 1% to about 70% (w/w)." *Id*. at 4:17-21. Gwozdz also discloses that "[p]harmaceutical solutions of the present invention can be produced by dissolving any difficult to solubilize therapeutic agent (i.e., hydrophobic or lipophilic therapeutic agents) in one or more tocopherols and/or tocotrienols and one or more alcohols and/or glycols as

Claim Language	Exemplary Prior Art Citations
	pharmaceutically acceptable solvents." *Id*. at 7:29-34. Li discloses use of ethanol in diazepam intranasal delivery systems at about 20%-60% concentrations. Li at 71-72 ("The peak DZ plasma concentration, observed within 2–3 min after [intranasal] administration, increased significantly with increasing EtOH concentrations in the IN formulations (20–60%)…"). Sonne discloses that "[t]he formulations according to the invention may be optimized with respect to bioadhesion, sprayability and viscosity, as desired" by incorporating "co-solvents" like "alcohols such as ethanol … or benzyl alcohol." Sonne at 6:47-53. Sonne also discloses that "[v]iscosity can be reduced by addition of co-solvents such as ethanol…" *Id*. at 3:60-67. Sonne further discloses a solution of diazepam, incorporated 55% w/w of a co-solvent, namely triacetin (13.75 g of triacetin within a total solution weight of 25 g). *Id*. at 11:1-13 (Example 11). Jamieson discloses benzodiazepine formulations containing 20% ethanol. *See* Jamieson at Table 12A. Wermeling V discloses that "[s]uitable preservatives for use in some embodiments include, but is not limited to, …benzyl alcohol… Typically, the preservative is added to the composition quantities of from about 0.01% to about 0.5% by weight." Wermeling V at ¶ [0033].
n-dodecyl beta-D-maltoside.	Meezan discloses that "[a]lkyl glycosides of the present invention can include, but are not limited to: alkyl glycosides, such as octyl-, nonyl-, decyl-, undecyl-, dodecyl-, tridecyl-,

Claim Language	Exemplary Prior Art Citations
	tetradecyl-, pentadecyl-, hexadecyl-, heptadecyl-, and octadecyl-α- or β-D-maltoside,…" Meezan at ¶ [0056]. * * * "Similarly, some preferred glycosides include maltose, sucrose, and glucose linked by glycosidic linkage to an alkyl chain of 9, 10, 12, 13, 14, 16, 18, 20, 22, or 24 carbon atoms, e.g., nonyl-, decyl-, dodecyl- and tetradecyl sucroside, glucoside, and maltoside, etc. These compositions are nontoxic, since they are degraded to an alcohol and an oligosaccharide, and amphipathic." *Id*. at ¶ [0058]. *See also id*. at ¶ [0061]. Meezan also discloses adding alkyl glycosides to formulations in amounts of "about 0.01-20%, preferably about 0.01-5%, more preferably about 0.01-2%, even more preferably 0.01-1%, and most preferably 0.01-0.125% by weight" while testing the effects of dodecyl maltoside as an absorption enhancer in amounts of 0.125%, 0.25%, 0.375%, and 0.50%. *Id*. at ¶ [0070]. Meezan also discloses that alkyl glycosides will increase the bioavailability of small molecules, and identifies molecules having molecular weight below 1.5 k Daltons as candidates for improved bioavailability. *Id*. at ¶ [0130]. Meezan further discloses alkylmaltosides, including dodecyl-beta-D-maltoside as a preferred alkyl glycoside compound. *Id*. at ¶¶ [0092], [0156] ("[A]t least two alkylmaltosides [including dodecyl-beta-D-maltoside] are effective in achieving sufficient absorption" of the drug substance studied), Table 1. Meezan specifically discloses compositions having an alkyl glycoside (such as dodecyl-beta-D-maltoside) in an amount of about 0.25%. *See, e.g., id*. at ¶¶ [0150]-[0151]. *See*

Claim Language	Exemplary Prior Art Citations
	also id. at Fig. 1, ¶¶ [0158]-[0159], Table I, and Example 6. Jamieson discloses the use of penetration enhancers in diazepam for intranasal spray formulations. *See* Jamieson at ¶ [0104] ("pharmaceutical compositions comprising the benzodiazepine (e.g., clonazepam, diazepam or lorazepam) of the present invention, for example, for intranasal administration… may further comprise one or more components including… mucosa penetration enhancing agent"), ¶ [0105] ("In preferred embodiments of the present invention, the pharmaceutical compositions… are formulation to be sprayable."). Cartt 2008 discloses that its benzodiazepine formulations may contain various excipients including "n-dodecyl β-D-maltoside." *See, e.g.*, Cartt 2008 at ¶¶ [0128]-[0129], [0168], [0183]. A POSA would have expected surfactants, such as alkyl glycosides to increase the bioavailability of intranasal formulations. *See e.g.* Sharma at 500-01, Ahsan at 27.
2. The pharmaceutical solution of claim 1, wherein the diazepam or pharmaceutically acceptable salt thereof is present in the pharmaceutical solution in a concentration from 1 to 20% (w/v).	*See* claim 1.
3. The pharmaceutical solution of claim 1, wherein the diazepam or pharmaceutically acceptable salt thereof is present in the pharmaceutical solution in a concentration from 10 mg/mL to 250 mg/mL.	*See* claim 1.
4. The pharmaceutical solution of claim 3, wherein the diazepam or pharmaceutically acceptable salt thereof is present in the	*See* claim 3.

Claim Language	Exemplary Prior Art Citations
pharmaceutical solution in a concentration from 20 mg/mL to 50 mg/mL.	
5. The pharmaceutical solution of claim 1, wherein the one or more natural or synthetic tocopherols or tocotrienols are selected from the group consisting of: α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, α-tocotrienol, β-tocotrienol, γ-tocotrienol, δ-tocotrienol, tocophersolan, and any combinations thereof.	*See* claim 1.
6. The pharmaceutical solution of claim 1, wherein the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, is in an amount from 45% to 85% (w/w).	*See* claim 1.
7. The pharmaceutical solution of claim 6, wherein the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, is in an amount from 60% to 75% (w/w).	*See* claim 6.
8. The pharmaceutical solution of claim 1, wherein the ethanol and benzyl alcohol is in a combined amount from 15% to 55% (w/w).	*See* claim 1.
9. The pharmaceutical solution of claim 8, wherein the ethanol and benzyl alcohol is in a combined amount from 25% to 40% (w/w).	*See* claim 8.
10. The pharmaceutical solution of claim 1, wherein the solution consists of diazepam, vitamin E, ethanol, benzyl alcohol, and n-dodecyl beta-D-maltoside.	*See* claim 1.
11. A pharmaceutical solution for nasal administration consisting of:	*See* claim 1.
diazepam or a pharmaceutically acceptable salt thereof;	*See* claim 1.

Claim Language	Exemplary Prior Art Citations
one or more natural or synthetic α-tocopherols, or any combinations thereof, in an amount from 30% to 95% (w/w);	*See* claim 1.
ethanol and benzyl alcohol in a combined amount from 10% to 70% (w/w); and	*See* claim 1.
n-dodecyl beta-D-maltoside.	*See* claim 1.
12. The pharmaceutical solution of claim 11, wherein the diazepam or pharmaceutically acceptable salt thereof is present in the pharmaceutical solution in a concentration from 1 to 20% (w/v).	*See* claims 11 and 2.
13. The pharmaceutical solution of claim 11, wherein the diazepam or pharmaceutically acceptable salt thereof is present in the pharmaceutical solution in a concentration from 10 mg/mL to 250 mg/mL.	*See* claims 11 and 3.
14. The pharmaceutical solution of claim 13, wherein the diazepam or pharmaceutically acceptable salt thereof is present in the pharmaceutical solution in a concentration from 20 mg/mL to 50 mg/mL.	*See* claims 13 and 4.
15. The pharmaceutical solution of claim 11, wherein the one or more natural or synthetic α-tocopherols, or any combinations thereof is in an amount from 45% to 85% (w/w).	*See* claims 11 and 6.
16. The pharmaceutical solution of claim 15, wherein the one or more natural or synthetic α-tocopherols, or any combinations thereof is in an amount from 60% to 75% (w/w).	*See* claims 15 and 7.
17. The pharmaceutical solution of claim 11, wherein the ethanol and benzyl alcohol is in a combined amount from 15% to 55% (w/w).	*See* claims 11 and 8.
18. The pharmaceutical solution of claim 17, wherein the ethanol and benzyl alcohol is in a combined amount from 25% to 40% (w/w).	*See* claims 17 and 9.

Exhibit C: Invalidity of U.S. Patent No. 11,793,786

WIPO Publication No. WO 2009/120933 to Gwozdz et al. (hereinafter "Gwozdz") is titled "Pharmaceutical Solutions and Method for Solubilizing Therapeutic Agents," and was published October 1, 2009. Gwozdz claims priority to U.S. Prov. App. No. 61/040,281 ("the '281 provisional"), filed March 28, 2008. All of the teachings and disclosure provided herein are supported in the specification of the '281 Provisional. Based on the filing date of the '281 Provisional, Gwozdz constitutes prior art under § 102(e)(1).

U.S. Patent Application Publication No. 2008/0279784 to Cartt et al. (hereinafter "Cartt 2008") is titled "Nasal Administration of Benzodiazepines," was published on November 13, 2008, and constitutes prior art under § 102(a) and/or § 102(e)(1).

U.S. Pat. 6,193,985 to Sonne (hereinafter "Sonne") is titled "Tocopherol Composition for Delivery of Biologically Active Agents," is dated February 27, 2001, and constitutes prior art under § 102(b).

U.S. Patent Application Publication No. 2008/0070904 to Jamieson et al. (hereinafter "Jamieson") is titled "Pharmaceutical Compositions of Benzodiazepines and Method of Use thereof," was published on March 20, 2008, and constitutes prior art under at least § 102(a).

Li et al., *Rapid-onset intranasal delivery of anticonvulsants: pharmacokinetic and pharmacodynamic evaluation in rabbits*, INTERNATIONAL JOURNAL OF PHARMACEUTICS 199:65-76 (2000) (hereinafter "Li") published in 2000 and constitutes prior art under § 102(b).

U.S. Patent Application Publication No. 2006/0046962 to Meezan et al. (hereinafter "Meezan") is titled "Absorption Enhancers for Drug Administration," and was published on March 2, 2006, and constitutes prior art under § 102(b).

U.S. Patent Application Publication No. 2004/0176359 to Wermeling (hereinafter "Wermeling V") is titled "Intranasal Benzodiazepine Compositions," and was published on September 9, 2004, and constitutes prior art under § 102(b).

USP 23/NF 18, Ed., "United States Pharmacopeia. The National Formulary," The United States Pharmacopoeial Convention Inc., Rockville (hereinafter "USP") was published in 1995, and constitutes prior art under § 102(b).

The "Florida EMS Manual" was published in 2005 and constitutes prior art under § 102(b).

Physician's Desk Reference (hereinafter "PDR") was published in 2000 and constitutes prior art under § 102(b).

U.S. Patent Application Publication No. 2007/0208011 to Cloyd et al. (hereinafter "Cloyd") was published on September 6, 2007, and constitutes prior art under § 102(b).

As set forth in the chart below, certain elements of the Asserted Claims of the '786 patent are disclosed, taught, suggested, and rendered obvious by the following combinations of prior art: (i) Gwozdz in view of Meezan; (ii) Gwozdz in view of Meezan and Cartt 2008; (iii) Sonne in view

of Meezan, optionally further in view of Cartt 2008, Cloyd, Florida EMS Manual, and/or USP; (iv) Li in view of Sonne and Meezan, optionally further in view of Cartt 2008, Florida EMS Manual, and/or USP; and (v) Sonne in view of Jamieson, Li, Meezan, and/or Wermeling V. The excerpts cited herein are exemplary. For any claim limitation, Defendants may rely on excerpts cited for any other limitation or additional excerpts not set forth fully herein to the extent necessary to provide a more comprehensive explanation for a reference's disclosure of a limitation. Where an excerpt refers to or discusses a figure or figure items, that figure and any additional descriptions of that figure should be understood to be incorporated by reference as if set forth fully therein. As set forth in the Preliminary Invalidity Contentions (incorporated herein in their entirety), to which this exhibit has been attached, a POSA at the time would have been motivated to combine the teachings of any groupings of the foregoing prior art references with his knowledge of the art. Such combinations would provide a reasonable expectation of success to arrive at the claimed invention(s), and thus each claim of this patent is invalid.

Claim Language	Exemplary Prior Art Citations
1. A pharmaceutical solution for nasal administration consisting of:	Gwozdz discloses pharmaceutical solutions that "are particularly useful in formulations to be administered to mucosal membranes, i.e. the nasal mucosa or lungs of a subject by any suitable means." Gwozdz at 9:19-22. Sonne discloses that "[t]he present invention provides the use of a tocopherol or a derivative thereof as a solvent and/or emulsifier for substantially insoluble and sparingly soluble biologically active agents, especially in the manufacture of pharmaceutical compositions. Such compositions are particularly suitable for transmucosal, and especially intranasal… administration…" Sonne at Abstract. Sonne further discloses that "[t]ransmucosal delivery is preferred however, and compositions according to the invention may be administered to mucosal membranes… [n]asal, rectal and oral cavity administrations are particularly preferred." *Id*. at 3:54-59. Li discloses experiments using intranasal delivery of anticonvulsants such as diazepam. *See* Li at Abstract, 67. Jamieson discloses benzodiazepine pharmaceutical formulations for transmucosal administration and, more specifically, for intranasal administration comprising multiple

Claim Language	Exemplary Prior Art Citations
	solvents. *See, e.g.*, Jamieson at [Claim 1], [Claim 13], [Claim 34]. Meezan discloses "a method of increasing absorption of a low molecular weight compound into the circulatory system of a subject by administering the compound via the... nasal,... delivery route..." Meezan at ¶ [0008]. Meezan also discloses that "[a] 'therapeutic composition'... can be compounded... with the usual non-toxic, pharmaceutically acceptable carriers for... solutions,... The carriers,... can include... other carriers suitable for use in manufacturing preparations, in solid, semisolid, or liquid form." *Id*. at ¶ [0049]. Wermeling V discloses pharmaceutical compositions for intranasal administration of effective amounts of benzodiazepines and specifically highlights the use of diazepam. Wermeling V at Abstract, ¶ [0026]. Wermeling V further discloses that the "principal advantages of intranasal route are non-invasive delivery, rapid drug absorption, and convenience." *Id*. at ¶ [0008] Cartt 2008 discloses nasal formulations for the administration of benzodiazepine drug compounds, including diazepam. Cartt 2008 at ¶ [0028].
a therapeutically effective amount of diazepam or a pharmaceutically acceptable salt thereof;	Gwozdz discloses that "[e]xemplary hydrophobic or lipophilic therapeutic agents which can be solubilized in accordance with the present invention include, but are in no way limited to,… benzodiazepenes such as Diazepam,…" Gwozdz at 8:6-18. Gwozdz also discloses that "…the solubility of Diazepam at room temperature is less than or equal to 6.67% in 190 proof ethanol. However, combining tocopherol and ethanol has been

Claim Language	Exemplary Prior Art Citations
	found to provide solubility of the Diazepam approaching the 10% level. By way of illustration, at 70% tocopherol:30% ethanol (200 proof), Diazepam is soluble to greater than or equal to 8% and at 95% tocopherol:5% ethanol (200 proof), Diazepam is soluble at greater than or equal to 9%." *Id*. at 7:12-19. Sonne discloses that diazepam was one preferred drug compound, with low water solubility, that could be developed in the tocopherol-based formulations, including exemplary solution formulations. *See* Sonne at 7:32 to 8:10 (Example 1, diazepam "nosedrop"); 8:11-27 (Example 1, diazepam nosedrop); and 11:1-13 (Example 11, solution containing diazepam and approximately 40% alpha-tocopherol, e.g. as a nosedrop). Sonne also discloses the intranasal administration of 2 mg, 2.5 mg, and 10 mg of diazepam. *See* Sonne at Fig. 1; Examples 1, 22, and 23; 7:32-58; 13:56 to 14:13; and 14:63-67. Sonne further discloses that "[t]he active substance may be present in an amount of from about 0.0001% to 50% of the total composition, preferably 0.001% to 40% (w/w)." Sonne at 5:52-54. *See also* Examples 1-3, 7-10, 19, 22-23. Li discloses experiments using intranasal delivery of anticonvulsants such as diazepam. *See* Li at Abstract, 67. Li further discloses 20 mg of diazepam dissolved in 1 ml of the carrier and that the resulting intranasal solutions provided a diazepam concentration of 20 mg/ml. *Id*. at 67, 70 (Table 1, reporting the 2% diazepam solution). Jamieson discloses compositions that include a therapeutically effective amount of a benzodiazepine, including specifically

Claim Language	Exemplary Prior Art Citations
	diazepam. *See, e.g.*, Jamieson at [Claim 8], [Claim 17]. [Claim 40]. Jamieson also discloses intranasal diazepam formulations where the amount is "typically present at a weight percent of between about 0.1% to about 20% and often between 0.1% and 10% often 0.25% to 6%." *Id*. at ¶ [0102]. Jamieson further discloses "[a] therapeutically effective amount of diazepam in the compositions of the present invention may be, for example between about 1.0 mg and about 40.0 mg per unit dose, more preferably between about 2.0 mg and about 10.0 mg per unit dose." *Id*. at ¶ [0118]. Jamieson also discloses that "[t]ypical unit doses delivered by these spray devices for intranasal delivery are between about 50 uL to about 300 uL, often 25 uL to about 150 uL, preferably a volume of about 100 uL…" *Id*. at ¶ [0127]. Cloyd discloses solution formulations containing "at least about 10 mg/ml of the benzodiazepine" where "the intranasal volume delivered to an individual in need of a benzodiazepine is… between about 50 µl to about 150 µl per nostril." Cloyd at ¶¶ [0055]-[0056]. Wermeling V discloses pharmaceutical compositions for intranasal administration of effective amounts of benzodiazepines and specifically highlights the use of diazepam. Wermeling V at Abstract, ¶ [0026]. Cartt 2008 discloses exemplary doses of diazepam to be delivered to patients per dose via nasal administration: "The dosage of Diazepam may vary by indication, however it is expected that a therapeutic dose will be in the range of about 1 to about 20, preferably

Claim Language	Exemplary Prior Art Citations
	about 2 to about 10 mg per dose….” Cartt 2008 at ¶ [0063]. Cartt 2008 also discloses that “[i]n some embodiments, the benzodiazepine or pharmaceutically acceptable salt thereof is present in a concentration of from about 0.05 mg/mL up to about 600 mg/mL.” *Id*. at ¶ [0034].
one or more natural or synthetic tocopherols or tocotrienols selected from the group consisting of α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, α-tocotrienol, β-tocotrienol, γ-tocotrienol, δ-tocotrienol, tocophersolan, any isomers thereof, any esters thereof, and any combinations thereof, in an amount from 30% to 95% (w/w);	Gwozdz discloses that “[t]ocopherols and/or tocotrienols for use in accordance with the present invention include a family of natural and synthetic compounds, also known by the generic names tocols or vitamin E. Alpha-tocopherol is the most abundant and active form of this family of compounds… Other members of this family include beta-, gamma-, and delta-tocopherol, alpha-, beta-, gamma-, and delta-tocotrienols, tocopsoralen, alpha-tocopherol derivatives and/or analogs such as tocopherol acetate, phosphate, succinate, nicotinate and linoleate, as well as isomers thereof and esters thereof. …In one embodiment of the present invention the tocopherol(s) and/or tocotrienol(s) employed is alpha-tocopherol.” Gwozdz at 5:26-6:15. *See also id*. at 7:20-28 (providing alpha-tocopheral solution ratios). Gwozdz also discloses that “[i]n accordance with the present invention, solutions of one or more tocopherols and/or tocotrienols and one or more alcohols and/or glycols are used in the solubilization of hydrophobic or lipophilic therapeutic agents thereby providing increased bioavailability of the therapeutic agent.” *Id*. at 7:3-8. Gwozdz further discloses that “…preferred for some embodiments is that alpha-tocopherol and ethanol constitute 60% to 99% and 1% to 40%, respectively, of the pharmaceutical solution. In other embodiments, the alpha-tocopherol and ethanol constitute

Claim Language	Exemplary Prior Art Citations
	approximately 70% to 90% and 10% to 30%, respectively, of the pharmaceutical solution. In still other embodiments, the tocopherol and ethanol are used at ratios of approximately 95:5, 90:10, 85:15, 80-20, 75:25, 70:30, 65:35, or 60:40, respectively." *Id*. at 7:20-28. Gwozdz also discloses that "[p]harmaceutical solutions of the present invention can be produced by dissolving any difficult to solubilize therapeutic agent (i.e., hydrophobic or lipophilic therapeutic agents) in one or more tocopherols and/or tocotrienols and one or more alcohols and/or glycols as pharmaceutically acceptable solvents." *Id*. at 7:29-34. Sonne discloses that "[t]he present invention is based on the surprising observation that tocopherols and derivatives thereof are excellent solvents for drugs which are substantially insoluble or sparingly soluble in water, whilst at the same time having a very low irritative potential for mucosal tissues." *Id*. at 2:54-58. Sonne also discloses that "[i]n one aspect, the present invention thus provides the use of a tocopherol or a derivative thereof as a solvent and/or emulsifier for substantially insoluble and sparingly soluble biologically active agents, especially in the manufacture of pharmaceutical compositions." *Id*. at 2:63-67. Sonne specifically discloses that: "Tocopherols are a range of natural and synthetic compounds, also known by the generic term Vitamin E. α-Tocopherol… is the most active and widely distributed in nature, and has been the most widely studied." Sonne at 3:4-10. Sonne further discloses that diazepam was one preferred drug compound, with low water solubility, that could be developed in the

Claim Language	Exemplary Prior Art Citations
	tocopherol-based formulations, including exemplary solution formulations. *See id*. at 7:32 to 8:10 (Example 1, diazepam "nosedrop"); 8:11-27 (Example 1, diazepam nosedrop); and 11:1-13 (Example 11, solution containing diazepam and approximately 40% alpha-tocopherol, e.g. as a nosedrop). Sonne also discloses formulations containing "1 to 95% (w/w) of the tocopherol or derivative thereof, preferably 20 to 95% (w/w), most preferably 35 to 80% (w/w)." *Id*. at 5:58-61. Sonne further discloses at least one exemplary solution formulation containing 10 g of α-tocopherol in a total solution weight of 25 g, equating to an α-tocopherol concentration of 40% w/w. *Id*. at 11:1-13 (Example 11). Sonne specifically discloses that "α-Tocopherol… is the most active and widely distributed in nature, and has been the most widely studied. Other members of the class include beta, gamma, and delta tocopherols…" Sonne at 3:7-12. *See also id.* at Examples 3, 7-10, 17-19, 22-23. Sonne further discloses that diazepam was shown to have a solubility of 12% w/w in 100 grams of α-tocopherol. *Id*. at 9:35-60 (Table 1). Sonne also discloses that: "Generally Speaking compositions of the invention may contain from 1 to 99.99% (w/w), preferably 20 to 99.99%, most preferably 40 to 99.99% (w/w) of the tocopherol or tocopherol derivative Solvent." *Id*. at 5:55-58. Jamieson discloses benzodiazepine compositions that include tocopherols. *See, e.g.*, Jamieson at [Claim 24], [Claim 49]. *See also id.* at ¶ [0209] ("Addition of an anti-oxidant to the formulations of the present

Claim Language	Exemplary Prior Art Citations
	invention used for intranasal delivery of benzodiazepines may provide desirable protective benefits to such formulations. Examples include, but are not limited to, tocopherol and derivatives thereof…"). USP discloses that vitamin E was well-known in the art at the time: "Vitamin E is a form of alpha tocopherol ($C_{29}H_{50}O_2$). It includes the following d- or dl-alpha tocopherol ($C_{29}H_{50}O_2$); d- or dl-alpha tocopheryl acetate ($C_{31}H_{52}O_3$); d- or dl-alpha tocopheryl acid succinate ($C_{33}H_{54}O_5$)." USP at 1631.
one or more alcohols in an amount from 10% to 70% (w/w), wherein the one or more alcohols comprises benzyl alcohol; and	Gwozdz discloses that "[i]n accordance with the present invention, solutions of one or more tocopherols and/or tocotrienols and one or more alcohols and/or glycols are used in the solubilization of hydrophobic or lipophilic therapeutic agents thereby providing increased bioavailability of the therapeutic agent." Gwozdz at 7:3-8. Gwozdz also discloses that "[e]xamples of alcohol(s) for use in the present invention include, but are not limited to ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, and any isomers thereof, and any combinations thereof." *Id*. at 6:16-19. Gwozdz further discloses that "[i]n some embodiments, the tocopherol(s) and/or tocotrienol(s) is in an amount from about 30% to about 99% (w/w) and the alcohol (s) and/or glycol (s) is in an amount from about 1% to about 70% (w/w)." *Id*. at 4:17-21. Gwozdz also discloses that "[p]harmaceutical solutions of the present invention can be produced by dissolving any difficult to solubilize therapeutic agent (i.e., hydrophobic or lipophilic therapeutic agents) in one or more tocopherols and/or tocotrienols and one or more alcohols and/or glycols as

Claim Language	Exemplary Prior Art Citations
	pharmaceutically acceptable solvents." *Id*. at 7:29-34. Li discloses use of ethanol in diazepam intranasal delivery systems at about 20%-60% concentrations. Li at 71-72 ("The peak DZ plasma concentration, observed within 2–3 min after [intranasal] administration, increased significantly with increasing EtOH concentrations in the IN formulations (20–60%)…"). Sonne discloses that "[t]he formulations according to the invention may be optimized with respect to bioadhesion, sprayability and viscosity, as desired" by incorporating "co-solvents" like "alcohols such as ethanol … or benzyl alcohol." Sonne at 6:47-53. Sonne also discloses that "[v]iscosity can be reduced by addition of co-solvents such as ethanol…" *Id*. at 3:60-67. Sonne further discloses a solution of diazepam, incorporated 55% w/w of a co-solvent, namely triacetin (13.75 g of triacetin within a total solution weight of 25 g). *Id*. at 11:1-13 (Example 11). Jamieson discloses benzodiazepine formulations containing 20% ethanol. *See* Jamieson at Table 12A. Wermeling V discloses that "[s]uitable preservatives for use in some embodiments include, but is not limited to, …benzyl alcohol… Typically, the preservative is added to the composition quantities of from about 0.01% to about 0.5% by weight." Wermeling V at ¶ [0033].
n-dodecyl beta-D-maltoside.	Meezan discloses that "[a]lkyl glycosides of the present invention can include, but are not limited to: alkyl glycosides, such as octyl-, nonyl-, decyl-, undecyl-, dodecyl-, tridecyl-,

Claim Language	Exemplary Prior Art Citations
	tetradecyl-, pentadecyl-, hexadecyl-, heptadecyl-, and octadecyl-α- or β-D-maltoside,…" Meezan at ¶ [0056]. * * * "Similarly, some preferred glycosides include maltose, sucrose, and glucose linked by glycosidic linkage to an alkyl chain of 9, 10, 12, 13, 14, 16, 18, 20, 22, or 24 carbon atoms, e.g., nonyl-, decyl-, dodecyl- and tetradecyl sucroside, glucoside, and maltoside, etc. These compositions are nontoxic, since they are degraded to an alcohol and an oligosaccharide, and amphipathic." *Id*. at ¶ [0058]. *See also id*. at ¶ [0061]. Meezan also discloses adding alkyl glycosides to formulations in amounts of "about 0.01-20%, preferably about 0.01-5%, more preferably about 0.01-2%, even more preferably 0.01-1%, and most preferably 0.01-0.125% by weight" while testing the effects of dodecyl maltoside as an absorption enhancer in amounts of 0.125%, 0.25%, 0.375%, and 0.50%. *Id*. at ¶ [0070]. Meezan also discloses that alkyl glycosides will increase the bioavailability of small molecules, and identifies molecules having molecular weight below 1.5 k Daltons as candidates for improved bioavailability. *Id*. at ¶ [0130]. Meezan further discloses alkylmaltosides, including dodecyl-beta-D-maltoside as a preferred alkyl glycoside compound. *Id*. at ¶¶ [0092], [0156] ("[A]t least two alkylmaltosides [including dodecyl-beta-D-maltoside] are effective in achieving sufficient absorption" of the drug substance studied), Table 1. Meezan specifically discloses compositions having an alkyl glycoside (such as dodecyl-beta-D-maltoside) in an amount of about 0.25%. *See, e.g., id*. at ¶¶ [0150]-[0151]. *See*

Claim Language	Exemplary Prior Art Citations
	also id. at Fig. 1, ¶¶ [0158]-[0159], Table I, and Example 6. Jamieson discloses the use of penetration enhancers in diazepam for intranasal spray formulations. *See* Jamieson at ¶ [0104] ("pharmaceutical compositions comprising the benzodiazepine (e.g., clonazepam, diazepam or lorazepam) of the present invention, for example, for intranasal administration… may further comprise one or more components including… mucosa penetration enhancing agent"), ¶ [0105] ("In preferred embodiments of the present invention, the pharmaceutical compositions… are formulation to be sprayable."). Cartt 2008 discloses that its benzodiazepine formulations may contain various excipients including "n-dodecyl β-D-maltoside." *See, e.g.*, Cartt 2008 at ¶¶ [0128]-[0129], [0168], [0183]. A POSA would have expected surfactants, such as alkyl glycosides to increase the bioavailability of intranasal formulations. *See e.g.* Sharma at 500-01, Ahsan at 27.
2. The pharmaceutical solution of claim 1, wherein the therapeutically effective amount of diazepam or pharmaceutically acceptable salt thereof is present in the pharmaceutical solution in a concentration from 1 to 20% (w/v).	*See* claim 1.
3. The pharmaceutical solution of claim 1, wherein the therapeutically effective amount of diazepam or pharmaceutically acceptable salt thereof is present in the pharmaceutical solution in a concentration from 10 mg/mL to 250 mg/mL.	*See* claim 1.
4. The pharmaceutical solution of claim 3, wherein the therapeutically effective amount of diazepam or pharmaceutically acceptable	*See* claim 3.

Claim Language	Exemplary Prior Art Citations
salt thereof is present in the pharmaceutical solution in a concentration from 20 mg/mL to 50 mg/mL.	
5. The pharmaceutical solution of claim 1, wherein the one or more natural or synthetic tocopherols or tocotrienols is in an amount from 45% to 85% (w/w).	*See* claim 1.
6. The pharmaceutical solution of claim 5, wherein the one or more natural or synthetic tocopherols or tocotrienols is in an amount from 60% to 75% (w/w).	*See* claim 5.
7. The pharmaceutical solution of claim 1, wherein the one or more alcohols is benzyl alcohol and a second alcohol selected from ethanol, propyl alcohol, butyl alcohol, pentanol, any isomers thereof, and any combinations thereof.	*See* claim 1.
8. The pharmaceutical solution of claim 1, wherein the one or more alcohols are in an amount from 15% to 55% (w/w).	*See* claim 1.
9. The pharmaceutical solution of claim 8, wherein the one or more alcohols are in an amount from 25% to 40% (w/w).	*See* claim 8.
10. The pharmaceutical solution of claim 1, wherein the solution consists of diazepam, vitamin E, benzyl alcohol, and n-dodecyl beta-D-maltoside.	*See* claim 1.
11. A pharmaceutical solution for nasal administration consisting of:	*See* claim 1.
a therapeutically effective amount of diazepam or a pharmaceutically acceptable salt thereof;	*See* claim 1.
one or more natural or synthetic α-tocopherols selected from the group consisting of tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, tocophersolan, any isomers thereof, any esters thereof, and any	*See* claim 1.

Claim Language	Exemplary Prior Art Citations
combinations thereof, in an amount from 30% to 95% (w/w);	
one of more alcohols in an amount from 10% to 70% (w/w)), wherein the one or more alcohols comprises benzyl alcohol; and	*See* claim 1.
n-dodecyl beta-D-maltoside.	*See* claim 1.
12. The pharmaceutical solution of claim 11, wherein the therapeutically effective amount of diazepam or pharmaceutically acceptable salt thereof is present in the pharmaceutical solution in a concentration from 1 to 20% (w/v).	*See* claims 11 and 2.
13. The pharmaceutical solution of claim 11, wherein the therapeutically effective amount of diazepam or pharmaceutically acceptable salt thereof is present in the pharmaceutical solution in a concentration from 10 mg/mL to 250 mg/mL.	*See* claims 11 and 3.
14. The pharmaceutical solution of claim 13, wherein the therapeutically effective amount of diazepam or pharmaceutically acceptable salt thereof is present in the pharmaceutical solution in a concentration from 20 mg/mL to 50 mg/mL.	*See* claims 13 and 4.
15. The pharmaceutical solution of claim 11, wherein the one or more natural or synthetic tocopherols is in an amount from 45% to 85% (w/w).	*See* claims 11 and 5.
16. The pharmaceutical solution of claim 15, wherein the one or more natural or synthetic tocopherols is in an amount from 60% to 75% (w/w).	*See* claims 15 and 6.
17. The pharmaceutical solution of claim 11, wherein the one or more alcohols is benzyl alcohol and a second alcohol selected from ethanol, propyl alcohol, butyl alcohol,	*See* claim 11.

Claim Language	Exemplary Prior Art Citations
pentanol, any isomers thereof, and any combinations thereof.	
18. The pharmaceutical solution of claim 11, wherein the one or more alcohols are in an amount from 15% to 55% (w/w).	*See* claim 11.
19. The pharmaceutical solution of claim 18, wherein the one or more alcohols are in an amount from 25% to 40% (w/w).	*See* claim 11.
20. The pharmaceutical solution of claim 1, wherein the therapeutically effective amount of diazepam or pharmaceutically acceptable salt thereof present in the pharmaceutical solution is from about 5 to about 20 mg.	*See* claim 1.
21. The pharmaceutical solution of claim 11, wherein the therapeutically effective amount of diazepam or pharmaceutically acceptable salt thereof present in the pharmaceutical solution is from about 1 mg to about 20 mg.	*See* claim 1.
22. The pharmaceutical solution of claim 1, wherein the n-dodecyl beta-D-maltoside is present in the pharmaceutical solution in an amount from about 0.01% (w/v) to about 1% (w/v).	*See* claim 1.
23. The pharmaceutical solution of claim 11, wherein the n-dodecyl beta-D-maltoside is present in the pharmaceutical solution in an amount from about 0.01% (w/v) to about 1% (w/v).	*See* claim 1.
24. The pharmaceutical solution of claim 1, wherein the n-dodecyl beta-D-maltoside is present in the pharmaceutical solution in an amount from about 0.125% (w/v) to about 0.5% (w/v).	*See* claim 1.
25. The pharmaceutical solution of claim 11, wherein the n-dodecyl beta-D-maltoside is present in the pharmaceutical solution in an	*See* claim 1.

Claim Language	Exemplary Prior Art Citations
amount from about 0.125% (w/v) to about 0.5% (w/v).	
26. The pharmaceutical solution of claim 1, wherein the α-tocopherol is Vitamin E USP.	*See* claim 1.
27. The pharmaceutical solution of claim 11, wherein the α-tocopherol is Vitamin E USP.	*See* claim 1.

Exhibit D: Invalidity of U.S. Patent No. 12,324,852

WIPO Publication No. WO 2009/120933 to Gwozdz et al. (hereinafter "Gwozdz") is titled "Pharmaceutical Solutions and Method for Solubilizing Therapeutic Agents," and was published October 1, 2009, and constitutes prior art under § 102(b).

U.S. Patent Application Publication No. 2006/0046962 to Meezan et al. (hereinafter "Meezan") is titled "Absorption Enhancers for Drug Administration," and was published on March 2, 2006, and constitutes prior art under § 102(b).

U.S. Pub. No. 2008/0279784 to Cartt et al. (hereinafter "Cartt 2008) is titled "Nasal Administration of Benzodiazepines" was published on November 13, 2008, and constitutes prior art under § 102(b).

USP 23/NF 18, Ed., "United States Pharmacopeia. The National Formulary," The United States Pharmacopoeial Convention Inc., Rockville (hereinafter "USP") was published in 1995, and constitutes prior art under § 102(b).

Diastat was initially approved by the FDA in 2005 and, thus, the corresponding drug product insert or label for Diastat (hereinafter "Diastat Label") constitutes prior art under § 102(b).

U.S. Pub. No. 2009/0258865 to Cartt et al. (hereinafter "Cartt 2009") is titled "Administration of Benzodiazepine Compositions," and was published on October 15, 2009, and constitutes prior art under § 102(b).

Clinical Trial No. NCT01364558 (hereinafter "NCT '558") was first posted by at least June 2, 2011, and constitutes prior art under § 102(b).

An abstract titled "A Pilot Study Assessing the Bioavailability and Pharmacokinetics of Diazepam After Intranasal and Intravenous Administration in Healthy Volunteers" (hereinafter "Agarwal") was published on October 4, 2011, and constitutes prior art under § 102(a).

A press release titled "Neurelis Announces Positive Results from Phase 1 Pharmacokinetic Study of NRL-01 (intranasal diazepam)" (hereinafter "Neurelis Press Release") was published on June 14, 2011, and constitutes prior art under § 102(a).

U.S. Pub. No. 2012/0252793 to Bream et al. (hereinafter "Bream") is titled "Intranasal Benzodiazepine Pharmaceutical Compositions," and was published on October 4, 2012, and constitutes prior art under § 102(b).

As set forth in the chart below, certain elements of the Asserted Claims of the '852 patent are disclosed, taught, suggested, and rendered obvious by Gwozdz in view of Meezan, Cartt 2008, and USP, optionally in view of the Diastat Label. Alternatively, as also set forth below, certain elements of the Asserted Claims of the '852 patent are disclosed, taught, suggested, and rendered obvious by Cartt 2009 in view of Meezan, further in view of NCT '558, Agarwal, and the Neurelis Press Release. As an additional alternative, certain elements of the Asserted Claims of the '852 patent are disclosed, taught, suggested, and rendered obvious by Cartt 2009 and Meezan, in view of the Diastat Label, NCT '558, Gwozdz, and USP. Additionally, the Asserted Claims of the '852

patent are disclosed, taught, suggested, and rendered obvious over Cartt 2009 in view of Gwozdz, Meezan, and/or Bream..

Further, as explained in Defendants' Preliminary Invalidity Contentions, the claims of the '852 patent should be limited to a priority date of March 14, 2024 in light of the new matter added to the specification via an amendment filed on that date. Accordingly, the approved prescribing information for Valtoco ("Valtoco Label"), as well as the Valtoco product itself, constitutes prior art against the '852 patent because it was FDA approved, published, and/or otherwise on sale and publicly available more than one year before March 14, 2024. As shown in the chart below, the Valtoco Label, which describes the Valtoco product, anticipates the claims of the '852 patent because it disclosed, expressly or inherently, all limitations of the claims of the '852 patent. Finally, the Valtoco product was used and administered by patients and healthcare professionals consistent with the Valtoco Label before March 14, 2024.

The excerpts cited herein are exemplary. For any claim limitation, Defendants may rely on excerpts cited for any other limitation or additional excerpts not set forth fully herein to the extent necessary to provide a more comprehensive explanation for a reference's disclosure of a limitation. Where an excerpt refers to or discusses a figure or figure items, that figure and any additional descriptions of that figure should be understood to be incorporated by reference as if set forth fully therein. As set forth in the Preliminary Invalidity Contentions (incorporated herein in their entirety), to which this exhibit has been attached, a POSA at the time would have been motivated to combine the teachings of any groupings of the foregoing prior art references with his knowledge of the art. Such combinations would provide a reasonable expectation of success to arrive at the claimed invention(s), and thus each claim of this patent is invalid.

Claim Language	Exemplary Prior Art Citations
1. A method of treating bouts of intermittent and stereotypic episodes of increased seizure activity in an epilepsy patient that is distinguishable from other seizures suffered by the patient comprising:	Cartt 2008 discloses that diazepam was known to be useful for the treatment of seizures. Cartt 2008 at ¶ [0003]. Cartt 2008 further discloses that "[n]asal formulations of benzodiazepines have been suggested for the acute treatment of seizure." *Id*. at ¶ [0007]. Cartt 2008 also discloses that benzodiazepines are anticonvulsants that can be administered for the "treatment of seizures, protection against seizure, reduction or amelioration of the intensity of seizure, reduction or amelioration of the frequency of seizure, and/or prevention of the occurrence or re-occurrence of seizure." *Id*. at ¶ [0136]. The Diastat Label discloses that diazepam could be used to treat "bouts of increased

Claim Language	Exemplary Prior Art Citations
	seizure activity" in patients, including "intermittent and periodic episodes of markedly increased seizure activity" that "were not only stereotypic but were judged by those conducting and participating in these studies to be distinguishable from other seizures suffered by that patient." Diastat Label at 1. Cartt 2009 discloses "pharmaceutical compositions comprising one or more benzodiazepine drugs for nasal administration, methods for producing and for using such compositions." Cartt 2009 at Abstract. Cartt 2009 further discloses that the benzodiazepine-containing intranasal formulations are "useful in preventing, treating, or ameliorating the symptoms of … seizures (such as those caused by epilepsy)." *Id*. at ¶ [0003]. *See also id.* at ¶ [0086]. NCT '558 describes three arms and interventions, which sought to investigate "the absolute bioavailability of two intranasal diazepam formulations" for the treatment of "epilepsy." NCT '558. Neurelis Press Release discloses that the formulation studied by NCT '558 "is being developed for the management of patients who require intermittent use of diazepam to control bouts of acute repetitive seizure activity." Neurelis Press Release at 1. Agarwal, reporting on NCT '558, discloses that the intranasal diazepam solution formulation was being investigated for the treatment of "acute repetitive seizures." Agarwal. Bream discloses methods for treating and/or preventing seizures, including acute repetitive seizures. Bream at [008], [0091].

Claim Language	Exemplary Prior Art Citations
	The Valtoco Label stated that "VALTOCO is a benzodiazepine indicated for the acute treatment of intermittent, stereotypic episodes of frequent seizure activity (i.e., seizure clusters, acute repetitive seizures) that are distinct from a patient's usual seizure pattern in patients with epilepsy 6 years of age and older." *See, e.g.*, Neurelis-00144572-599 at -572 (Valtoco Label, Rev. 02/2021). Further, the Valtoco product was used and administered by patients and healthcare professionals consistent with the Valtoco Label.
administering a single spray of 100 µL to one nasal mucosal membrane of the patient of a pharmaceutical solution consisting of:	Gwozdz discloses that the pharmaceutical solution is "particularly useful in formulations to be administered to mucosal membranes, i.e. the nasal mucosa or lungs of a subject by any suitable means." Gwozdz at 9:19-22. Gwozdz also discloses that its "solutions can be administered via, for example, a metered dose inhaler or nebulizer, or in a mist sprayer" "for administration" "to one or more mucosal membranes, including the nasal mucosal membranes." *Id*. at 9:28-10:2. Meezan discloses "a method of increasing absorption of a low molecular weight compound into the circulatory system of a subject by administering the compound via the... nasal,... delivery route..." Meezan at ¶ [0008]. Cartt 2008 discloses nasal formulations of diazepam and that "[n]asal preparations are generally administered in metered sprays having volumes of less than 250 µl, preferably less than 150 µl, and ideally from 25 to 100 µl, since administration of larger volumes usually exceeds the capacity of the nasal sinuses and results in volumes in excess of about 250 µl bypassing the sinuses and flowing down the back of the throat where it is swallowed." Cartt 2008 at ¶ [0007].

Claim Language	Exemplary Prior Art Citations
	Cartt 2008 specifically discloses that "[a]s a nasal formulation, diazepam may be administered in 25 to 250 µl metered sprays. In some preferred embodiments, diazepam is administered in 50 to 150 µl, especially about 100 µl, metered sprays. In some embodiments, a first metered spray is applied to a first nostril and if necessary a second metered spray is applied to a second nostril." *Id*. at ¶ [0064]. NCT '558 discloses that one tested intranasal diazepam formulation was described by NCT '558 as a "solution" which outperformed a "suspension" formulation. NCT '558 Agarwal, reporting on NCT '558, discloses that the 10 mg dose of the intranasal diazepam solution formulation resulted in a "[b]ioavailability" that "approached 100% and was significantly ($p<0.05$) greater than the IN suspension, as was Cmax." Agarwal. Neurelis Press Release, also reporting on NCT '588, discloses that the "NRL-1 intranasal solution formulation" as the "lead intranasal formulation." Neurelis Press Release at 1. Cartt 2009 discloses intranasal diazepam solution formulations. Cartt 2009 at Abstract. Cartt 2009 further discloses that its compositions may be formulated such that diazepam is fully dissolved so that "the benzodiazepine drug is formulated as a solution." *Id*. at ¶ [0168]. Cartt 2009 also discloses that vitamin E (see below) can form emulsions having drawbacks which can be avoided by the formulations being "solutions of one or more benzodiazepine drugs in Vitamin E and one or more lower alkyl alcohols." *Id*. at ¶ [0135]. Cartt 2009 further discloses that its intranasal diazepam solution formulations could be

Claim Language	Exemplary Prior Art Citations
	administered in one or both nostrils, preferably in "about 100 μL metered sprays." Cartt 2009 at ¶¶ [0029], [0060]. Cartt 2009 also discloses that such administration was well-known in the art: "Mucosal membrane preparations are generally administered in metered sprays having volumes of … ideally from 25 to 100 μL. Although not prohibited in this invention, administration of volumes larger than about 300 μL per dose usually exceeds the absorption capacity of the membranes. This results in a large portion of the pharmaceutically-active ingredient being lost. The dosage volume of preparations, in particular nasal preparations, preferably ranges from 25 to 100 μL. Volumes in excess of the aforementioned ranges may bypass the sinuses and flow down the back of the throat where the excess is swallowed." *Id*. at ¶ [0144]. A POSA at the time would know that commercial nasal spray products typically deliver 100-200 μL (i.e., 0.1-0.2 mL) per spray, as the human nasal cavity can only receive and retain about 100-150 μL of liquid. *See*, *e.g.*, Wermeling, D. et al., "Pharmacokinetics and pharmacodynamics of a new intranasal midazolam formulation in healthy volunteers." Anesth Analg 2006; 103:344-349, 344 (teaching that "[t]he adult nasal cavity can only receive and retain about 100-150 μL of liquid, requiring the dose of midazolam be solubilized within this volume. A nasal formulation with a concentration of 2.5 mg per 100 μL is necessary to give a single spray per naris."). NCT '558 discloses that the diazepam solution was administered as a "nasal spray." NCT '558.

Claim Language	Exemplary Prior Art Citations
	Agarwal discloses confirmation that the diazepam solution was administered intranasally. Agarwal. The Neurelis Press Release also discloses that "NRL-01 (intranasal diazepam) is a proprietary formulation of diazepam delivered via a commercially available nasal sprayer." Neurelis Press Release at 2. The Valtoco Label stated that Valtoco is a "[n]asal spray" containing "5 mg, 7.5 mg, or 10 mg of diazepam in [100 µL]." *See, e.g.*, Neurelis-00144572-599 at -575 (Valtoco Label, Rev. 02/2021). "VALTOCO 5 mg and 10 mg doses are administered as a single spray intranasally into one nostril." *Id*. Thus, consistent with the Valtoco Label, the Valtoco product was administered as a single spray of 100 µL to one nasal mucosal membrane of the patient by patients and healthcare professionals.
56.47 mg of vitamin E USP +/−5%;	Gwozdz discloses "the use of one or more tocopherols and/or tocotrienols and one or more alcohols and/or glycols as pharmaceutically acceptable solvents for solubilizing therapeutic agents, in particular hydrophobic or lipophilic therapeutic agents." Gwozdz at 4:29-33. Gwozdz also discloses that which would have been well known to a POSA at the time: "Tocopherols and/or tocotrienols for use in accordance with the present invention include a family of natural and synthetic compounds, also known by the generic names tocols or vitamin E." Gwozdz at 5:33-6:2. Gwozdz further discloses that "[i]n one embodiment of the present invention the tocopherol (s) and/or tocotrienol (s) employed is alpha-tocopherol." *Id*. at 6:13-15.

Claim Language	Exemplary Prior Art Citations
	Gwozdz also discloses that "the tocopherol(s) and/or tocotrienol(s) is in an amount from about 30% to about 99% (w/w)." *Id*. at 4:17-19. USP discloses that vitamin E was well-known in the art at the time: "Vitamin E is a form of alpha tocopherol ($C_{29}H_{50}O_2$). It includes the following d- or dl-alpha tocopherol ($C_{29}H_{50}O_2$); d- or dl-alpha tocopheryl acetate ($C_{31}H_{52}O_3$); d- or dl-alpha tocopheryl acid succinate ($C_{33}H_{54}O_5$)." USP at 1631. Cartt 2009 discloses pharmaceutical compositions for nasal administration that contain "a benzodiazepine drug; one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); and one or more alcohols or glycols, or any combinations thereof, in an amount from about 5% to about 70% (w/w), preferably about 10% to about 70% (w/w) in a pharmaceutically-acceptable formulation for administration to one or more nasal mucosal membranes of the patient." Cartt 2009 at ¶ [0010]. Cartt 2009 further discloses that "Vitamin E can provide an effective carrier for benzodiazepine drugs." *Id*. at ¶ [0134]. Cartt 2009 specifically discloses that the carrier system of its compositions may contain "about 50% to about 90% (w/w) Vitamin E and about 10% to about 50% (w/w) lower alcohol" or "about 65% to about 75% (w/w) Vitamin E and about 25% to about 35% (w/w) lower alkyl alcohol." *Id*. at ¶ [0162]. The Valtoco Label stated that "[t]he inactive ingredients in VALTOCO nasal spray include benzyl alcohol (10.5 mg per 0.1 mL), dehydrated alcohol, n-dodecyl beta-D-maltoside, and vitamin E." *See, e.g.*, Neurelis-00144572-599 at -587 (Valtoco Label, Rev.

Claim Language	Exemplary Prior Art Citations
	02/2021). Further, a POSA would have understood that Valtoco contained 56.47 mg of vitamin E USP +/−5%, consistent with Dr. Stuart Madden's statement that Valtoco contains that amount of Vitamin E. Neurelis-02049865-881.
10 mg of diazepam;	Gwozdz discloses that "[e]xemplary hydrophobic or lipophilic therapeutic agents which can be solubilized in accordance with the present invention include, but are in no way limited to,… benzodiazepenes such as Diazepam,…" Gwozdz at 8:6-18. Gwozdz discloses diazepam as a preferred therapeutic agent, for use in its solubilizing solutions, and that the solubility of diazepam can be increased from less than or equal to 6.67% (in ethanol) to "approaching the 10% level" (when incorporating tocopherol into the solution). *Id*. at 7:12-16. Cartt 2008 discloses that "[d]iazepam is a benzodiazepine drug having sedative, tranquilizing and muscle relaxing properties. It is classified as an anxiolytic and skeletal muscle relaxant. It possesses anxiolytic, anticonvulsant, sedative, skeletal muscle relaxant and amnesic properties" and that exemplary doses of diazepam delivered via nasal administration "may vary by indication, however it is expected that a therapeutic dose will be in the range of about 1 to about 20, preferably about 2 to about 10 mg per dose…." Cartt 2008 at ¶ [0063]. Cartt 2008 also discloses that "[i]n some embodiments, the benzodiazepine or pharmaceutically acceptable salt thereof is present in a concentration of from about 0.05 mg/mL up to about 600 mg/mL." *Id*. at ¶ [0034]. Cartt 2009 discloses that "[t]he dosage of diazepam may vary by indication, however it

Claim Language	Exemplary Prior Art Citations
	is expected that a therapeutic dose will be in the range of about 1 to about 20, preferably about 2 to about 10 mg per dose…" Cartt 2009 at ¶ [0086]. *See also id.* at ¶ [0147]. NCT '558 discloses the use of a 10 mg dose of diazepam. NCT '558. Agarwal discloses the use of a 10 mg dose of diazepam. Agarwal. The Neurelis Press Release discloses the use of a 10 mg dose of diazepam. Neurelis Press Release at 1. The Valtoco Label stated that Valtoco is a "[n]asal spray" containing "5 mg, 7.5 mg, or 10 mg of diazepam in [100 μL." *See, e.g.*, Neurelis-00144572-599 at -575 (Valtoco Label, Rev. 02/2021). Thus, a POSA would have understood that Valtoco contained 10 mg of diazepam, consistent with Dr. Stuart Madden's statement that Valtoco contains that amount of diazepam. Neurelis-02049865-881.
0.25 mg of dodecyl maltoside;	Gwozdz discloses a wide range of types of excipients that can be included in its benzodiazepine solution formulations. Gwozdz at 10:3-16, 12:12-22. Cartt 2008 discloses that its benzodiazepine formulations may contain various excipients including "n-dodecyl β-D-maltoside." *See, e.g.*, Cartt 2008 at ¶¶ [0128]-[0129], [0168], [0183]. Meezan discloses enhanced bioavailability of therapeutic agents using alkyl glycoside or saccharide alkyl ester: "Alkyl glycosides of the present invention can include, but are not limited to: alkyl glycosides, such as octyl-, nonyl-, decyl-, undecyl-, dodecyl-, tridecyl-, tetradecyl-, pentadecyl-,hexadecyl-, heptadecyl-, and octadecyl-α- or β-D-maltoside, -glucoside or -sucroside…." while

Claim Language	Exemplary Prior Art Citations
	further disclosing that "some preferred glycosides include maltose, sucrose, and glucose linked by glycosidic linkage to an alkyl chain of 9, 10, 12, 13, 14, 16, 18, 20, 22, or 24 carbon atoms, e.g., nonyl-, decyl-, dodecyl- and tetradecyl sucroside, glucoside, and maltoside, etc." Meezan at ¶¶ [0056], [0058]. Meezan further discloses alkylmaltosides, including dodecyl maltoside, as a preferred alkyl glycoside compound. *Id*. at ¶¶ [0092], [0156]. Meezan specifically discloses compositions having an alkyl glycoside (such as dodecyl-beta-D-maltoside) in an amount of about 0.25%. *See, e.g., id*. at ¶¶ [0150]-[0151]. *See also id.* at Fig. 1, ¶¶ [0158]-[0159], Table I, and Example 6. Meezan also discloses preferred alkyl glycoside concentrations, stating that intranasal delivery of a lipophilic therapeutic compound like diazepam "with 0.125% and 0.250% alkyl glycoside" resulted in "about 43% to about 90% bioavailability, respectively," as compared to only 3% bioavailability when the alkyl glycoside compound was not present. *Id*. at ¶ [0150]. Cartt 2009 discloses pharmaceutical compositions that may contain an alkyl glycoside such as dodecyl maltoside. Cartt 2009 at ¶¶ [0019], [0138], [0142]-[0143], [0210]. Cartt 2009 further discloses the use of a "penetration enhancer" like alkyl glycosides in intranasal diazepam solution formulations. Cartt 2009 at ¶ [0058]. Cartt further explains that "[t]he term 'penetration enhancer', means any material which acts to increase absorption

Claim Language	Exemplary Prior Art Citations
	across the mucosa and/or increases bioavailability." *Id*. at ¶ [0139]. Cartt 2009 also discloses that the penetration enhancer may be an alkyl glycoside, such as dodecyl maltoside specifically, where "the amount of alkyl glycoside in the composition is in a range of about 0.01% (w/v) to about 1% (w/v)." *Id*. at ¶ [0058]. A POSA would have expected surfactants, such as alkyl glycosides to increase the bioavailability of intranasal formulations. *See e.g.* Sharma at 500-01, Ahsan at 27. The Valtoco Label stated that "[t]he inactive ingredients in VALTOCO nasal spray include benzyl alcohol (10.5 mg per 0.1 mL), dehydrated alcohol, n-dodecyl beta-D-maltoside, and vitamin E." *See, e.g.*, Neurelis-00144572-599 at -587 (Valtoco Label, Rev. 02/2021). A POSA would have understood that Valtoco contained 0.25 mg of dodecyl maltoside, consistent with Dr. Stuart Madden's statement that Valtoco contains that amount of DDM. Neurelis-02049865-881.
10.50 mg of benzyl alcohol +/−5%, and a sufficient quantity of ethanol;	Gwozdz discloses that "[i]n accordance with the present invention, solutions of one or more tocopherols and/or tocotrienols and one or more alcohols and/or glycols are used in the solubilization of hydrophobic or lipophilic therapeutic agents thereby providing increased bioavailability of the therapeutic agent." Gwozdz at 7:3-8. Gwozdz further discloses that "[e]xamples of alcohol (s) for use in the present invention include, but are not limited to ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, and any isomers thereof, and any combinations thereof." *Id*. at 6:16-7:2. Gwozdz also discloses that that the pharmaceutical solutions should contain the

Claim Language	Exemplary Prior Art Citations
	alcohol excipient(s) "in an amount from about 1% to about 70% (w/w)." *Id*. at 4:17-21. Cartt 2008 discloses benzyl alcohol and ethanol as solvents that may be used to prepare intranasal diazepam formulations. Cartt 2008 at ¶ [0182]. Meezan similarly discloses benzyl alcohol as a potential "pharmaceutically acceptable carrier." Meezan at ¶ [0074]. Cartt 2009 discloses pharmaceutical compositions for nasal administration that contain "a benzodiazepine drug; one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); and one or more alcohols or glycols, or any combinations thereof, in an amount from about 5% to about 70% (w/w), preferably about 10% to about 70% (w/w) in a pharmaceutically-acceptable formulation for administration to one or more nasal mucosal membranes of the patient." Cartt 2009 at ¶ [0010]. Cartt 2009 specifically discloses that the one or more alcohols may be chosen from benzyl alcohol and/or ethanol. *Id*. at ¶¶ [0013], [0136]. Cartt 2009 also discloses that vitamin E can form emulsions having drawbacks which can be avoided by the formulations being "solutions of one or more benzodiazepine drugs in Vitamin E and one or more lower alkyl alcohols." *Id*. at ¶ [0135]. Cartt 2009 specifically discloses that the "[l]ower alkyl alcohols" include a limited number of alcohols, including benzyl alcohol and ethanol. *Id*. at ¶ [0136]. Cartt 2009 further discloses that the carrier system of its compositions may contain "about 50% to about 90% (w/w) Vitamin E and about 10% to about 50% (w/w) lower alcohol" or

Claim Language	Exemplary Prior Art Citations
	"about 65% to about 75% (w/w) Vitamin E and about 25% to about 35% (w/w) lower alkyl alcohol." *Id*. at ¶ [0162]. The Valtoco Label stated that "[t]he inactive ingredients in VALTOCO nasal spray include benzyl alcohol (10.5 mg per 0.1 mL), dehydrated alcohol, n-dodecyl beta-D-maltoside, and vitamin E." *See, e.g.*, Neurelis-00144572-599 at -587 (Valtoco Label, Rev. 02/2021). Thus, a POSA would have understood that Valtoco contained 10.50 mg of benzyl alcohol and a sufficient quantity of ethanol, consistent with Dr. Stuart Madden's statement that Valtoco contains that amount of benzyl alcohol and ethanol. Neurelis-02049865-881.
wherein administering the single spray of the pharmaceutical solution to the patient achieves 92.5% to 107.5% of the bioavailability of an equivalent dose of diazepam administered intravenously and is safe and effective in treating the bouts of intermittent and stereotypic episodes of increased seizure activity in the patient; and	Meezan discloses preferred alkyl glycoside concentrations, stating that intranasal delivery of a lipophilic therapeutic compound like diazepam "with 0.125% and 0.250% alkyl glycoside" resulted in "about 43% to about 90% bioavailability, respectively," as compared to only 3% bioavailability when the alkyl glycoside compound was not present. Meezan at ¶ [0150]. NCT '558 discloses a goal being "to assess the bioavailability and pharmacokinetics of two formulations of diazepam after intranasal (nasal spray) and injectable diazepam after intravenous (I.V.) administration." NCT '558. NCT '558 also discloses three arms and interventions, which sought to investigate "the absolute bioavailability of two intranasal diazepam formulations" for the treatment of "epilepsy." *Id*. Agarwal, reporting on NCT '558, discloses that the 10 mg dose of the intranasal diazepam solution formulation resulted in a "[b]ioavailability" that "approached 100%

Claim Language	Exemplary Prior Art Citations
	and was significantly ($p<0.05$) greater than the IN suspension, as was Cmax." Agarwal. The Neurelis Press Release, reporting on the results of NCT '558, discloses that its "lead intranasal formulation, NRL-1, revealed promising pharmacokinetic results. In its evaluation of a 10 mg diazepam dose in the NRL-1 intranasal solution formulation, the study showed the following: • NRL-1 is well-tolerated, with only mild adverse events reported • Similar bioavailability to intravenous administration of diazepam (100% vs. 96%)…" Neurelis Press Release at 1. The mere recitation of an inherent or latent property of an otherwise obvious formulation will not render the formulation patentable. *In re Kao*, 639 F.3d 1057, 1070 (Fed. Cir. 2011); *Santarus, Inc. v. Par Pharmaceutical, Inc.*, 694 F.3d 1344 (Fed. Cir. 2012). The Valtoco Label stated that "VALTOCO is a benzodiazepine indicated for the acute treatment of intermittent, stereotypic episodes of frequent seizure activity (i.e., seizure clusters, acute repetitive seizures) that are distinct from a patient's usual seizure pattern in patients with epilepsy 6 years of age and older." *See, e.g.*, Neurelis-00144572-599 at -572 (Valtoco Label, Rev. 02/2021). The Valtoco Label disclosed that "[t]he absolute bioavailability of VALTOCO relative to intravenous diazepam was 97%." *Id*. at -4587. Thus, the Valtoco label expressly disclosed that Valtoco achieved a bioavailability of 92.5% to 107.5% of the bioavailability of an equivalent dose of diazepam administered intravenously and is safe and effective in treating the bouts of intermittent and

Claim Language	Exemplary Prior Art Citations
	stereotypic episodes of increased seizure activity in the patient, which is also an inherent property of Valtoco.
wherein administering the single spray of the pharmaceutical solution to the one nasal mucosal membrane of the patient results in a treatment selected from the group consisting of a reduction in the severity of the seizure, a reduction in the probability that the patient will experience a repeat seizure, an increase in the interval between a current seizure and a next seizure in the patient, a reduction in the frequency of seizure in the patient and combinations thereof.	Cartt 2008 also discloses that benzodiazepines are anticonvulsants that can be administered for the "treatment of seizures, protection against seizure, reduction or amelioration of the intensity of seizure, reduction or amelioration of the frequency of seizure, and/or prevention of the occurrence or re-occurrence of seizure." Cartt 2008 at ¶ [0136]. The Diastat Label discloses that diazepam could be used to treat "bouts of increased seizure activity" in patients, including "intermittent and periodic episodes of markedly increased seizure activity" that "were not only stereotypic but were judged by those conducting and participating in these studies to be distinguishable from other seizures suffered by that patient." Diastat Label at 1. The mere recitation of an inherent or latent property of an otherwise obvious formulation will not render the formulation patentable. *In re Kao*, 639 F.3d 1057, 1070 (Fed. Cir. 2011); *Santarus, Inc. v. Par Pharmaceutical, Inc.*, 694 F.3d 1344 (Fed. Cir. 2012). The Valtoco Label stated that "VALTOCO is a benzodiazepine indicated for the acute treatment of intermittent, stereotypic episodes of frequent seizure activity (i.e., seizure clusters, acute repetitive seizures) that are distinct from a patient's usual seizure pattern in patients with epilepsy 6 years of age and older." *See, e.g.*, Neurelis-00144572-599 at -572 (Valtoco Label, Rev. 02/2021). Thus, consistent with the Valtoco Label, patients and healthcare professionals administered a single spray of the Valtoco solution to the one nasal mucosal membrane of the patient, which resulted in a treatment selected from the group

Claim Language	Exemplary Prior Art Citations
	consisting of a reduction in the severity of the seizure, a reduction in the probability that the patient will experience a repeat seizure, an increase in the interval between a current seizure and a next seizure in the patient, a reduction in the frequency of seizure in the patient and combinations thereof.
2. The method of claim 1, wherein the treatment achieves 96% of the bioavailability of an equivalent dose of diazepam administered intravenously.	*See* claim 1.
3. The method of claim 1, where the treatment achieves a Tmax of about 1.5 hours.	*See* claim 1. Agarwal, describing NCT '558, discloses that the "[m]edian time to maximum concentration (Tmax) was 1hr and 1.5hr for suspension and formulation, respectively. The mean $T_{1/2}$ was similar for all three formulations. Both investigational intranasal formulations were well tolerated." Agarwal. The Neurelis Press Release, also reporting on NCT '558, discloses that "the NRL-1 intranasal solution formulation" achieved a "Tmax of 1.5 hours" and a "Cmax of approximately 272 ng/ml." Neurelis Press Release. The mere recitation of an inherent or latent property of an otherwise obvious formulation will not render the formulation patentable. *In re Kao*, 639 F.3d 1057, 1070 (Fed. Cir. 2011); *Santarus, Inc. v. Par Pharmaceutical, Inc.*, 694 F.3d 1344 (Fed. Cir. 2012).
4. The method of claim 1, wherein the pharmaceutical solution is substantially free of water.	*See* claim 1. Gwozdz discloses that "[t]he present invention is directed to the use of one or more tocopherols and/or tocotrienols and one or more alcohols and/or glycols as pharmaceutically acceptable solvents for solubilizing therapeutic agents, in particular

Claim Language	Exemplary Prior Art Citations
	hydrophobic or lipophilic therapeutic agents." Gwozdz at 4:29-33. Gwozdz does not discuss or teach the inclusion of water as an additional component of its pharmaceutical solutions. Gwozdz further discloses that "many therapeutic agents are so slightly soluble in water that a therapeutically effective amount cannot be dissolved in a volume of aqueous solvent that is amenable to application to a mucosal membrane. Use of a pharmaceutical solution of the present invention, however, provides for improved ability to dissolve lipophilic and lipophilic therapeutic agents, thus providing a useful delivery system for administration of such agents to one or more mucosal membranes, including the nasal mucosal membranes." *Id*. at 9:25-34. S*ee also id*. at 4:29-33. Cartt 2009 discloses that "the solution is at least substantially free of water. (In some embodiments, 'substantially free of water' indicates that the solution contains less than about 1%, less than about 0.5%, less than about 0.25% or less than about 0.1% water.)." Cartt 2009 at ¶¶ [0046]-[0047]. In view of Meezan, a POSA would have known to make the claimed intranasal diazepam formulation as a non-aqueous solution: "Meezan '962 is not limited to water soluble therapeutic drugs and discloses using alkyl glycosides in aqueous or non-aqueous systems." IPR2019-00451, Paper 44 at 45-46.
5. The method of claim 1, wherein the single spray of 100 μL is administered to one nasal mucosal membrane of the patient as a single metered spray.	*See* claim 1.
6. A method of treating bouts of intermittent and stereotypic episodes of increased seizure activity in an epilepsy patient that is	*See* claim 1.

Claim Language	Exemplary Prior Art Citations
distinguishable from other seizures suffered by the patient comprising:	
administering a single spray of 100 µL of a stable pharmaceutical solution to one nasal mucosal membrane of the patient and administering a second single spray of 100 µL of the pharmaceutical solution to a second nasal mucosal membrane of the patient, the 100 µL of the pharmaceutical solution consisting of:	*See* claim 1. Cartt 2009 discloses that solution formulations containing diazepam, Vitamin E USP, and dehydrated ethanol "were setup on stability at 25° C./60% RH, 30° C./65% RH and 40° C./75% RH." Cartt 2009 at ¶¶ [0200], [0204]. Cartt 2009 further discloses the results of those stability tests, showing that the solution formulations were "stable," including at "25° C and 60% relative humidity for at least 3 months." *Id*. at ¶¶ [0204]-[0210]. Meezan discloses "that therapeutic compositions comprising of least one drug and at least one surfactant, wherein the surfactant is comprised of at least one alkyl glycoside and/or at least one saccharide alkyl ester are stable, non-toxic, non-irritating, anti-bacterial compositions that increase bioavailability of the drug and have no observable adverse effects when administered to a subject." Meezan at ¶ [0048]. *See also id.* at ¶ [0162]. It would have also been well known to a POSA that any pharmaceutical formulation intended for administration to a patient must be "stable" to ensure it is safe and effective. *See, e.g.*, FDA, GUIDANCE FOR INDUSTRY: Q1A(R2) STABILITY TESTING OF NEW DRUG SUBSTANCES AND PRODUCTS (rev. 2, Nov. 2003); ICH, ICH HARMONISED TRIPARTITE GUIDELINE: EVALUATION FOR STABILITY DATA Q1E (Feb. 2003). The Valtoco Label stated that Valtoco is a "[n]asal spray" containing "5 mg, 7.5 mg, or 10 mg of diazepam in [100 µL]." *See, e.g.*, Neurelis-00144572-599 at -575 (Valtoco Label, Rev. 02/2021). "VALTOCO 5 mg and 10 mg doses are administered as a single spray

Claim Language	Exemplary Prior Art Citations
	intranasally into one nostril." *Id*. "Administration of 15 mg and 20 mg doses requires two nasal spray devices, one spray into each nostril." *Id*.
56.47 mg of vitamin E USP +/−5%;	*See* claim 1.
7.5 mg of diazepam;	*See* claim 1.
0.25 mg of dodecyl maltoside;	*See* claim 1.
10.50 mg of benzyl alcohol +/−5%, and a sufficient quantity of ethanol;	*See* claim 1.
wherein administering the single spray and the second single spray of the pharmaceutical solution to the patient achieves 92.5% to 107.5% of the bioavailability of an equivalent dose of diazepam administered intravenously and is safe and effective in treating the bouts of intermittent and stereotypic episodes of increased seizure activity in the patient; and	*See* claim 1. Cartt 2008 specifically discloses that "[i]n some embodiments, a first metered spray is applied to a first nostril and if necessary a second metered spray is applied to a second nostril." *Id*. at ¶ [0064]. Cartt 2009 discloses that its intranasal diazepam solution formulations could be administered in one or both nostrils, preferably in "about 100 µL metered sprays." Cartt 2009 at ¶¶ [0029], [0060].
wherein administering the single spray and the second single spray of the pharmaceutical solution to the patient results in a treatment selected from the group consisting of a reduction in the severity of the seizure, a reduction in the probability that the patient will experience a repeat seizure, an increase in the interval between a current seizure and a next seizure in the patient, a reduction in the frequency of seizure in the patient and combinations thereof.	*See* claim 1.
7. The method of claim 6, wherein the treatment achieves 96% of the bioavailability of an equivalent dose of diazepam administered intravenously.	*See* claim 6.

Claim Language	Exemplary Prior Art Citations
8. The method of claim 6, where the treatment achieves a Tmax of about 1.5 hours.	*See* claims 6 and 3.
9. The method of claim 6, wherein the pharmaceutical solution is substantially free of water.	*See* claims 6 and 4.
10. A method of treating bouts of intermittent and stereotypic episodes of increased seizure activity in an epilepsy patient that is distinguishable from other seizures suffered by the patient comprising:	*See* claim 1.
administering as a single spray of 100 μL to one nasal mucosal membrane of the patient of a pharmaceutical solution consisting of:	*See* claim 1.
56.47 mg of vitamin E USP +/−5%;	*See* claim 1.
5 mg of diazepam;	*See* claim 1.
0.25 mg of dodecyl maltoside;	*See* claim 1.
10.50 mg of benzyl alcohol +/−5%, and a sufficient quantity of ethanol;	*See* claim 1.
wherein administering the single spray of the pharmaceutical solution to the patient achieves 92.5% to 107.5% of the bioavailability of an equivalent dose of diazepam administered intravenously and is safe and effective in treating the bouts of intermittent and stereotypic episodes of increased seizure activity in the patient; and	*See* claim 1.
wherein administering the single spray of the pharmaceutical solution to the patient achieves results in a treatment selected from the group consisting of a reduction in the severity of the seizure, a reduction in the probability that the patient will experience a repeat seizure, an increase in the interval between a current seizure and a next seizure in the patient, a	*See* claim 1.

Claim Language	Exemplary Prior Art Citations
reduction in the frequency of seizure in the patient and combinations thereof.	
11. The method of claim 10, wherein the treatment achieves 96% of the bioavailability of an equivalent dose of diazepam administered intravenously.	*See* claim 10.
12. The method of claim 10, where the treatment achieves a Tmax of about 1.5 hours.	*See* claims 10 and 3.
13. The method of claim 10, wherein the pharmaceutical solution is substantially free of water.	*See* claims 10 and 4.
14. A method of treating bouts of intermittent and stereotypic episodes of increased seizure activity in an epilepsy patient that is distinguishable from other seizures suffered by the patient comprising:	*See* claim 1.
administering a single spray of 100 μL of a stable pharmaceutical solution to one nasal mucosal membrane of the patient and administering a second single spray of 100 μL of the pharmaceutical solution to a second nasal mucosal membrane of the patient, the 100 μL of the pharmaceutical solution consisting of:	*See* claim 6.
56.47 mg of vitamin E USP +/−5%;	*See* claim 1.
10 mg of diazepam;	*See* claim 1.
0.25 mg of dodecyl maltoside;	*See* claim 1.
10.50 mg of benzyl alcohol +/−5%, and a sufficient quantity of ethanol;	*See* claim 1.
wherein administering the single spray and the second single spray of the pharmaceutical solution to the patient achieves 92.5% to 107.5% of the bioavailability of an equivalent dose of diazepam administered intravenously and is safe and effective in treating the bouts of	*See* claim 6.

Claim Language	Exemplary Prior Art Citations
intermittent and stereotypic episodes of increased seizure activity in the patient;	
wherein administering the single spray and the second single spray of the pharmaceutical solution to the patient results in a treatment selected from the group consisting of a reduction in the severity of the seizure, a reduction in the probability that the patient will experience a repeat seizure, an increase in the interval between a current seizure and a next seizure in the patient, a reduction in the frequency of seizure in the patient and combinations thereof.	*See* claim 6.
15. The method of claim 14, wherein the treatment achieves 96% of the bioavailability of an equivalent dose of diazepam administered intravenously.	*See* claim 14.
16. The method of claim 14, where the treatment achieves a Tmax of about 1.5 hours.	*See* claims 14 and 3.
17. The method of claim 14, wherein the pharmaceutical solution is substantially free of water.	*See* claims 14 and 4.
18. The method of claim 1, wherein administering the single spray of the pharmaceutical solution to the patient achieves 96% to 97% of the bioavailability of an equivalent dose of diazepam administered intravenously.	*See* claim 1.
19. The method of claim 14, wherein administering the single spray and the second single spray of the pharmaceutical solution to the patient achieves 96% to 97% of the bioavailability of an equivalent dose of diazepam administered intravenously.	*See* claim 14.
20. The method of claim 1, wherein administering the single spray of the pharmaceutical solution to the one nasal mucosal membrane of the patient results in	*See* claim 1. Agarwal, describing NCT '558, discloses that the diazepam solution formulation exhibited a

Claim Language	Exemplary Prior Art Citations
treatment in less than about 5 minutes and treatment over about 24 hours.	similar half-life as the comparator IV formulation, and provided data that a POSA could use to extrapolate a half-life, treatment-time, AUC value within the relevant claim limitations. Agarwal. The Neurelis Press Release, also reporting on NCT '558, discloses that the formulation was able "to quickly and efficiently deliver, via intranasal administration, clinically relevant diazepam levels offers a more acceptable method of rescue therapy" based on the pharmacokinetic data. Neurelis Press Release at 2. The mere recitation of an inherent or latent property of an otherwise obvious formulation will not render the formulation patentable. *In re Kao*, 639 F.3d 1057, 1070 (Fed. Cir. 2011); *Santarus, Inc. v. Par Pharmaceutical, Inc.*, 694 F.3d 1344 (Fed. Cir. 2012).
21. The method of claim 6, wherein administering the single spray and the second single spray of the pharmaceutical solution to the patient results in treatment in less than about 5 minutes and treatment over about 24 hours.	*See* claims 6 and 20.
22. The method of claim 10, wherein administering the single spray of the pharmaceutical solution to the patient results in treatment in less than about 5 minutes and treatment over about 24 hours.	*See* claims 10 and 20.
23. The method of claim 14, wherein administering the single spray and the second single spray of the pharmaceutical solution to the patient results in treatment in less than about 5 minutes and treatment over about 24 hours.	*See* claims 14 and 20.
24. The method of claim 1, wherein administering the single spray of the pharmaceutical solution to the one nasal	*See* claim 1.

Claim Language	Exemplary Prior Art Citations
mucosal membrane of the patient exhibits a half-life ($t_{1/2}$) of about 49.2 hours.	Agarwal, describing NCT '558, discloses that the diazepam solution formulation exhibited a similar half-life as the comparator IV formulation, and provided data that a POSA could use to extrapolate a half-life, treatment-time, AUC value within the relevant claim limitations. Agarwal. Agarwal, further referencing the NCT '558 results, discloses that the "mean $T_{1/2}$ was similar for all three formulations. Both investigational intranasal formulations were well tolerated." Agarwal. The Neurelis Press Release, also reporting on NCT '558, discloses that the formulation was able "to quickly and efficiently deliver, via intranasal administration, clinically relevant diazepam levels offers a more acceptable method of rescue therapy" based on the pharmacokinetic data. Neurelis Press Release at 2. The mere recitation of an inherent or latent property of an otherwise obvious formulation will not render the formulation patentable. *In re Kao*, 639 F.3d 1057, 1070 (Fed. Cir. 2011); *Santarus, Inc. v. Par Pharmaceutical, Inc.*, 694 F.3d 1344 (Fed. Cir. 2012).
25. The method of claim 6, wherein administering the single spray and the second single spray of the pharmaceutical solution to the patient exhibits a half-life ($t_{1/2}$) of about 49.2 hours.	*See* claims 6 and 24.
26. The method of claim 10, wherein administering the single spray of the pharmaceutical solution to the patient exhibits a half-life ($t_{1/2}$) of about 49.2 hours.	*See* claims 10 and 24.
27. The method of claim 14, wherein administering the single spray and the second single spray of the pharmaceutical solution to	*See* claims 14 and 24.

Claim Language	Exemplary Prior Art Citations
the patient exhibits a half-life ($t_{1/2}$) of about 49.2 hours.	
28. The method of claim 1, wherein dodecyl maltoside is n-dodecyl-β-D-maltoside.	*See* claim 1.
29. The method of claim 6, wherein dodecyl maltoside is n-dodecyl-β-D-maltoside.	*See* claim 6.
30. The method of claim 10, wherein dodecyl maltoside is n-dodecyl-β-D-maltoside.	*See* claim 10.
31. The method of claim 14, wherein dodecyl maltoside is n-dodecyl-β-D-maltoside.	*See* claim 14.

Exhibit E: Invalidity of U.S. Patent No. 12,337,061

WIPO Publication No. WO 2009/120933 to Gwozdz et al. (hereinafter "Gwozdz") is titled "Pharmaceutical Solutions and Method for Solubilizing Therapeutic Agents," and was published October 1, 2009, and constitutes prior art under § 102(b).

U.S. Patent Application Publication No. 2006/0046962 to Meezan et al. (hereinafter "Meezan") is titled "Absorption Enhancers for Drug Administration," and was published on March 2, 2006, and constitutes prior art under § 102(b).

U.S. Pub. No. 2008/0279784 to Cartt et al. (hereinafter "Cartt 2008) is titled "Nasal Administration of Benzodiazepines" was published on November 13, 2008, and constitutes prior art under § 102(b).

USP 23/NF 18, Ed., "United States Pharmacopeia. The National Formulary," The United States Pharmacopoeial Convention Inc., Rockville (hereinafter "USP") was published in 1995, and constitutes prior art under § 102(b).

Diastat was initially approved by the FDA in 2005 and, thus, the corresponding drug product insert or label for Diastat (hereinafter "Diastat Label") constitutes prior art under § 102(b).

U.S. Pub. No. 2009/0258865 to Cartt et al. (hereinafter "Cartt 2009") is titled "Administration of Benzodiazepine Compositions," and was published on October 15, 2009, and constitutes prior art under § 102(b).

Clinical Trial No. NCT01364558 (hereinafter "NCT '558") was first posted by at least June 2, 2011, and constitutes prior art under § 102(b).

An abstract titled "A Pilot Study Assessing the Bioavailability and Pharmacokinetics of Diazepam After Intranasal and Intravenous Administration in Healthy Volunteers" (hereinafter "Agarwal") was published on October 4, 2011, and constitutes prior art under § 102(b).

A press release titled "Neurelis Announces Positive Results from Phase 1 Pharmacokinetic Study of NRL-01 (intranasal diazepam)" (hereinafter "Neurelis Press Release") was published on June 14, 2011, and constitutes prior art under § 102(a).

U.S. Pub. No. 2012/0252793 to Bream et al. (hereinafter "Bream") is titled "Intranasal Benzodiazepine Pharmaceutical Compositions," and was published on October 4, 2012, and constitutes prior art under § 102(b).

As set forth in the chart below, certain elements of the Asserted Claims of the '061 patent are disclosed, taught, suggested, and rendered obvious by Gwozdz in view of Meezan, Cartt 2008, and USP, optionally in view of the Diastat Label. Alternatively, as also set forth below, certain elements of the Asserted Claims of the '061 patent are disclosed, taught, suggested, and rendered obvious by Cartt 2009 in view of Meezan, further in view of NCT '558, Agarwal, and the Neurelis Press Release. As an additional alternative, certain elements of the Asserted Claims of the '061 patent are disclosed, taught, suggested, and rendered obvious by Cartt 2009 and Meezan, in view of the Diastat Label, NCT '558, Gwozdz, and USP. Additionally, the Asserted Claims of the '061

patent are disclosed, taught, suggested, and rendered obvious over Cartt 2009 in view of Gwozdz, Meezan, and/or Bream.

Further, as explained in Defendants' Preliminary Invalidity Contentions, the claims of the '061 patent should be limited to a priority date of December 13, 2023 in light of the new matter added to specification via an amendment filed on that date. Accordingly, the approved prescribing information for Valtoco ("Valtoco Label"), as well as the Valtoco product itself, constitutes prior art against the '061 patent because it was FDA approved, published, and/or otherwise on sale and publicly available more than one year before December 13, 2023. As shown in the chart below, the Valtoco Label, which describes the Valtoco product, anticipates the claims of the '061 patent because it disclosed, expressly or inherently, all limitations of the claims of the '061 patent. Finally, the Valtoco product was used and administered by patients and healthcare professionals consistent with the Valtoco Label before December 13, 2023.

The excerpts cited herein are exemplary. For any claim limitation, Defendants may rely on excerpts cited for any other limitation or additional excerpts not set forth fully herein to the extent necessary to provide a more comprehensive explanation for a reference's disclosure of a limitation. Where an excerpt refers to or discusses a figure or figure items, that figure and any additional descriptions of that figure should be understood to be incorporated by reference as if set forth fully therein. As set forth in the Preliminary Invalidity Contentions (incorporated herein in their entirety), to which this exhibit has been attached, a POSA at the time would have been motivated to combine the teachings of any groupings of the foregoing prior art references with his knowledge of the art. Such combinations would provide a reasonable expectation of success to arrive at the claimed invention(s), and thus each claim of this patent is invalid.

Claim Language	Exemplary Prior Art Citations
1. A method of treating bouts of intermittent and stereotypic episodes of increased seizure activity in an epilepsy patient that is distinguishable from other seizures suffered by the patient consisting of:	Cartt 2008 discloses that diazepam was known to be useful for the treatment of seizures. Cartt 2008 at ¶ [0003]. Cartt 2008 further discloses that "[n]asal formulations of benzodiazepines have been suggested for the acute treatment of seizure." *Id*. at ¶ [0007]. Cartt 2008 also discloses that benzodiazepines are anticonvulsants that can be administered for the "treatment of seizures, protection against seizure, reduction or amelioration of the intensity of seizure, reduction or amelioration of the frequency of seizure, and/or prevention of the occurrence or re-occurrence of seizure." *Id*. at ¶ [0136]. The Diastat Label discloses that diazepam could be used to treat "bouts of increased

Claim Language	Exemplary Prior Art Citations
	seizure activity" in patients, including "intermittent and periodic episodes of markedly increased seizure activity" that "were not only stereotypic but were judged by those conducting and participating in these studies to be distinguishable from other seizures suffered by that patient." Diastat Label at 1. Cartt 2009 discloses "pharmaceutical compositions comprising one or more benzodiazepine drugs for nasal administration, methods for producing and for using such compositions." Cartt 2009 at Abstract. Cartt 2009 further discloses that the benzodiazepine-containing intranasal formulations are "useful in preventing, treating, or ameliorating the symptoms of … seizures (such as those caused by epilepsy)." *Id*. at ¶ [0003]. *See also id.* at ¶ [0086]. NCT '558 describes three arms and interventions, which sought to investigate "the absolute bioavailability of two intranasal diazepam formulations" for the treatment of "epilepsy." NCT '558. Neurelis Press Release discloses that the formulation studied by NCT '558 "is being developed for the management of patients who require intermittent use of diazepam to control bouts of acute repetitive seizure activity." Neurelis Press Release at 1. Agarwal, reporting on NCT '558, discloses that the intranasal diazepam solution formulation was being investigated for the treatment of "acute repetitive seizures." Agarwal. Bream discloses methods for treating and/or preventing seizures, including acute repetitive seizures. Bream at [008], [0091].

Claim Language	Exemplary Prior Art Citations
	The Valtoco Label stated that "VALTOCO is a benzodiazepine indicated for the acute treatment of intermittent, stereotypic episodes of frequent seizure activity (i.e., seizure clusters, acute repetitive seizures) that are distinct from a patient's usual seizure pattern in patients with epilepsy 6 years of age and older." *See, e.g.*, Neurelis-00144572-599 at -572 (Valtoco Label, Rev. 02/2021). Further, the Valtoco product was used and administered by patients and healthcare professionals consistent with the Valtoco Label.
administering a single spray of 100 µL of a stable pharmaceutical solution to a nostril of the patient, the pharmaceutical solution containing:	Gwozdz further discloses that the pharmaceutical solution is "particularly useful in formulations to be administered to mucosal membranes, i.e. the nasal mucosa or lungs of a subject by any suitable means." *Id*. at 9:19-22. Gwozdz also discloses that its "solutions can be administered via, for example, a metered dose inhaler or nebulizer, or in a mist sprayer" "for administration" "to one or more mucosal membranes, including the nasal mucosal membranes." *Id*. at 9:28-10:2. Meezan discloses "a method of increasing absorption of a low molecular weight compound into the circulatory system of a subject by administering the compound via the... nasal,... delivery route..." Meezan at ¶ [0008]. Cartt 2008 discloses nasal formulations of diazepam and that "[n]asal preparations are generally administered in metered sprays having volumes of less than 250 µl, preferably less than 150 µl, and ideally from 25 to 100 µl, since administration of larger volumes usually exceeds the capacity of the nasal sinuses and results in volumes in excess of about 250 µl bypassing the sinuses and flowing down the back of the throat where it is swallowed." Cartt 2008 at ¶ [0007].

Claim Language	Exemplary Prior Art Citations
	Cartt 2008 specifically discloses that "[a]s a nasal formulation, diazepam may be administered in 25 to 250 µl metered sprays. In some preferred embodiments, diazepam is administered in 50 to 150 µl, especially about 100 µl, metered sprays. In some embodiments, a first metered spray is applied to a first nostril and if necessary a second metered spray is applied to a second nostril." *Id*. at ¶ [0064]. NCT '558 discloses that one tested intranasal diazepam formulation was described by NCT '558 as a "solution" which outperformed a "suspension" formulation. NCT '558 Agarwal, reporting on NCT '558, discloses that the 10 mg dose of the intranasal diazepam solution formulation resulted in a "[b]ioavailability" that "approached 100% and was significantly ($p<0.05$) greater than the IN suspension, as was Cmax." Agarwal. Neurelis Press Release, also reporting on NCT '588, discloses that the "NRL-1 intranasal solution formulation" as the "lead intranasal formulation." Neurelis Press Release at 1. Cartt 2009 discloses intranasal diazepam solution formulations. Cartt 2009 at Abstract. Cartt 2009 further discloses that its compositions may be formulated such that diazepam is fully dissolved so that "the benzodiazepine drug is formulated as a solution." *Id*. at ¶ [0168]. Cartt 2009 also discloses that vitamin E (see below) can form emulsions having drawbacks which can be avoided by the formulations being "solutions of one or more benzodiazepine drugs in Vitamin E and one or more lower alkyl alcohols." *Id*. at ¶ [0135]. Cartt 2009 further discloses that its intranasal diazepam solution formulations could be

Claim Language	Exemplary Prior Art Citations
	administered in one or both nostrils, preferably in "about 100 μL metered sprays." Cartt 2009 at ¶¶ [0029], [0060]. Cartt 2009 also discloses that such administration was well-known in the art: "Mucosal membrane preparations are generally administered in metered sprays having volumes of … ideally from 25 to 100 μL. Although not prohibited in this invention, administration of volumes larger than about 300 μL per dose usually exceeds the absorption capacity of the membranes. This results in a large portion of the pharmaceutically-active ingredient being lost. The dosage volume of preparations, in particular nasal preparations, preferably ranges from 25 to 100 μL. Volumes in excess of the aforementioned ranges may bypass the sinuses and flow down the back of the throat where the excess is swallowed." *Id*. at ¶ [0144]. Cartt 2009 discloses that solution formulations containing diazepam, Vitamin E USP, and dehydrated ethanol "were setup on stability at 25° C./60% RH, 30° C./65% RH and 40° C./75% RH." Cartt 2009 at ¶¶ [0200], [0204]. Cartt 2009 further discloses the results of those stability tests, showing that the solution formulations were "stable," including at "25° C and 60% relative humidity for at least 3 months." *Id*. at ¶¶ [0204]-[0210]. A POSA at the time would know that commercial nasal spray products typically deliver 100-200 μL (i.e., 0.1-0.2 mL) per spray, as the human nasal cavity can only receive and retain about 100-150 μL of liquid. *See*, *e.g.*, Wermeling, D. et al., "Pharmacokinetics and pharmacodynamics of a new intranasal midazolam formulation in healthy volunteers." Anesth Analg 2006; 103:344-349, 344 (teaching that "[t]he adult nasal cavity can only receive and retain about

Claim Language	Exemplary Prior Art Citations
	100-150 µL of liquid, requiring the dose of midazolam be solubilized within this volume. A nasal formulation with a concentration of 2.5 mg per 100 µL is necessary to give a single spray per naris."). NCT '558 discloses that the diazepam solution was administered as a "nasal spray." NCT '558. Agarwal discloses confirmation that the diazepam solution was administered intranasally. Agarwal. The Neurelis Press Release also discloses that "NRL-01 (intranasal diazepam) is a proprietary formulation of diazepam delivered via a commercially available nasal sprayer." Neurelis Press Release at 2. Meezan discloses "that therapeutic compositions comprising of least one drug and at least one surfactant, wherein the surfactant is comprised of at least one alkyl glycoside and/or at least one saccharide alkyl ester are stable, non-toxic, non-irritating, anti-bacterial compositions that increase bioavailability of the drug and have no observable adverse effects when administered to a subject." Meezan at ¶ [0048]. *See also id.* at ¶ [0162]. It would have also been well known to a POSA that any pharmaceutical formulation intended for administration to a patient must be "stable" to ensure it is safe and effective. *See, e.g.*, FDA, GUIDANCE FOR INDUSTRY: Q1A(R2) STABILITY TESTING OF NEW DRUG SUBSTANCES AND PRODUCTS (rev. 2, Nov. 2003); ICH, ICH HARMONISED TRIPARTITE GUIDELINE: EVALUATION FOR STABILITY DATA Q1E (Feb. 2003). The Valtoco Label stated that Valtoco is a "[n]asal spray" containing "5 mg, 7.5 mg, or 10 mg of diazepam in [100 µL." *See, e.g.*,

Claim Language	Exemplary Prior Art Citations
	Neurelis-00144572-599 at -575 (Valtoco Label, Rev. 02/2021). "VALTOCO 5 mg and 10 mg doses are administered as a single spray intranasally into one nostril." *Id*. Thus, consistent with the Valtoco Label, the Valtoco product was administered as a single spray of 100 µL to one nasal mucosal membrane of the patient by patients and healthcare professionals.
56.47 mg of vitamin E USP;	Gwozdz discloses "the use of one or more tocopherols and/or tocotrienols and one or more alcohols and/or glycols as pharmaceutically acceptable solvents for solubilizing therapeutic agents, in particular hydrophobic or lipophilic therapeutic agents." Gwozdz at 4:29-33. Gwozdz also discloses that which would have been well known to a POSA at the time: "Tocopherols and/or tocotrienols for use in accordance with the present invention include a family of natural and synthetic compounds, also known by the generic names tocols or vitamin E." Gwozdz at 5:33-6:2. Gwozdz further discloses that "[i]n one embodiment of the present invention the tocopherol (s) and/or tocotrienol (s) employed is alpha-tocopherol." *Id*. at 6:13-15. Gwozdz also discloses that "the tocopherol(s) and/or tocotrienol(s) is in an amount from about 30% to about 99% (w/w)." *Id*. at 4:17-19. USP discloses that vitamin E was well-known in the art at the time: "Vitamin E is a form of alpha tocopherol ($C_{29}H_{50}O_2$). It includes the following d- or dl-alpha tocopherol ($C_{29}H_{50}O_2$); d- or dl-alpha tocopheryl acetate ($C_{31}H_{52}O_3$); d- or dl-alpha tocopheryl acid succinate ($C_{33}H_{54}O_5$)." USP at 1631.

Claim Language	Exemplary Prior Art Citations
	Cartt 2009 discloses pharmaceutical compositions for nasal administration that contain "a benzodiazepine drug; one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); and one or more alcohols or glycols, or any combinations thereof, in an amount from about 5% to about 70% (w/w), preferably about 10% to about 70% (w/w) in a pharmaceutically-acceptable formulation for administration to one or more nasal mucosal membranes of the patient." Cartt 2009 at ¶ [0010]. Cartt 2009 further discloses that "Vitamin E can provide an effective carrier for benzodiazepine drugs." *Id*. at ¶ [0134]. Cartt 2009 specifically discloses that the carrier system of its compositions may contain "about 50% to about 90% (w/w) Vitamin E and about 10% to about 50% (w/w) lower alcohol" or "about 65% to about 75% (w/w) Vitamin E and about 25% to about 35% (w/w) lower alkyl alcohol." *Id*. at ¶ [0162]. The Valtoco Label stated that "[t]he inactive ingredients in VALTOCO nasal spray include benzyl alcohol (10.5 mg per 0.1 mL), dehydrated alcohol, n-dodecyl beta-D-maltoside, and vitamin E." *See, e.g.*, Neurelis-00144572-599 at -587 (Valtoco Label, Rev. 02/2021). Further, a POSA would have understood that Valtoco contained 56.47 mg of vitamin E USP +/−5%, consistent with Dr. Stuart Madden's statement that Valtoco contains that amount of Vitamin E. Neurelis-02049865-881.
10 mg of diazepam;	Gwozdz discloses that "[e]xemplary hydrophobic or lipophilic therapeutic agents which can be solubilized in accordance with the present invention include, but are in no way

Claim Language	Exemplary Prior Art Citations
	limited to,… benzodiazepenes such as Diazepam,…" Gwozdz at 8:6-18. Gwozdz discloses diazepam as a preferred therapeutic agent, for use in its solubilizing solutions, and that the solubility of diazepam can be increased from less than or equal to 6.67% (in ethanol) to "approaching the 10% level" (when incorporating tocopherol into the solution). *Id*. at 7:12-16. Cartt 2008 discloses that "[d]iazepam is a benzodiazepine drug having sedative, tranquilizing and muscle relaxing properties. It is classified as an anxiolytic and skeletal muscle relaxant. It possesses anxiolytic, anticonvulsant, sedative, skeletal muscle relaxant and amnesic properties" and that exemplary doses of diazepam delivered via nasal administration "may vary by indication, however it is expected that a therapeutic dose will be in the range of about 1 to about 20, preferably about 2 to about 10 mg per dose…" Cartt 2008 at ¶ [0063]. Cartt 2008 also discloses that "[i]n some embodiments, the benzodiazepine or pharmaceutically acceptable salt thereof is present in a concentration of from about 0.05 mg/mL up to about 600 mg/mL." *Id*. at ¶ [0034]. Cartt 2009 discloses that "[t]he dosage of diazepam may vary by indication, however it is expected that a therapeutic dose will be in the range of about 1 to about 20, preferably about 2 to about 10 mg per dose…" Cartt 2009 at ¶ [0086]. *See also id.* at ¶ [0147]. NCT '558 discloses the use of a 10 mg dose of diazepam. NCT '558. Agarwal discloses the use of a 10 mg dose of diazepam. Agarwal.

Claim Language	Exemplary Prior Art Citations
	The Neurelis Press Release discloses the use of a 10 mg dose of diazepam. Neurelis Press Release at 1. The Valtoco Label stated that Valtoco is a "[n]asal spray" containing "5 mg, 7.5 mg, or 10 mg of diazepam in [100 µL]." *See, e.g.*, Neurelis-00144572-599 at -575 (Valtoco Label, Rev. 02/2021). Thus, a POSA would have understood that Valtoco contained 10 mg of diazepam, consistent with Dr. Stuart Madden's statement that Valtoco contains that amount of diazepam. Neurelis-02049865-881.
0.25 mg of dodecyl maltoside;	Gwozdz discloses a wide range of types of excipients that can be included in its benzodiazepine solution formulations. Gwozdz at 10:3-16, 12:12-22. Cartt 2008 discloses that its benzodiazepine formulations may contain various excipients including "n-dodecyl β-D-maltoside." *See, e.g.*, Cartt 2008 at ¶¶ [0128]-[0129], [0168], [0183]. Meezan discloses enhanced bioavailability of therapeutic agents using alkyl glycoside or saccharide alkyl ester: "Alkyl glycosides of the present invention can include, but are not limited to: alkyl glycosides, such as octyl-, nonyl-, decyl-, undecyl-, dodecyl-, tridecyl-, tetradecyl-, pentadecyl-,hexadecyl-, heptadecyl-, and octadecyl-α- or β-D-maltoside, -glucoside or -sucroside…." while further disclosing that "some preferred glycosides include maltose, sucrose, and glucose linked by glycosidic linkage to an alkyl chain of 9, 10, 12, 13, 14, 16, 18, 20, 22, or 24 carbon atoms, e.g., nonyl-, decyl-, dodecyl- and tetradecyl sucroside, glucoside, and maltoside, etc." Meezan at ¶¶ [0056], [0058]. Meezan further discloses alkylmaltosides, including dodecyl maltoside, as a preferred

Claim Language	Exemplary Prior Art Citations
	alkyl glycoside compound. *Id*. at ¶¶ [0092], [0156]. Meezan specifically discloses compositions having an alkyl glycoside (such as dodecyl-beta-D-maltoside) in an amount of about 0.25%. *See, e.g., id*. at ¶¶ [0150]-[0151]. *See also id.* at Fig. 1, ¶¶ [0158]-[0159], Table I, and Example 6. Meezan also discloses preferred alkyl glycoside concentrations, stating that intranasal delivery of a lipophilic therapeutic compound like diazepam "with 0.125% and 0.250% alkyl glycoside" resulted in "about 43% to about 90% bioavailability, respectively," as compared to only 3% bioavailability when the alkyl glycoside compound was not present. *Id*. at ¶ [0150]. Cartt 2009 discloses pharmaceutical compositions that may contain an alkyl glycoside such as dodecyl maltoside. Cartt 2009 at ¶¶ [0019], [0138], [0142]-[0143], [0210]. Cartt 2009 further discloses the use of a "penetration enhancer" like alkyl glycosides in intranasal diazepam solution formulations. Cartt 2009 at ¶ [0058]. Cartt further explains that "[t]he term 'penetration enhancer', means any material which acts to increase absorption across the mucosa and/or increases bioavailability." *Id*. at ¶ [0139]. Cartt 2009 also discloses that the penetration enhancer may be an alkyl glycoside, such as dodecyl maltoside specifically, where "the amount of alkyl glycoside in the composition is in a range of about 0.01% (w/v) to about 1% (w/v)." *Id*. at ¶ [0058]. A POSA would have expected surfactants, such as alkyl glycosides to increase the

Claim Language	Exemplary Prior Art Citations
	bioavailability of intranasal formulations. *See e.g.* Sharma at 500-01, Ahsan at 27. The Valtoco Label stated that "[t]he inactive ingredients in VALTOCO nasal spray include benzyl alcohol (10.5 mg per 0.1 mL), dehydrated alcohol, n-dodecyl beta-D-maltoside, and vitamin E." *See, e.g.*, Neurelis-00144572-599 at -587 (Valtoco Label, Rev. 02/2021). A POSA would have understood that Valtoco contained 0.25 mg of dodecyl maltoside, consistent with Dr. Stuart Madden's statement that Valtoco contains that amount of DDM. Neurelis-02049865-881.
10.50 mg of benzyl alcohol; and a sufficient quantity of ethanol;	Gwozdz discloses that "[i]n accordance with the present invention, solutions of one or more tocopherols and/or tocotrienols and one or more alcohols and/or glycols are used in the solubilization of hydrophobic or lipophilic therapeutic agents thereby providing increased bioavailability of the therapeutic agent." Gwozdz at 7:3-8. Gwozdz further discloses that "[e]xamples of alcohol (s) for use in the present invention include, but are not limited to ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, and any isomers thereof, and any combinations thereof." *Id*. at 6:16-7:2. Gwozdz also discloses that that the pharmaceutical solutions should contain the alcohol excipient(s) "in an amount from about 1% to about 70% (w/w)." *Id*. at 4:17-21. Cartt 2008 discloses benzyl alcohol and ethanol as solvents that may be used to prepare intranasal diazepam formulations. Cartt 2008 at ¶ [0182]. Meezan similarly discloses benzyl alcohol as a potential "pharmaceutically acceptable carrier." Meezan at ¶ [0074].

Claim Language	Exemplary Prior Art Citations
	Cartt 2009 discloses pharmaceutical compositions for nasal administration that contain "a benzodiazepine drug; one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); and one or more alcohols or glycols, or any combinations thereof, in an amount from about 5% to about 70% (w/w), preferably about 10% to about 70% (w/w) in a pharmaceutically-acceptable formulation for administration to one or more nasal mucosal membranes of the patient." Cartt 2009 at ¶ [0010]. Cartt 2009 specifically discloses that the one or more alcohols may be chosen from benzyl alcohol and/or ethanol. *Id*. at ¶¶ [0013], [0136]. Cartt 2009 also discloses that vitamin E can form emulsions having drawbacks which can be avoided by the formulations being "solutions of one or more benzodiazepine drugs in Vitamin E and one or more lower alkyl alcohols." *Id*. at ¶ [0135]. Cartt 2009 specifically discloses that the "[l]ower alkyl alcohols" include a limited number of alcohols, including benzyl alcohol and ethanol. *Id*. at ¶ [0136]. Cartt 2009 further discloses that the carrier system of its compositions may contain "about 50% to about 90% (w/w) Vitamin E and about 10% to about 50% (w/w) lower alcohol" or "about 65% to about 75% (w/w) Vitamin E and about 25% to about 35% (w/w) lower alkyl alcohol." *Id*. at ¶ [0162]. The Valtoco Label stated that "[t]he inactive ingredients in VALTOCO nasal spray include benzyl alcohol (10.5 mg per 0.1 mL), dehydrated alcohol, n-dodecyl beta-D-maltoside, and vitamin E." *See, e.g.*, Neurelis-00144572-599 at -587 (Valtoco Label, Rev. 02/2021). Thus, a POSA would have understood that Valtoco contained 10.50 mg of

Claim Language	Exemplary Prior Art Citations
	benzyl alcohol and a sufficient quantity of ethanol, consistent with Dr. Stuart Madden's statement that Valtoco contains that amount of benzyl alcohol and ethanol. Neurelis-02049865-881.
wherein administering the single spray of the pharmaceutical solution achieves 96% to 97% of the bioavailability of an equivalent dose of diazepam administered intravenously; wherein administering the single spray of the pharmaceutical solution is safe and effective in treating the bouts of intermittent and stereotypic episodes of increased seizure activity in the patient; and	Meezan discloses preferred alkyl glycoside concentrations, stating that intranasal delivery of a lipophilic therapeutic compound like diazepam "with 0.125% and 0.250% alkyl glycoside" resulted in "about 43% to about 90% bioavailability, respectively," as compared to only 3% bioavailability when the alkyl glycoside compound was not present. Meezan at ¶ [0150]. NCT '558 discloses a goal being "to assess the bioavailability and pharmacokinetics of two formulations of diazepam after intranasal (nasal spray) and injectable diazepam after intravenous (I.V.) administration." NCT '558. NCT '558 also discloses three arms and interventions, which sought to investigate "the absolute bioavailability of two intranasal diazepam formulations" for the treatment of "epilepsy." *Id*. Agarwal, reporting on NCT '558, discloses that the 10 mg dose of the intranasal diazepam solution formulation resulted in a "[b]ioavailability" that "approached 100% and was significantly ($p<0.05$) greater than the IN suspension, as was Cmax." Agarwal. The Neurelis Press Release, reporting on the results of NCT '558, discloses that its "lead intranasal formulation, NRL-1, revealed promising pharmacokinetic results. In its evaluation of a 10 mg diazepam dose in the NRL-1 intranasal solution formulation, the study showed the following:

Claim Language	Exemplary Prior Art Citations
	• NRL-1 is well-tolerated, with only mild adverse events reported • Similar bioavailability to intravenous administration of diazepam (100% vs. 96%)…" Neurelis Press Release at 1. The mere recitation of an inherent or latent property of an otherwise obvious formulation will not render the formulation patentable. *In re Kao*, 639 F.3d 1057, 1070 (Fed. Cir. 2011); *Santarus, Inc. v. Par Pharmaceutical, Inc.*, 694 F.3d 1344 (Fed. Cir. 2012). The Valtoco Label stated that "VALTOCO is a benzodiazepine indicated for the acute treatment of intermittent, stereotypic episodes of frequent seizure activity (i.e., seizure clusters, acute repetitive seizures) that are distinct from a patient's usual seizure pattern in patients with epilepsy 6 years of age and older." *See, e.g.*, Neurelis-00144572-599 at -572 (Valtoco Label, Rev. 02/2021). The Valtoco Label disclosed that "[t]he absolute bioavailability of VALTOCO relative to intravenous diazepam was 97%." *Id*. at -4587. Thus, the Valtoco label expressly disclosed that Valtoco achieved a bioavailability of 96 % to 97 % of the bioavailability of an equivalent dose of diazepam administered intravenously and is safe and effective in treating the bouts of intermittent and stereotypic episodes of increased seizure activity in the patient, which is also an inherent property of Valtoco.
wherein administering the single spray of the pharmaceutical solution results in a treatment selected from the group consisting of a reduction in the severity of the seizure, a reduction in the probability that the patient will experience a repeat seizure, an increase in the interval between a current seizure and a next	Cartt 2008 also discloses that benzodiazepines are anticonvulsants that can be administered for the "treatment of seizures, protection against seizure, reduction or amelioration of the intensity of seizure, reduction or amelioration of the frequency of seizure,

Claim Language	Exemplary Prior Art Citations
seizure in the patient, a reduction in the frequency of seizure in the patient and combinations thereof.	and/or prevention of the occurrence or re-occurrence of seizure." Cartt 2008 at ¶ [0136]. The Diastat Label discloses that diazepam could be used to treat "bouts of increased seizure activity" in patients, including "intermittent and periodic episodes of markedly increased seizure activity" that "were not only stereotypic but were judged by those conducting and participating in these studies to be distinguishable from other seizures suffered by that patient." Diastat Label at 1. The mere recitation of an inherent or latent property of an otherwise obvious formulation will not render the formulation patentable. *In re Kao*, 639 F.3d 1057, 1070 (Fed. Cir. 2011); *Santarus, Inc. v. Par Pharmaceutical, Inc.*, 694 F.3d 1344 (Fed. Cir. 2012). The Valtoco Label stated that "VALTOCO is a benzodiazepine indicated for the acute treatment of intermittent, stereotypic episodes of frequent seizure activity (i.e., seizure clusters, acute repetitive seizures) that are distinct from a patient's usual seizure pattern in patients with epilepsy 6 years of age and older." *See, e.g.*, Neurelis-00144572-599 at -572 (Valtoco Label, Rev. 02/2021). Thus, consistent with the Valtoco Label, patients and healthcare professionals administered a single spray of the Valtoco solution to the one nasal mucosal membrane of the patient, which resulted in a treatment selected from the group consisting of a reduction in the severity of the seizure, a reduction in the probability that the patient will experience a repeat seizure, an increase in the interval between a current seizure and a next seizure in the patient, a reduction in the frequency of seizure in the patient and combinations thereof.

Claim Language	Exemplary Prior Art Citations
2. The method of claim 1, wherein the pharmaceutical solution is stable at 25° C. and 60% relative humidity for at least 3 months.	*See* claim 1. Cartt 2009 discloses that solution formulations containing diazepam, Vitamin E USP, and dehydrated ethanol "were setup on stability at 25° C./60% RH, 30° C./65% RH and 40° C./75% RH." Cartt 2009 at ¶¶ [0200], [0204]. Cartt 2009 further discloses the results of those stability tests, showing that the solution formulations were "stable," including at "25° C and 60% relative humidity for at least 3 months." *Id*. at ¶¶ [0204]-[0210]. Meezan discloses "that therapeutic compositions comprising of least one drug and at least one surfactant, wherein the surfactant is comprised of at least one alkyl glycoside and/or at least one saccharide alkyl ester are stable, non-toxic, non-irritating, anti-bacterial compositions that increase bioavailability of the drug and have no observable adverse effects when administered to a subject." Meezan at ¶ [0048]. *See also id.* at ¶ [0162]. It would have also been well known to a POSA that any pharmaceutical formulation intended for administration to a patient must be "stable" to ensure it is safe and effective. *See, e.g.*, FDA, GUIDANCE FOR INDUSTRY: Q1A(R2) STABILITY TESTING OF NEW DRUG SUBSTANCES AND PRODUCTS (rev. 2, Nov. 2003); ICH, ICH HARMONISED TRIPARTITE GUIDELINE: EVALUATION FOR STABILITY DATA Q1E (Feb. 2003). The mere recitation of an inherent or latent property, such as stability, of an otherwise obvious formulation will not render the formulation patentable. *In re Kao*, 639 F.3d 1057, 1070 (Fed. Cir. 2011); *Santarus, Inc. v. Par Pharmaceutical, Inc.*, 694 F.3d 1344 (Fed. Cir. 2012).

Claim Language	Exemplary Prior Art Citations
3. The method of claim 1, wherein administering the single spray of the pharmaceutical solution results in treatment in less than about 5 minutes.	*See* claim 1. Agarwal, describing NCT '558, discloses that the diazepam solution formulation exhibited a similar half-life as the comparator IV formulation, and provided data that a POSA could use to extrapolate a half-life, treatment-time, AUC value within the relevant claim limitations. Agarwal. The Neurelis Press Release, also reporting on NCT '558, discloses that the formulation was able "to quickly and efficiently deliver, via intranasal administration, clinically relevant diazepam levels offers a more acceptable method of rescue therapy" based on the pharmacokinetic data. Neurelis Press Release at 2. The mere recitation of an inherent or latent property of an otherwise obvious formulation will not render the formulation patentable. *In re Kao*, 639 F.3d 1057, 1070 (Fed. Cir. 2011); *Santarus, Inc. v. Par Pharmaceutical, Inc.*, 694 F.3d 1344 (Fed. Cir. 2012).
4. The method of claim 3, wherein administering the single spray of the pharmaceutical solution results in treatment over about 24 hours.	*See* claim 3. Agarwal, describing NCT '558, discloses that the diazepam solution formulation exhibited a similar half-life as the comparator IV formulation, and provided data that a POSA could use to extrapolate a half-life, treatment-time, AUC value within the relevant claim limitations. Agarwal. The Neurelis Press Release, also reporting on NCT '558, discloses that the formulation was able "to quickly and efficiently deliver, via intranasal administration, clinically relevant diazepam levels offers a more acceptable method of rescue therapy" based on the pharmacokinetic data. Neurelis Press Release at 2.

Claim Language	Exemplary Prior Art Citations
	The mere recitation of an inherent or latent property of an otherwise obvious formulation will not render the formulation patentable. *In re Kao*, 639 F.3d 1057, 1070 (Fed. Cir. 2011); *Santarus, Inc. v. Par Pharmaceutical, Inc.*, 694 F.3d 1344 (Fed. Cir. 2012).
5. A method of treating bouts of intermittent and stereotypic episodes of increased seizure activity in an epilepsy patient that is distinguishable from other seizures suffered by the patient consisting of:	*See* claim 1.
administering a single spray of 100 µL of a stable pharmaceutical solution to a nostril of the patient and administering a second single spray of 100 µL of the pharmaceutical solution to a second nostril of the patient, each of the 100 µL of the pharmaceutical solution containing:	*See* claim 1. Cartt 2009 discloses that solution formulations containing diazepam, Vitamin E USP, and dehydrated ethanol "were setup on stability at 25° C./60% RH, 30° C./65% RH and 40° C./75% RH." Cartt 2009 at ¶¶ [0200], [0204]. Cartt 2009 further discloses the results of those stability tests, showing that the solution formulations were "stable," including at "25° C and 60% relative humidity for at least 3 months." *Id*. at ¶¶ [0204]-[0210]. Meezan discloses "that therapeutic compositions comprising of least one drug and at least one surfactant, wherein the surfactant is comprised of at least one alkyl glycoside and/or at least one saccharide alkyl ester are stable, non-toxic, non-irritating, anti-bacterial compositions that increase bioavailability of the drug and have no observable adverse effects when administered to a subject." Meezan at ¶ [0048]. *See also id.* at ¶ [0162]. It would have also been well known to a POSA that any pharmaceutical formulation intended for administration to a patient must be "stable" to ensure it is safe and effective. *See, e.g.*, FDA, GUIDANCE FOR INDUSTRY: Q1A(R2) STABILITY TESTING OF NEW DRUG SUBSTANCES AND PRODUCTS (rev. 2, Nov.

Claim Language	Exemplary Prior Art Citations
	2003); ICH, ICH HARMONISED TRIPARTITE GUIDELINE: EVALUATION FOR STABILITY DATA Q1E (Feb. 2003). The Valtoco Label stated that Valtoco is a "[n]asal spray" containing "5 mg, 7.5 mg, or 10 mg of diazepam in [100 µL]." *See, e.g.*, Neurelis-00144572-599 at -575 (Valtoco Label, Rev. 02/2021). "VALTOCO 5 mg and 10 mg doses are administered as a single spray intranasally into one nostril." *Id*. "Administration of 15 mg and 20 mg doses requires two nasal spray devices, one spray into each nostril." *Id*.
56.47 mg of vitamin E USP;	*See* claim 1.
10 mg of diazepam;	*See* claim 1.
0.25 mg of dodecyl maltoside;	*See* claim 1.
10.50 mg of benzyl alcohol; and	*See* claim 1.
a sufficient quantity of ethanol;	*See* claim 1.
wherein administering the single spray and administering the second single spray of the pharmaceutical solution achieves 96% to 97% of the bioavailability of an equivalent dose of diazepam administered intravenously;	*See* claim 1.
wherein administering the single spray and administering the second single spray of the pharmaceutical solution is safe and effective in treating the bouts of intermittent and stereotypic episodes of increased seizure activity in the patient; and	*See* claim 1.
wherein administering the single spray and administering the second single spray of the pharmaceutical solution results in a treatment selected from the group consisting of a reduction in the severity of the seizure, a reduction in the probability that the patient will experience a repeat seizure, an increase in the	*See* claim 1.

Claim Language	Exemplary Prior Art Citations
interval between a current seizure and a next seizure in the patient, a reduction in the frequency of seizure in the patient and combinations thereof.	
6. The method of claim 5, wherein the pharmaceutical solution is stable at 25° C. and 60% relative humidity for at least 3 months.	*See* claims 5 and 2.
7. The method of claim 5, wherein administering the single spray and administering the second single spray of the pharmaceutical solution results in treatment in less than about 5 minutes.	*See* claims 5 and 3.
8. The method of claim 7, wherein administering the single spray and administering the second single spray of the pharmaceutical solution results in treatment over about 24 hours.	*See* claims 7 and 4.
9. The method of claim 1, wherein the single spray of 100 μL is administered to a nostril of the patient as a single metered spray.	*See* claim 1.
10. The method of claim 5, wherein the single spray of 100 μL and the second single spray of 100 μL are each administered to a nostril of the patient as a single metered spray.	*See* claims 5 and 1.
11. The method of claim 1, wherein the ethanol is dehydrated ethanol.	*See* claim 1. USP discloses that "dehydrated ethanol" contains "not less than 99.2 percent, by weight, corresponding to not less than 99.5 percent, by volume, at 15.56°, of C_2H_5OH." USP at 42-43. It would have been well known to a POSA that it is preferable to use dehydrated ethanol instead of ethanol with higher water content, particularly in a spray formulation with a poorly water-soluble drug like diazepam. *See*, *e.g.*, Gwozdz at 1:10-17; Cartt 2008 at ¶ [0007].

Claim Language	Exemplary Prior Art Citations
12. The method of claim 5, wherein the ethanol is dehydrated ethanol.	*See* claims 5 and 11.
13. The method of claim 1, wherein the dodecyl maltoside is n-dodecyl-β-D-maltoside.	*See* claim 1.
14. The method of claim 5, wherein the dodecyl maltoside is n-dodecyl-β-D-maltoside.	*See* claim 1.
15. The method of claim 1, wherein the pharmaceutical solution exhibits an approximate area under a blood plasma concentration curve measuring total drug exposure across time ($AUC_{0-\infty}$) of 7338 hours*ng/ml.	*See* claim 1. Agarwal, describing NCT '558, discloses that the diazepam solution formulation exhibited a similar half-life as the comparator IV formulation, and provided data that a POSA could use to extrapolate a half-life, treatment-time, AUC value within the relevant claim limitations. Agarwal. The Neurelis Press Release, also reporting on NCT '558, discloses that the formulation was able "to quickly and efficiently deliver, via intranasal administration, clinically relevant diazepam levels offers a more acceptable method of rescue therapy" based on the pharmacokinetic data. Neurelis Press Release at 2. The mere recitation of an inherent or latent property of an otherwise obvious formulation will not render the formulation patentable. *In re Kao*, 639 F.3d 1057, 1070 (Fed. Cir. 2011); *Santarus, Inc. v. Par Pharmaceutical, Inc.*, 694 F.3d 1344 (Fed. Cir. 2012).
16. The method of claim 5, wherein the pharmaceutical solution exhibits an approximate area under a blood plasma concentration curve measuring total drug exposure across time ($AUC_{0-\infty}$) of 7338 hours*ng/mL.	*See* claims 5 and 15.

Claim Language	Exemplary Prior Art Citations
17. The method of claim 1, wherein the pharmaceutical solution exhibits an approximate C_{max} of 272 ng/mL.	*See* claim 1. Agarwal, reporting on NCT '558, discloses that the 10 mg dose of the intranasal diazepam solution formulation resulted in a "[b]ioavailability" that "approached 100% and was significantly ($p<0.05$) greater than the IN suspension, as was Cmax." Agarwal. The Neurelis Press Release, also reporting on NCT '558, discloses that "the NRL-1 intranasal solution formulation" achieved a "Tmax of 1.5 hours" and a "Cmax of approximately 272 ng/ml." Neurelis Press Release. The mere recitation of an inherent or latent property of an otherwise obvious formulation will not render the formulation patentable. *In re Kao*, 639 F.3d 1057, 1070 (Fed. Cir. 2011); *Santarus, Inc. v. Par Pharmaceutical, Inc.*, 694 F.3d 1344 (Fed. Cir. 2012).
18. The method of claim 5, wherein the pharmaceutical solution exhibits an approximate C_{max} of 272 ng/mL.	*See* claims 5 and 17.
19. The method of claim 1, wherein the pharmaceutical solution exhibits an approximate T_{max} of 1.5 hours.	*See* claim 1. Agarwal, describing NCT '558, discloses that the "[m]edian time to maximum concentration (Tmax) was 1hr and 1.5hr for suspension and formulation, respectively. The mean $T_{1/2}$ was similar for all three formulations. Both investigational intranasal formulations were well tolerated." Agarwal. The Neurelis Press Release, also reporting on NCT '558, discloses that "the NRL-1 intranasal solution formulation" achieved a "Tmax of 1.5 hours" and a "Cmax of approximately 272 ng/ml." Neurelis Press Release.

Claim Language	Exemplary Prior Art Citations
	The mere recitation of an inherent or latent property of an otherwise obvious formulation will not render the formulation patentable. *In re Kao*, 639 F.3d 1057, 1070 (Fed. Cir. 2011); *Santarus, Inc. v. Par Pharmaceutical, Inc.*, 694 F.3d 1344 (Fed. Cir. 2012).
20. The method of claim 5, wherein the pharmaceutical solution exhibits an approximate T_{max} of 1.5 hours.	*See* claims 5 and 19.
21. A method of treating bouts of intermittent and stereotypic episodes of increased seizure activity in an epilepsy patient that is distinguishable from other seizures suffered by the patient comprising:	*See* claim 1.
administering a single spray of 100 µL +/−5% of a stable pharmaceutical solution to a nostril of the patient, the pharmaceutical solution containing:	*See* claim 1.
56.47 mg of vitamin E USP +/−5%;	*See* claim 1.
10 mg of diazepam;	*See* claim 1.
0.25 mg of dodecyl maltoside +/−5%;	*See* claim 1.
10.50 mg of benzyl alcohol +/−5%; and	*See* claim 1.
a sufficient quantity of ethanol;	*See* claim 1.
wherein administering the single spray of the pharmaceutical solution achieves 92.5% to 107.5% of the bioavailability of an equivalent dose of diazepam administered intravenously;	*See* claim 1.
wherein administering the single spray of the pharmaceutical solution is safe and effective in treating the bouts of intermittent and stereotypic episodes of increased seizure activity in the patient; and	*See* claim 1.
wherein administering the single spray of the pharmaceutical solution results in a treatment selected from the group consisting of a	*See* claim 1.

Claim Language	Exemplary Prior Art Citations
reduction in the severity of the seizure, a reduction in the probability that the patient will experience a repeat seizure, an increase in the interval between a current seizure and a next seizure in the patient, a reduction in the frequency of seizure in the patient and combinations thereof.	
22. The method of claim 21, wherein the pharmaceutical solution is stable at 25° C. and 60% relative humidity for at least 3 months.	*See* claims 21 and 2.
23. The method of claim 21, wherein administering the single spray of the pharmaceutical solution results in treatment in less than about 5 minutes.	*See* claims 21 and 3.
24. The method of claim 21, wherein administering the single spray of the pharmaceutical solution results in treatment over about 24 hours.	*See* claims 21 and 4.
25. The method of claim 21, wherein the single spray of 100 μL is administered to a nostril of the patient as a single metered spray.	*See* claims 21 and 4.
26. The method of claim 21, wherein the ethanol is dehydrated ethanol.	*See* claims 21 and 11.
27. The method of claim 21, wherein the dodecyl maltoside is n-dodecyl-β-D-maltoside.	*See* claims 21 and 1.
28. The method of claim 21, wherein the pharmaceutical solution exhibits an approximate area under a blood plasma concentration curve measuring total drug exposure across time ($AUC_{0-\infty}$) of 7338 hours*ng/mL.	*See* claims 21 and 15.
29. The method of claim 21, wherein the pharmaceutical solution exhibits an approximate C_{max} of 272 ng/mL.	*See* claims 21 and 17.

Claim Language	Exemplary Prior Art Citations
30. The method of claim 21, wherein the pharmaceutical solution exhibits an approximate T_{max} of 1.5 hours.	*See* claims 21 and 19.
31. The method of claim 21, wherein the pharmaceutical solution exhibits a half-life of about 49.2 hours.	*See* claim 21. Agarwal, describing NCT '558, discloses that the diazepam solution formulation exhibited a similar half-life as the comparator IV formulation, and provided data that a POSA could use to extrapolate a half-life, treatment-time, AUC value within the relevant claim limitations. Agarwal. Agarwal, further referencing the NCT '558 results, discloses that the "mean $T_{1/2}$ was similar for all three formulations. Both investigational intranasal formulations were well tolerated." Agarwal. The Neurelis Press Release, also reporting on NCT '558, discloses that the formulation was able "to quickly and efficiently deliver, via intranasal administration, clinically relevant diazepam levels offers a more acceptable method of rescue therapy" based on the pharmacokinetic data. Neurelis Press Release at 2. The mere recitation of an inherent or latent property of an otherwise obvious formulation will not render the formulation patentable. *In re Kao*, 639 F.3d 1057, 1070 (Fed. Cir. 2011); *Santarus, Inc. v. Par Pharmaceutical, Inc.*, 694 F.3d 1344 (Fed. Cir. 2012).
32. The method of claim 21, wherein the absolute bioavailability is 96% to 97%.	*See* claims 21 and 1.
33. A method of treating bouts of intermittent and stereotypic episodes of increased seizure activity in an epilepsy patient that is distinguishable from other seizures suffered by the patient comprising:	*See* claim 5.

Claim Language	Exemplary Prior Art Citations
administering a single spray of 100 μL +/−5% of a stable pharmaceutical solution to a nostril of the patient and administering a second single spray of 100 μL +/−5% of the pharmaceutical solution to a second nostril of the patient, each of the 100 μL +/−5% of the pharmaceutical solution containing:	*See* claims 5 and 21.
56.47 mg of vitamin E USP +/−5%;	*See* claim 1.
10 mg of diazepam;	*See* claim 1.
0.25 mg of dodecyl maltoside +/−5%;	*See* claim 1.
10.50 mg of benzyl alcohol +/−5%; and	*See* claim 1.
a sufficient quantity of ethanol;	*See* claim 1.
wherein administering the single spray and administering the second single spray of the pharmaceutical solution achieves 92.5% to 107.5% of the bioavailability of an equivalent dose of diazepam administered intravenously;	*See* claim 1.
wherein administering the single spray and administering the second single spray of the pharmaceutical solution is safe and effective in treating the bouts of intermittent and stereotypic episodes of increased seizure activity in the patient; and	*See* claim 5.
wherein administering the single spray and administering the second single spray of the pharmaceutical solution results in a treatment selected from the group consisting of a reduction in the severity of the seizure, a reduction in the probability that the patient will experience a repeat seizure, an increase in the interval between a current seizure and a next seizure in the patient, a reduction in the frequency of seizure in the patient and combinations thereof.	*See* claim 1.

Claim Language	Exemplary Prior Art Citations
34. The method of claim 33, wherein the pharmaceutical solution is stable at 25° C. and 60% relative humidity for at least 3 months.	*See* claims 33 and 2.
35. The method of claim 33, wherein administering the single spray and the second single spray of the pharmaceutical solution results in treatment in less than about 5 minutes.	*See* claims 33 and 3.
36. The method of claim 33, wherein administering the single spray and the second single spray of the pharmaceutical solution results in treatment over about 24 hours.	*See* claims 33 and 4.
37. The method of claim 33, wherein the single spray of 100 μL +/−5% and the second single spray of 100 μL +/−5% are each administered to a nostril of the patient as a single metered spray.	*See* claims 33 and 5.
38. The method of claim 33, wherein the ethanol is dehydrated ethanol.	*See* claims 33 and 11.
39. The method of claim 33, wherein the dodecyl maltoside is n-dodecyl-β-D-maltoside.	*See* claims 33 and 1.
40. The method of claim 33, wherein the pharmaceutical solution exhibits an approximate T_{max} of 1.5 hours.	*See* claims 33 and 19.
41. The method of claim 33, wherein the pharmaceutical solution exhibits a half-life of about 49.2 hours.	*See* claims 33 and 31.
42. The method of claim 33, wherein the absolute bioavailability is 96% to 97%.	*See* claims 33 and 1.
43. A method of treating bouts of intermittent and stereotypic episodes of increased seizure activity in an epilepsy patient that is distinguishable from other seizures suffered by the patient comprising:	*See* claim 1.

Claim Language	Exemplary Prior Art Citations
administering a single spray of 100 μL +/−5% of a stable pharmaceutical solution to a nostril of the patient and administering a second single spray of 100 μL +/−5% of the pharmaceutical solution to a second nostril of the patient, each of the 100 μL +/−5% of the pharmaceutical solution containing:	*See* claims 5 and 21.
56.47 mg of vitamin E USP +/−5%;	*See* claim 1.
7.5 mg of diazepam;	*See* claim 1.
0.25 mg of dodecyl maltoside +/−5%;	*See* claim 1.
10.50 mg of benzyl alcohol +/−5%; and	*See* claim 1.
a sufficient quantity of ethanol;	*See* claim 1.
wherein administering the single spray and administering the second single spray of the pharmaceutical solution achieves 92.5% to 107.5% of the bioavailability of an equivalent dose of diazepam administered intravenously;	*See* claim 5.
wherein administering the single spray and administering the second single spray of the pharmaceutical solution is safe and effective in treating the bouts of intermittent and stereotypic episodes of increased seizure activity in the patient; and	*See* claim 5.
wherein administering the single spray and administering the second single spray of the pharmaceutical solution results in a treatment selected from the group consisting of a reduction in the severity of the seizure, a reduction in the probability that the patient will experience a repeat seizure, an increase in the interval between a current seizure and a next seizure in the patient, a reduction in the frequency of seizure in the patient and combinations thereof.	*See* claim 5.

Claim Language	Exemplary Prior Art Citations
44. The method of claim 43, wherein the pharmaceutical solution is stable at 25° C. and 60% relative humidity for at least 3 months.	*See* claims 43 and 2.
45. The method of claim 43, wherein administering the single spray and the second single spray of the pharmaceutical solution results in treatment in less than about 5 minutes.	*See* claims 43, 5, and 3.
46. The method of claim 43, wherein administering the single spray and the second single spray of the pharmaceutical solution results in treatment over about 24 hours.	*See* claims 43, 5, and 4.
47. The method of claim 43, wherein the single spray of 100 μL +/−5% and the second single spray of 100 μL +/−5% are each administered to a nostril of the patient as a single metered spray.	*See* claims 43 and 5.
48. The method of claim 43, wherein the ethanol is dehydrated ethanol.	*See* claims 43 and 11.
49. The method of claim 43, wherein the dodecyl maltoside is n-dodecyl-β-D-maltoside.	*See* claims 43 and 1.
50. The method of claim 43, wherein the pharmaceutical solution exhibits an approximate T_{max} of 1.5 hours.	*See* claims 43 and 19.
51. The method of claim 43, wherein the pharmaceutical solution exhibits a half-life of about 49.2 hours.	*See* claims 43 and 31.
52. The method of claim 43, wherein the absolute bioavailability is 96% to 97%.	*See* claims 43 and 1.
53. A method of treating bouts of intermittent and stereotypic episodes of increased seizure activity in an epilepsy patient that is distinguishable from other seizures suffered by the patient comprising:	*See* claim 1.

Claim Language	Exemplary Prior Art Citations
administering a single spray of 100 μL +/−5% of a stable pharmaceutical solution to a nostril of the patient, the pharmaceutical solution containing:	*See* claim 1.
56.47 mg of vitamin E USP +/−5%;	*See* claim 1.
5 mg of diazepam;	*See* claim 1.
0.25 mg of dodecyl maltoside +/−5%;	*See* claim 1.
10.50 mg of benzyl alcohol +/−5%; and	*See* claim 1.
a sufficient quantity of ethanol;	*See* claim 1.
wherein administering the single spray of the pharmaceutical solution achieves 92.5% to 107.5% of the bioavailability of an equivalent dose of diazepam administered intravenously;	*See* claim 1.
wherein administering the single spray of the pharmaceutical solution is safe and effective in treating the bouts of intermittent and stereotypic episodes of increased seizure activity in the patient; and	*See* claim 1.
wherein administering the single spray of the pharmaceutical solution results in a treatment selected from the group consisting of a reduction in the severity of the seizure, a reduction in the probability that the patient will experience a repeat seizure, an increase in the interval between a current seizure and a next seizure in the patient, a reduction in the frequency of seizure in the patient and combinations thereof.	*See* claim 1.
54. The method of claim 53, wherein the pharmaceutical solution is stable at 25° C. and 60% relative humidity for at least 3 months.	*See* claims 53 and 2.
55. The method of claim 53, wherein administering the single spray of the pharmaceutical solution results in treatment in less than about 5 minutes.	*See* claims 53 and 3.

Claim Language	Exemplary Prior Art Citations
56. The method of claim 53, wherein administering the single spray of the pharmaceutical solution results in treatment over about 24 hours.	*See* claims 53 and 4.
57. The method of claim 53, wherein the single spray of 100 μL is administered to a nostril of the patient as a single metered spray.	*See* claims 53 and 1.
58. The method of claim 53, wherein the ethanol is dehydrated ethanol.	*See* claims 53 and 11.
59. The method of claim 53, wherein the dodecyl maltoside is n-dodecyl-β-D-maltoside.	*See* claims 53 and 1.
60. The method of claim 53, wherein the pharmaceutical solution exhibits an approximate T_{max} of 1.5 hours.	*See* claims 53 and 19.
61. The method of claim 53, wherein the pharmaceutical solution exhibits a half-life of about 49.2 hours.	*See* claims 53 and 31.
62. The method of claim 53, wherein the absolute bioavailability is 96% to 97%.	*See* claims 53 and 1.

Exhibit F

Exhibit F: Invalidity of U.S. Patent No. 12,521,400

U.S. Patent Application Publication No. 2008/0279784 to Cartt et al. (hereinafter "Cartt 2008") is titled "Nasal Administration of Benzodiazepines," was published on November 13, 2008, and constitutes prior art under § 102(a) and/or § 102(e)(1).

U.S. Pat. 6,193,985 to Sonne (hereinafter "Sonne") is titled "Tocopherol Composition for Delivery of Biologically Active Agents," is dated February 27, 2001, and constitutes prior art under § 102(b).

Li et al., *Rapid-onset intranasal delivery of anticonvulsants: pharmacokinetic and pharmacodynamic evaluation in rabbits*, INTERNATIONAL JOURNAL OF PHARMACEUTICS 199:65-76 (2000) (hereinafter "Li") published in 2000 and constitutes prior art under § 102(b).

U.S. Patent Application Publication No. 2006/0046962 to Meezan et al. (hereinafter "Meezan") is titled "Absorption Enhancers for Drug Administration," and was published on March 2, 2006, and constitutes prior art under § 102(b).

USP 23/NF 18, Ed., "United States Pharmacopeia. The National Formulary," The United States Pharmacopoeial Convention Inc., Rockville (hereinafter "USP") was published in 1995, and constitutes prior art under § 102(b).

The "Florida EMS Manual" was published in 2005 and constitutes prior art under § 102(b).

Physician's Desk Reference (hereinafter "PDR") was published in 2000 and constitutes prior art under § 102(b).

U.S. Patent Application Publication No. 2007/0208011 to Cloyd et al. (hereinafter "Cloyd") was published on September 6, 2007, and constitutes prior art under § 102(b).

U.S. Patent Application Publication No. 2008/0070904 to Jamieson et al. (hereinafter "Jamieson") is titled "Pharmaceutical Compositions of Benzodiazepines and Method of Use thereof," was published on March 20, 2008, and constitutes prior art under at least § 102(a).

U.S. Patent Application Publication No. 2004/0176359 to Wermeling (hereinafter "Wermeling") is titled "Intranasal Benzodiazepine Compositions," was published on September 9, 2004, and constitutes prior art under § 102(b).

U.S. Patent No. 6,627,211 ("Choi") issued on September 30, 2003 and is prior art under § 102(b).

PCT Publication No. WO2009/046444A2 ("Costantino '444") published on April 09, 2009, and claims priority to four provisional applications 60/977,848 (filed on October 5, 2007), 60/982,680 (filed on October 25, 2007), 60/985,918 (filed on November 6, 2007), and 60/989,370 (filed on November 20, 2007). Costantino '444 constitutes prior art under pre-AIA § 102(e)(1).

As set forth in the chart below, all elements of the claims of the '400 patent are disclosed, taught, suggested, and rendered obvious by the following combinations of prior art: (i) Sonne optionally in view of Meezan, Cartt 2008, Cloyd, Florida EMS Manual, and/or USP; (ii) Li in view of Sonne,

optionally further in view of Meezan, Cartt 2008, Florida EMS Manual, and/or USP; (iii) Sonne in view of Jamieson, Li, Meezan, and/or Wermeling; and (iv) Sonne in view of Choi, Costantino '444, and/or Meezan.

The excerpts cited herein are exemplary. For any claim limitation, Defendants may rely on excerpts cited for any other limitation or additional excerpts not set forth fully herein to the extent necessary to provide a more comprehensive explanation for a reference's disclosure of a limitation. Where an excerpt refers to or discusses a figure or figure items, that figure and any additional descriptions of that figure should be understood to be incorporated by reference as if set forth fully therein. As set forth in the Preliminary Invalidity Contentions (incorporated herein in their entirety), to which this exhibit has been attached, a POSA at the time would have been motivated to combine the teachings of any groupings of the foregoing prior art references with his knowledge of the art. Such combinations would provide a reasonable expectation of success to arrive at the claimed invention(s), and thus each claim of this patent is invalid.

Claim Language	Exemplary Prior Art Citations
1. A pharmaceutical composition for intranasal administration comprising:	Sonne discloses that "[t]he present invention provides the use of a tocopherol or a derivative thereof as a solvent and/or emulsifier for substantially insoluble and sparingly soluble biologically active agents, especially in the manufacture of pharmaceutical compositions. Such compositions are particularly suitable for transmucosal, and especially intranasal… administration…" Sonne at Abstract. Sonne further discloses that "[t]ransmucosal delivery is preferred however, and compositions according to the invention may be administered to mucosal membranes… [n]asal, rectal and oral cavity administrations are particularly preferred." *Id*. at 3:54-59. *See also id*. at Example 11, Claim 4. Li discloses experiments using intranasal delivery of anticonvulsants such as diazepam. *See* Li at Abstract, 67. Meezan discloses "a method of increasing absorption of a low molecular weight compound into the circulatory system of a subject by administering the compound via the... nasal,... delivery route..." Meezan at ¶ [0008].

Claim Language	Exemplary Prior Art Citations
	Meezan also discloses that "[a] 'therapeutic composition'... can be compounded... with the usual non-toxic, pharmaceutically acceptable carriers for... solutions,... The carriers,... can include... other carriers suitable for use in manufacturing preparations, in solid, semisolid, or liquid form." *Id*. at ¶ [0049]. Further, Meezan discloses that the "compositions of the invention can consist of a pharmaceutically acceptable carrier[,] [a] 'pharmaceutically acceptable carrier' is an aqueous or non-aqueous agent, for example alcoholic or oleaginous, or a mixture thereof." Meezan at ¶ [0074]. Cartt 2008 discloses nasal formulations for the administration of benzodiazepine drug compounds, including diazepam. Cartt 2008 at ¶ [0028]. Wermeling discloses pharmaceutical compositions for intranasal administration of effective amounts of benzodiazepines including diazepam. Wermeling at Abstract, ¶ [0026]. *See also id*. at ¶ [0008] (teaching that that the "principal advantages of intranasal route are non-invasive delivery, rapid drug absorption, and convenience."); ¶ [0012] (disclosing that "there is a need for intranasal benzodiazepine compositions with improved properties, such as for example, rapid absorption and time to peak concentration.").
about 1 to about 20 mg of diazepam	Sonne discloses that diazepam was one preferred drug compound, with low water solubility, that could be developed in the tocopherol-based formulations, including exemplary solution formulations. *See* Sonne at 7:32 to 8:10 (Example 1, diazepam "nosedrop"); 8:11-27 (Example 1, diazepam nosedrop); and 11:1-13 (Example 11, solution containing diazepam and approximately 40% alpha-tocopherol, e.g. as a nosedrop).

Claim Language	Exemplary Prior Art Citations
	Sonne also discloses the intranasal administration of 2 mg, 2.5 mg, and 10 mg of diazepam. *See* Sonne at Fig. 1; Examples 1, 22, and 23; 7:32-58; 13:56 to 14:13; and 14:63-67. Sonne further discloses that "[t]he active substance may be present in an amount of from about 0.0001% to 50% of the total composition, preferably 0.001% to 40% (w/w)." Sonne at 5:52-54; *see also* Examples 1-3, 7-10, 19, 22-23. Sonne includes diazepam in the listing of such active substances. *Id*. at 5:34. Li discloses experiments using intranasal delivery of anticonvulsants such as diazepam. *See* Li at Abstract, 67. Li further discloses 20 mg of diazepam dissolved in 1 ml of the carrier and that the resulting intranasal solutions provided a diazepam concentration of 20 mg/ml. *Id*. at 67, 70 (Table 1, reporting the 2% diazepam solution). Cloyd discloses solution formulations containing "at least about 10 mg/ml of the benzodiazepine" where "the intranasal volume delivered to an individual in need of a benzodiazepine is… between about 50 µl to about 150 µl per nostril." Cloyd at ¶¶ [0055]-[0056]. Cartt 2008 discloses exemplary doses of diazepam to be delivered to patients per dose via nasal administration: "The dosage of Diazepam may vary by indication, however it is expected that a therapeutic dose will be in the range of about 1 to about 20, preferably about 2 to about 10 mg per dose…." Cartt 2008 at ¶ [0063]. Jamieson discloses "[a] therapeutically effective amount of diazepam in the compositions of the present invention may be,

Claim Language	Exemplary Prior Art Citations
	for example between about 1.0 mg and about 40.0 mg per unit dose, more preferably between about 2.0 mg and about 10.0 mg per unit dose." Jamieson at ¶ [0118]. *See also id.* at Claims 7, 8, 16, 17, 39, and 40 (disclosing a therapeutically effective amount of diazepam); and ¶ [0102] (disclosing intranasal formulations where the amount of a benzodiazepine such as diazepam is "typically present at a weight percent of between about 0.1% to about 20% and often between 0.1% and 10% often 0.25% to 6%."). Wermeling discloses pharmaceutical compositions for intranasal administration of effective amounts of benzodiazepines including diazepam. Wermeling at Abstract, ¶ [0026].
dissolved in about 45% to about 85% (w/w) of one or more natural or synthetic tocopherols or tocotrienols selected from the group consisting of α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, α-tocotrienol, β-tocotrienol, γ-tocotrienol, δ-tocotrienol, tocophersolan, any esters thereof and any combinations thereof, and	Sonne discloses that "[t]he present invention is based on the surprising observation that tocopherols and derivatives thereof are excellent solvents for drugs which are substantially insoluble or sparingly soluble in water, whilst at the same time having a very low irritative potential for mucosal tissues." Sonne at 2:54-58. Sonne also discloses that "[i]n one aspect, the present invention thus provides the use of a tocopherol or a derivative thereof as a solvent and/or emulsifier for substantially insoluble and sparingly soluble biologically active agents, especially in the manufacture of pharmaceutical compositions." *Id*. at 2:63-67. Sonne teaches that tocopherols may may include α-tocopherol or Vitamin E. *Id.* at 3:4-10 ("Tocopherols are a range of natural and synthetic compounds, also known by the generic term Vitamin E. α-Tocopherol… is the most active and widely distributed in nature, and has been the most widely studied.").

Claim Language	Exemplary Prior Art Citations
	Sonne further discloses that diazepam was one preferred drug compound, with low water solubility, that could be developed in the tocopherol-based formulations, including exemplary solution formulations. *See id*. at 7:32 to 8:10 (Example 1, diazepam "nosedrop"); 8:11-27 (Example 1, diazepam nosedrop); and 11:1-13 (Example 11, solution containing diazepam and approximately 40% alpha-tocopherol, e.g. as a nosedrop). Sonne also discloses formulations containing "1 to 95% (w/w) of the tocopherol or derivative thereof, preferably 20 to 95% (w/w), most preferably 35 to 80% (w/w)." *Id*. at 5:58-61. Sonne further discloses at least one exemplary solution formulation containing 10 g of α-tocopherol in a total solution weight of 25 g, equating to an α-tocopherol concentration of 40% w/w. *Id*. at 11:1-13 (Example 11). Sonne also discloses that: "Generally Speaking compositions of the invention may contain from 1 to 99.99% (w/w), preferably 20 to 99.99%, most preferably 40 to 99.99% (w/w) of the tocopherol or tocopherol derivative Solvent." *Id*. at 5:55-58. USP discloses that vitamin E was well-known in the art at the time: "Vitamin E is a form of alpha tocopherol ($C_{29}H_{50}O_2$). It includes the following d- or dl-alpha tocopherol ($C_{29}H_{50}O_2$); d- or dl-alpha tocopheryl acetate ($C_{31}H_{52}O_3$); d- or dl-alpha tocopheryl acid succinate ($C_{33}H_{54}O_5$)." USP at 1631. Jamieson discloses the use of benzodiazepine compositions that include tocopherols. *See, e.g.*, Claim 24, Claim 49. *See also id.* at ¶ [0209] ("Addition of an anti-oxidant to the formulations of the present invention used for intranasal delivery of benzodiazepines may provide desirable protective benefits to such

Claim Language	Exemplary Prior Art Citations
	formulations. Examples include, but are not limited to, tocopherol and derivatives thereof…").
about 25% to about 40% (w/w) of one or more alcohols selected from the group consisting of ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, and any combinations thereof,	Li discloses use of ethanol in diazepam intranasal delivery systems at about 20%-60% concentrations. Li at 71-72 ("The peak DZ plasma concentration, observed within 2–3 min after [intranasal] administration, increased significantly with increasing EtOH concentrations in the IN formulations (20–60%)…"). *See also id*. at Abstract, 67 (disclosing the benefit of using ethanol in intranasal administration of diazepam); 66 (disclosing that "[t]he present study was carried out to investigate the absorption characteristics and [pharmacodynamic] response of three anticonvulsants, the benzodiazepines, [diazepam] and [clonazepam], and the new monocarbamate anticonvulsant… after their [intranasal] administration as solutions in aqueous cosolvent system containing various proportions of [propylene glycol] and [ethanol] in the presence of 1% [sodium glycocholate]."); and 67 (disclosing a studied solution that contained about 20 mg diazepam in 30% ethanol in about 1 ml of vehicle). Sonne discloses that "[t]he formulations according to the invention may be optimized with respect to bioadhesion, sprayability and viscosity, as desired" by incorporating "co-solvents" like "alcohols such as ethanol … or benzyl alcohol." Sonne at 6:47-53. Sonne also discloses that "[v]iscosity can be reduced by addition of co-solvents such as ethanol…" *Id*. at 3:60-67. Sonne further discloses a solution of diazepam, incorporated 55% w/w of a co-solvent, namely triacetin (13.75 g of triacetin within a total

Claim Language	Exemplary Prior Art Citations
	solution weight of 25 g). *Id*. at 11:1-13 (Example 11). Jamieson discloses the use intranasal administration of formulations that contain benzodiazepines and cosolvents. *See* Jamieson at Abstract (inventions that "include[] benzodiazepine compositions formulated for intranasal administration, comprising a binary solvent system comprising a first solvent in which the benzodiazepine is soluble, the first solvent capable of penetrating nasal mucosal tissue, and a second solvent in which the benzodiazepine in less soluble."). *See also id*. at Table 12A (disclosing benzodiazepine formulations containing 20% ethanol). Wermeling discloses that suitable diluents for its intranasal compositions of effective amounts of benzodiazepines, including diazepam, may include alcohols. Wermeling at ¶ [0030]. Wermeling discloses that benzyl alcohol is a "suitable preservative" for use in its disclosed formulations. *Id*. at ¶ [0033] ("the composition contains a preservative that is chosen in quantities that preserve the composition, but preferably does not cause irritation to the nasal mucosa."). Choi further discloses the use of a vehicle containing about 30-60% of ethanol, a glycol, water, and a biological surfactant for intranasal solution composition of diazepam, which is administered in a volume of 100 µl by means of a Pfeiffer spray device. Choi at 2:53-58, 7:921; 7:25-28; 8:56-62. Costantino '444 further discloses the intranasal delivery of about 1 mg to about 20 mg diazepam as a spray in a volume from about 25 µl to about 250 µl using about 0.1 to about 85% of cosolvent (including ethanol) as vehicle, one or more mucosal delivery enhancing agent and additional ingredients such as antioxidants (including α-tocopherol), preservatives,

Claim Language	Exemplary Prior Art Citations
	flavoring agents, and coloring agents. Costantino '444 at 10:16-19, 15:22-33, 16:15-21, 16:33-17:13, 17:14-25; 26:25-29.
wherein the pharmaceutical composition is a solution	Sonne discloses that diazepam was one preferred drug compound, with low water solubility, that could be developed in the tocopherol-based formulations, including exemplary solution formulations. *See* Sonne at 7:32 to 8:10 (Example 1, diazepam "nosedrop"); 8:11-27 (Example 1, diazepam nosedrop); and 11:1-13 (Example 11, solution containing diazepam and approximately 40% alpha-tocopherol, e.g. as a nosedrop). Sonne also discloses that "[t]he compositions of the invention may be used directly as solutions of the bioactive agent in the tocopherol solvent." *Id*. at 3:60-61. Li discloses intranasal diazepam solutions, stating that that "[f]or [intranasal] application, the test formulations were prepared in 30% EtOH—60% PG—10% water, plus or minus 1% SGC. All the nasal formulations were prepared just prior to the experiment by dissolving [diazepam] (20 mg), CZ (4.2 mg), or MCA (100 mg) in 1 ml of the aforementioned vehicles." Li at 67. *See also id.* at 70 (Table 1, reporting the 2% diazepam solution); 74 (disclosing that nasal administration of diazepam "formulations in 1% SGC containing EtOH:PG:water cosolvent…").
of 50 µL to 150 µL, and	Sonne states that the formulations described therein for administration to the nose must be administered in small volumes of "about 100 µL." Sonne at 7:25-30. Similarly, Cloyd discloses that liquid compositions for intranasal administration preferably have a volume "from about 50 µl to about 150 µl." Cloyd at ¶¶ [0055]-[0056]. Thus, Sonne optionally in view of Meezan,

Claim Language	Exemplary Prior Art Citations
	Cartt 2008, Cloyd, USP, and/or Florida EMS Manual discloses and renders obvious the claimed requirement that the pharmaceutical solution has a volume of "50 µL to 150 µL." Li explains that, for intranasal administration, "100 µl of the IN formulations [was administered] into each nostril within 5 s by means of a Pfeiffer spray device." Li at 67. *See also id*. at 66 (disclosing that a "constraint concerning nasal administration is that a small administration volume is required; it is not generally possible to administer more than approximately 150 µl per nostril."). Cartt 2008 further discloses that "[n]asal preparations are generally administered in metered sprays having volumes of less than 250 µl, preferably less than 150 µl, and ideally from 25 to 100 µl, since administration of larger volumes usually exceeds the capacity of the nasal sinuses and results in volumes in excess of about 250 µl bypassing the sinuses and flowing down the back of the throat where it is swallowed." Cartt 2008 at ¶ [0007]. Cartt 2008 also discloses that "[a]s a nasal formulation, diazepam may be administered in 25 to 250 µl metered sprays. In some preferred embodiments, diazepam is administered in 50 to 150 µl, especially about 100 µl, metered sprays. . In some embodiments, a first metered spray is applied to a first nostril and if necessary a second metered spray is applied to a second nostril." *Id*. at ¶ [0064].
wherein the pharmaceutical composition is in a pharmaceutically-acceptable spray formulation.	Sonne discloses solutions in spray form as a conventional form used for the compositions. Sonne at 3:54-67, 6:33-34.
2. The pharmaceutical composition of claim 1, wherein the natural or synthetic tocopherols or tocotrienols are selected from the group consisting of: α-tocopherol, β-tocopherol, γ-	*See* claim 1. Sonne discloses that "α-Tocopherol… is the most active and widely distributed in nature,

Claim Language	Exemplary Prior Art Citations
tocopherol, δ-tocopherol, tocophersolan, any esters thereof and any combinations thereof.	and has been the most widely studied. Other members of the class include beta, gamma, and delta tocopherols…" Sonne at 3:7-12. *See also id.* at Examples 3, 7-10, 17-19, 22-23, and 3:4-10 ("Tocopherols are a range of natural and synthetic compounds, also known by the generic term Vitamin E. α-Tocopherol… is the most active and widely distributed in nature, and has been the most widely studied."). Sonne also discloses that diazepam was shown to have a solubility of 12% w/w in 100 grams of α-tocopherol. *Id*. at 9:35-60 (Table 1). Sonne further discloses at least one exemplary solution formulation containing 10 g of α-tocopherol in a total solution weight of 25 g, equating to an α-tocopherol concentration of 40% w/w. *Id*. at 11:1-13 (Example 11). Jamieson discloses the use of benzodiazepine compositions that include tocopherols. *See, e.g.*, Claim 24, Claim 49. *See also id.* at ¶ [0209].
3. The pharmaceutical composition of claim 1, wherein the natural or synthetic tocopherols or tocotrienols is α-tocopherol.	*See* claims 1 and 2.
4. The pharmaceutical composition of claim 1, wherein the one or more alcohols is selected from the group consisting of ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, isomers thereof and any combinations thereof.	*See* claim 1. Sonne discloses that "[t]he formulations according to the invention may be optimized with respect to bioadhesion, sprayability and viscosity, as desired" by incorporating "co-solvents" like "alcohols such as ethanol … or benzyl alcohol." *Id*. at 6:47-53. Additionally, when disclosing that the "compositions of the invention may be used directly as solutions of the bioactive agent in the tocopherol solvent," Sonne discloses that the viscosity of such a solution "may be too high for certain applications, for example to achieve a sprayable formulation for nasal

Claim Language	Exemplary Prior Art Citations
	application," and, because of that, "[v]iscosity can be reduced by addition of co-solvents such as ethanol…" *Id*. at 3:60-67. Li discloses the development of a diazepam intranasal solution, whereby the carrier vehicle contained "30% EtOH—60% PG—10% water, plus or minus 1% SGC," (Li, p. 67), which represents 60% propylene glycol (PG), 30% ethanol (EtOH), and 10% water, plus/minus 1% sodium glycholate (SGC).[1] Jamieson discloses benzodiazepine formulations containing 20% ethanol. Jamieson at Table 12A. Wermeling discloses benzyl alcohol for use in its formulations. Wermeling at ¶ [0033].
5. The pharmaceutical composition of claim 1, wherein the diazepam is present in the pharmaceutical solution at a concentration of about 10 mg/mL to about 250 mg/mL.	*See* claim 1. Sonne discloses that the "administration of drugs with very low water solubility to the nose is difficult, because of the limited volume which is acceptable for the nose (about 100 μL)." Sonne at 7:25-28. Sonne discloses that diazepam was one preferred drug compound, with low water solubility, that could be developed in the tocopherol-based formulations, including exemplary solution formulations. *See* Sonne at 7:32 to 8:10 (Example 1, diazepam "nosedrop"); 8:11-27 (Example 1, diazepam nosedrop); and 11:1-13 (Example 11, solution containing diazepam and approximately 40% alpha-tocopherol, e.g. as a nosedrop). Sonne also discloses the intranasal administration of 2 mg, 2.5 mg, and 10 mg of

[1] A POSA would have understood that the formulations additionally containing 1% SGC would require that the percentages of the other three components (propylene glycol, ethanol, and water) would need to be adjusted to account for the additional 1% of SGC; however, the amount of SGC is small and does not materially impact the analysis related to the amounts and concentrations disclosed by Li.

Claim Language	Exemplary Prior Art Citations
	diazepam. *See* Sonne at Fig. 1; Examples 1, 22, and 23; 7:32-58; 13:56 to 14:13; and 14:63-67. Sonne further discloses that "[t]he active substance may be present in an amount of from about 0.0001% to 50% of the total composition, preferably 0.001% to 40% (w/w)," and that that the "administration of drugs with very low water solubility to the nose is difficult, because of the limited volume which is acceptable for the nose (about 100 µL)." Sonne at 7:25-28. Additionally, Cloyd discloses solution formulations containing "at least about 10 mg/ml of the benzodiazepine" where "the intranasal volume delivered to an individual in need of a benzodiazepine is… between about 50 µl to about 150 µl per nostril." Cloyd at ¶¶ [0055]-[0056]. Similarly, Cartt 2008 discloses exemplary doses of diazepam to be delivered to patients per dose via nasal administration: "The dosage of Diazepam may vary by indication, however it is expected that a therapeutic dose will be in the range of about 1 to about 20, preferably about 2 to about 10 mg per dose…." Cartt 2008 at ¶ [0063]. Cartt 2008 further discloses that "[n]asal preparations are generally administered in metered sprays having volumes of less than 250 µl, preferably less than 150 µl, and ideally from 25 to 100 µl, since administration of larger volumes usually exceeds the capacity of the nasal sinuses and results in volumes in excess of about 250 µl bypassing the sinuses and flowing down the back of the throat where it is swallowed." Cartt 2008 at ¶ [0007]. Cartt 2008 specifically discloses that "[a]s a nasal formulation, diazepam may be administered in 25 to 250 µl metered sprays. In some preferred embodiments, diazepam is

Claim Language	Exemplary Prior Art Citations
	administered in 50 to 150 µl, especially about 100 µl, metered sprays. In some embodiments, a first metered spray is applied to a first nostril and if necessary a second metered spray is applied to a second nostril." *Id*. at ¶ [0064]. Li states that 20 mg of diazepam was dissolved in 1 ml of the carrier. Li at 67. Li further states that the resulting intranasal solutions provided a diazepam concentration of 20 mg/ml. *Id.* at p. 67, 70 (Table 1, reporting the 2% diazepam solution). Li discloses that a "constraint concerning nasal administration is that a small administration volume is required; it is not generally possible to administer more than approximately 150 µl per nostril." Li at 66. Jamieson discloses "[a] therapeutically effective amount of diazepam in the compositions of the present invention may be, for example between about 1.0 mg and about 40.0 mg per unit dose, more preferably between about 2.0 mg and about 10.0 mg per unit dose." Jamieson at ¶ [0118].
6. The pharmaceutical composition of claim 1, wherein the pharmaceutical solution comprises one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof in an amount from about 60% to about 75% (w/w).	*See* claim 1. Sonne expressly discloses that diazepam could be formulated for intranasal administration as a solution containing α-tocopherol, including in an amount ranging from about 40% to about 99.99% (w/w). *See, e.g.*, Sonne at 5:58-61, 7:32-8:27, 10:20-11:13. Accordingly, for the reasons discussed above, a POSA would have been motivated to develop the Sonne solution formulation containing α-tocopherol, and it would have been a matter of routine experimentation and optimization to utilize the tocopherol in an amount ranging from about 60-75% (w/w). Additionally, Li discloses the development of a diazepam intranasal solution, whereby the

Claim Language	Exemplary Prior Art Citations
	carrier vehicle contained "30% EtOH—60% PG—10% water, plus or minus 1% SGC," (Li, p. 67), which represents 60% propylene glycol (PG), 30% ethanol (EtOH), and 10% water, plus/minus 1% sodium glycholate (SGC).[2] A POSA would have been motivated to replace the 60% propylene glycol present in the Li intranasal diazepam solution with the α-tocopherol solvent taught by Sonne, and would have a reasonable expectation of success. Utilizing α-tocopherol in the same amount as was present for propylene glycol (60%)
7. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition further comprises at least one additional ingredient selected from the group consisting of stabilizers, coloring agents, pH adjusters, buffering agents, preservatives, wetting agents, flavoring agents and combinations thereof.	*See* claim 1. Sonne discloses that "[t]he compositions of the invention may take any of the conventional pharmaceutical forms known in the art, and may be formulated in conventional manner, optionally with one or more pharmaceutically acceptable carriers or excipients. Thus for example the compositions may take the form of… sprays,…" Sonne at 6:29-35. "The formulations according to the invention may be optimized with respect to bioadhesion, sprayability and viscosity, as desired." *Id.* at 6:36-49. Sonne also discloses the use of excipients in such compositions: "To ensure that the formulations have a reasonable shelf-life it may be desirable to include preservatives Such as benzalkonium chloride, Sodium edetate, Sorbic acid, potassium Sorbate, phenoxyethanol, phenetanol, parabens or others known in the art. Addition of odour- or taste-masking compounds can also be desirable." *Id*. at 7:4-9; *see also id*. at claim 10.

[2] A POSA would have understood that the formulations additionally containing 1% SGC would require that the percentages of the other three components (propylene glycol, ethanol, and water) would need to be adjusted to account for the additional 1% of SGC; however, the amount of SGC is small and does not materially impact the analysis related to the amounts and concentrations disclosed by Li.

Claim Language	Exemplary Prior Art Citations
	Meezan discloses a range of excipients including "…a Surfactant, emollient, lubricant, Stabilizer, dye, perfume, preservative, acid or base for adjustment of pH, a Solvent, emulsifier, gelling agent, moisturizer, Stabilizer, wetting agent, time release agent, humectant, or other component…" among others. Meezan at ¶ [0074]. Li discloses intranasal formulations that include propylene glycol and ethanol, as well as sodium glycocholate as it was "known to enhance intranasal absorption while producing minimal irritation and morphological alteration in the nasal mucosa." Li at 70-71.
8. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition further comprises an absorption enhancer.	*See* claim 1. Li discloses formulations containing absorption enhancers, such sodium glycocholate (SGC). Li at 69. Additionally, Sonne discloses that bioadhesive compounds may be included in the pharmaceutical compositions, stating that "[i]t is also possible to enhance the bioadhesive properties of the formulations according to the present invention by addition of bioadhesive polymers such as: polyacrylic polymers such as carbomer and carbomer derivatives, e.g. Polycarbophil or Carbopol etc; cellulose derivatives such as hydroxymethyl-cellulose, hydroxyethylcellulose, hydroxypropyl-cellulose or sodium carboxymethylcellulose etc; natural polymers like gelatin, sodium alginate, pectin etc; [and] more generally, any physiologically acceptable polymer showing bioadhesive characteristics may be used." Sonne at 6:59-7:3. Meezan discloses alkyl glycoside absorption enhancers, stating:

Claim Language	Exemplary Prior Art Citations
	Alkyl glycosides of the present invention can include, but are not limited to: alkyl glycosides, such as octyl-, nonyl-, decyl-, undecyl-, dodecyl-, tridecyl-, tetradecyl-, pentadecyl-,hexadecyl-, heptadecyl-, and octadecyl-α- or β-D-maltoside, -glucoside or -sucroside…. … Similarly, some preferred glycosides include maltose, sucrose, and glucose linked by glycosidic linkage to an alkyl chain of 9, 10, 12, 13, 14, 16, 18, 20, 22, or 24 carbon atoms, e.g., nonyl-, decyl-, dodecyl- and tetradecyl sucroside, glucoside, and maltoside, etc. These compositions are nontoxic, since they are degraded to an alcohol and an oligosaccharide, and amphipathic. Meezan at ¶¶ [0056]-[0058]. Further, Meezan explicitly identifies alkylmaltosides, including dodecyl-beta-D-maltoside, as a preferred alkyl glycoside compound. *Id*. at ¶¶ [0092], [0156]. *See also id*. at Table I; ¶¶ [0150]-[0151]; Fig. 1; ¶¶ [0158]-[0159]; and Example 6. Jamieson discloses the use of penetration enhancers in diazepam for intranasal spray formulations. *See* Jamieson at ¶ [0104] (disclosing "pharmaceutical compositions comprising the benzodiazepine (e.g., clonazepam, diazepam or lorazepam)… for intranasal administration… may further comprise one or more components including… mucosa penetration enhancing agent"); and ¶ [0142] (disclosing that, due to the "highly lipophilic nature of lipophilic nature of the

Claim Language	Exemplary Prior Art Citations
	benzodiazepines a combination of Surfactants, strong solubilizing solvents, and carrier solutions are often used.”).
9. The pharmaceutical composition of claim 8, wherein the absorption enhancer is present in the pharmaceutical composition at a concentration of up to 20% (w/v).	*See* claims 1 and 8. Li discloses formulations containing absorption enhancers, such sodium glycocholate (SGC), at concentrations of 1%. Li at 67, 69. Sonne discloses various exemplary embodiments containing xanthan gum and poloxamer 188 (both bioadhesives compounds) in amounts including 0.025% (w/w) (xanthan gum component of Example 8); 0.03% (w/w) (xanthan gum component of Examples 9 and 10); 1% (w/w) (poloxamer 188 component of Example 9); and 3.0% (w/w) (poloxamer 188 component of Example 10). Sonne at 10:20-67. Meezan discloses adding alkyl glycosides to formulations in amounts of “about 0.01-20%, preferably about 0.01-5%, more preferably about 0.01-2%, even more preferably 0.01-1%, and most preferably 0.01-0.125% by weight.” Meezan at ¶ [0070]. Further, Meezan tested the effects of dodecyl maltoside as an absorption enhancer in preferred amounts of 0.125%, 0.25%, 0.375%, and 0.50%. *Id*.
10. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition is about 100 µL.	*See* claim 1. Sonne further discloses that “[t]he active substance may be present in an amount of from about 0.0001% to 50% of the total composition, preferably 0.001% to 40% (w/w),” and that that the “administration of drugs with very low water solubility to the nose is difficult, because of the limited volume

Claim Language	Exemplary Prior Art Citations
	which is acceptable for the nose (about 100 µL).” Sonne at 7:25-28. Further, Sonne states that the formulations described therein for administration to the nose must be administered in small volumes of “about 100 µL.” Sonne at 7:25-30. Cloyd discloses the “the intranasal volume delivered to an individual in need of a benzodiazepine is… between about 50 µl to about 150 µl per nostril.” Cloyd at ¶¶ [0055]-[0056]. Cartt 2008 further discloses that “[n]asal preparations are generally administered in metered sprays having volumes of less than 250 µl, preferably less than 150 µl, and ideally from 25 to 100 µl, since administration of larger volumes usually exceeds the capacity of the nasal sinuses and results in volumes in excess of about 250 µl bypassing the sinuses and flowing down the back of the throat where it is swallowed.” Cartt 2008 at ¶ [0007]. Cartt 2008 specifically discloses that “[a]s a nasal formulation, diazepam may be administered in 25 to 250 µl metered sprays. In some preferred embodiments, diazepam is administered in 50 to 150 µl, especially about 100 µl, metered sprays. In some embodiments, a first metered spray is applied to a first nostril and if necessary a second metered spray is applied to a second nostril.” *Id*. at ¶ [0064]. Li explains that, for intranasal administration, “100 µl of the IN formulations [was administered] into each nostril within 5 s by means of a Pfeiffer spray device.” Li at 67. *See also id*. at 66 (disclosing that a “constraint concerning nasal administration is that a small administration volume is required; it is not generally possible to administer more than approximately 150 µl per nostril.”).

Claim Language	Exemplary Prior Art Citations
11. The pharmaceutical composition of claim 1, wherein the therapeutically effective amount of the diazepam is about 2 mg to about 10 mg.	*See* claim 1. Li states that 20 mg of diazepam was dissolved in 1 ml of the carrier. *Id*. at 67. Li further states that the resulting intranasal solutions provided a diazepam concentration of 20 mg/ml. *Id.* at p. 67, 70 (Table 1, reporting the 2% diazepam solution). Further, as discussed, the volume of a nasal spray that can be administered to the nasal passage (due to the small physical dimensions of the nasal passage) is about 100 µL (0.1 ml). *See, e.g.*, Sonne at 2:30-33. Even accounting for the volume of a single spray of 0.1-0.2 ml, a single spray of the Li solution containing 20 mg/ml would include 2-4 mg of diazepam, which meets the claimed requirement of "about 2 to about 10 mg" of diazepam. Additionally, Fig. 1 of Sonne illustrates the intranasal administration of 2.5 mg diazepam (Sonne at 7:15-18), and Examples 1, 22, and 23 of Sonne report the administration of amounts of diazepam including 2 mg, 2.5 mg, and 10 mg. Sonne at 7:32-58; 13:56 to 14:13; and 14:63-67. Further, Cartt 2008 discloses exemplary doses of diazepam to be delivered to patients per dose via nasal administration: "The dosage of Diazepam may vary by indication, however it is expected that a therapeutic dose will be in the range of about 1 to about 20, preferably about 2 to about 10 mg per dose…." Cartt 2008 at ¶ [0063]. Jamieson discloses "[a] therapeutically effective amount of diazepam in the compositions of the present invention may be, for example between about 1.0 mg and about 40.0 mg per unit dose, more preferably between about 2.0 mg and about 10.0 mg per unit dose." Jamieson at ¶ [0118]. *See also id.* at Claims 7, 8, 16, 17, 39, and 40 (disclosing a therapeutically effective amount of diazepam);

Claim Language	Exemplary Prior Art Citations
	and ¶ [0102] (disclosing intranasal formulations where the amount of a benzodiazepine such as diazepam is "typically present at a weight percent of between about 0.1% to about 20% and often between 0.1% and 10% often 0.25% to 6%.").
12. A pharmaceutical composition for intranasal administration comprising:	*See* claim 1.
about 1 to about 20 mg of diazepam	*See* claim 1.
dissolved in about 45% to about 85% (w/w) of α-tocopherol, and	*See* claims 1 and 3.
about 25% to about 40% (w/w) of one or more alcohols selected from the group consisting of ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, isomers thereof and any combinations thereof,	*See* claim 1.
wherein the pharmaceutical composition is a solution	*See* claim 1.
of 50 μL to 150 μL, and	*See* claim 1.
wherein the pharmaceutical composition is in a pharmaceutically-acceptable spray formulation for intranasal administration.	*See* claim 1.
13. The pharmaceutical composition of claim 12, wherein the diazepam is present in the pharmaceutical solution at a concentration of about 10 mg/mL to about 250 mg/mL.	*See* claims 12 and 5.
14. The pharmaceutical composition of claim 12, wherein the diazepam is about 2 mg to about 10 mg.	*See* claims 12 and 11.
15. The pharmaceutical composition of claim 12, wherein the pharmaceutical solution	*See* claims 12 and 6.

Claim Language	Exemplary Prior Art Citations
comprises α-tocopherol in an amount from about 60% to about 75% (w/w).	
16. The pharmaceutical composition of claim 12, wherein the pharmaceutical composition further comprises at least one additional ingredient selected from the group consisting of stabilizers, coloring agents, pH adjusters, buffering agents, preservatives, wetting agents, flavoring agents and combinations thereof.	*See* claims 12 and 7.
17. The pharmaceutical composition of claim 12, wherein the pharmaceutical composition further comprises an absorption enhancer.	*See* claims 12 and 8.
18. The pharmaceutical composition of claim 17, wherein the absorption enhancer is present in the pharmaceutical composition at a concentration of up to 20% (w/v).	*See* claims 17 and 9.
19. The pharmaceutical composition of claim 12, wherein the pharmaceutical composition is about 100 µL.	*See* claims 12 and 10.
20. A pharmaceutical composition for intranasal administration comprising:	*See* claim 1.
about 1 to about 20 mg of diazepam	*See* claim 1.
dissolved in about 45% to about 85% (w/w) of α-tocopherol and	*See* claims 1 and 3.
about 25% to about 40% (w/w) of one or more alcohols selected from the group consisting of ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, and any combinations thereof,	*See* claim 1.
wherein the pharmaceutical composition is a solution	*See* claim 1.

Claim Language	Exemplary Prior Art Citations
of about 100 μL, and	*See* claims 1 and 10.
wherein the pharmaceutical composition is in a pharmaceutically-acceptable spray formulation for intranasal administration.	*See* claim 1.
21. The pharmaceutical composition of claim 20, wherein the pharmaceutical composition further comprises an absorption enhancer.	*See* claims 20 and 8.

Exhibits G-H

Exhibit G: Obviousness-Type Double Patenting Claim Chart for U.S. Patent No. 12,324,852

Claim Language	Exemplary Prior Art Citations
1. A method of treating bouts of intermittent and stereotypic episodes of increased seizure activity in an epilepsy patient that is distinguishable from other seizures suffered by the patient comprising: administering a single spray of 100 μL to one nasal mucosal membrane of the patient of a pharmaceutical solution consisting of: 56.47 mg of vitamin E USP +/−5%; 10 mg of diazepam; 0.25 mg of dodecyl maltoside; 10.50 mg of benzyl alcohol +/−5%, and a sufficient quantity of ethanol; wherein administering the single spray of the pharmaceutical solution to the patient achieves 92.5% to 107.5% of the bioavailability of an equivalent dose of diazepam administered intravenously and is safe and effective in treating the bouts of intermittent and stereotypic episodes of increased seizure activity in the patient; and wherein administering the single spray of the pharmaceutical solution to the one nasal mucosal membrane of the patient results in a treatment selected from the group consisting of a reduction in the severity of the seizure, a reduction in the probability that the patient will experience a repeat seizure, an increase in the interval between a current seizure and a next seizure in the patient, a reduction in the frequency of seizure in the patient and combinations thereof.	Claim 18 of the ’546 patent discloses a pharmaceutical solution for nasal administration consisting of about 56.47% (w/v) vitamin E, about 10.5% (w/v) benzyl alcohol, about 10% (w/v) diazepam, about 0.25% (w/v) dodecyl maltoside, and sufficient quantity of dehydrated ethanol. To the extent that the claims of the ’546 patent do not expressly recite a method of treating bouts of intermittent and stereotypic episodes of increased seizure activity in an epilepsy patient by administering a single spray of 100 μL of the recited formulation to one nasal mucosal membrane, or do not expressly recite the recited bioavailability range and treatment outcomes, such features were well-known and obvious in view of claim 18 of the ’546 patent and based on the prior art references cited in the obviousness chart for this limitation in the ’852 patent.
2. The method of claim 1, wherein the treatment achieves 96% of the bioavailability of an equivalent dose of diazepam administered intravenously.	*See* claim 1.
3. The method of claim 1, where the treatment achieves a Tmax of about 1.5 hours.	*See* claim 1.
4. The method of claim 1, wherein the pharmaceutical solution is substantially free of water.	*See* claim 1.

Claim Language	Exemplary Prior Art Citations
5. The method of claim 1, wherein the single spray of 100 μL is administered to one nasal mucosal membrane of the patient as a single metered spray.	*See* claim 1.
6. A method of treating bouts of intermittent and stereotypic episodes of increased seizure activity in an epilepsy patient that is distinguishable from other seizures suffered by the patient comprising: administering a single spray of 100 μL of a stable pharmaceutical solution to one nasal mucosal membrane of the patient and administering a second single spray of 100 μL of the pharmaceutical solution to a second nasal mucosal membrane of the patient, the 100 μL of the pharmaceutical solution consisting of: 56.47 mg of vitamin E USP +/−5%; 7.5 mg of diazepam; 0.25 mg of dodecyl maltoside; 10.50 mg of benzyl alcohol +/−5%, and a sufficient quantity of ethanol; wherein administering the single spray and the second single spray of the pharmaceutical solution to the patient achieves 92.5% to 107.5% of the bioavailability of an equivalent dose of diazepam administered intravenously and is safe and effective in treating the bouts of intermittent and stereotypic episodes of increased seizure activity in the patient; and wherein administering the single spray and the second single spray of the pharmaceutical solution to the patient results in a treatment selected from the group consisting of a reduction in the severity of the seizure, a reduction in the probability that the patient will experience a repeat seizure, an increase in the interval between a current seizure and a next seizure in the patient, a reduction in the frequency of seizure in the patient and combinations thereof.	*See* claim 1. Claim 19 of the ’546 patent discloses a pharmaceutical solution for nasal administration consisting of 5–15% (w/v) diazepam, 0.01–1% (w/v) dodecyl maltoside, 45–65% (w/v) vitamin E, 10–25% (w/v) ethanol, and 5–15% (w/v) benzyl alcohol. A POSA would understand that claim 19 of the ’546 patent covers diazepam formulations containing 5–15 mg/spray. To the extent that the claims of the ’546 patent do not expressly recite a method of treating bouts of intermittent and stereotypic episodes of increased seizure activity in an epilepsy patient by administering a first and second single spray of 100 μL of the recited formulation to alternating nasal mucosal membranes, or do not expressly recite the recited bioavailability range and treatment outcomes, such features were well-known and obvious in view of claims 18 and 19 of the ’546 patent and based on the prior art references cited in the obviousness chart for this limitation in the ’852 patent.
7. The method of claim 6, wherein the treatment achieves 96% of the bioavailability of an equivalent dose of diazepam administered intravenously.	*See* claim 6.

Claim Language	Exemplary Prior Art Citations
8. The method of claim 6, where the treatment achieves a Tmax of about 1.5 hours.	*See* claims 6 and 3.
9. The method of claim 6, wherein the pharmaceutical solution is substantially free of water.	*See* claims 6 and 4.
10. A method of treating bouts of intermittent and stereotypic episodes of increased seizure activity in an epilepsy patient that is distinguishable from other seizures suffered by the patient comprising: administering as a single spray of 100 μL to one nasal mucosal membrane of the patient of a pharmaceutical solution consisting of: 56.47 mg of vitamin E USP +/−5%; 5 mg of diazepam; 0.25 mg of dodecyl maltoside; 10.50 mg of benzyl alcohol +/−5%, and a sufficient quantity of ethanol; wherein administering the single spray of the pharmaceutical solution to the patient achieves 92.5% to 107.5% of the bioavailability of an equivalent dose of diazepam administered intravenously and is safe and effective in treating the bouts of intermittent and stereotypic episodes of increased seizure activity in the patient; and wherein administering the single spray of the pharmaceutical solution to the patient achieves results in a treatment selected from the group consisting of a reduction in the severity of the seizure, a reduction in the probability that the patient will experience a repeat seizure, an increase in the interval between a current seizure and a next seizure in the patient, a reduction in the frequency of seizure in the patient and combinations thereof.	*See* claim 1.
11. The method of claim 10, wherein the treatment achieves 96% of the bioavailability of an equivalent dose of diazepam administered intravenously.	*See* claim 10.
12. The method of claim 10, where the treatment achieves a Tmax of about 1.5 hours.	*See* claims 10 and 3.

Claim Language	Exemplary Prior Art Citations
13. The method of claim 10, wherein the pharmaceutical solution is substantially free of water.	*See* claims 10 and 4.
14. A method of treating bouts of intermittent and stereotypic episodes of increased seizure activity in an epilepsy patient that is distinguishable from other seizures suffered by the patient comprising: administering a single spray of 100 μL of a stable pharmaceutical solution to one nasal mucosal membrane of the patient and administering a second single spray of 100 μL of the pharmaceutical solution to a second nasal mucosal membrane of the patient, the 100 μL of the pharmaceutical solution consisting of: 56.47 mg of vitamin E USP +/−5%; 10 mg of diazepam; 0.25 mg of dodecyl maltoside; 10.50 mg of benzyl alcohol +/−5%, and a sufficient quantity of ethanol; wherein administering the single spray and the second single spray of the pharmaceutical solution to the patient achieves 92.5% to 107.5% of the bioavailability of an equivalent dose of diazepam administered intravenously and is safe and effective in treating the bouts of intermittent and stereotypic episodes of increased seizure activity in the patient; wherein administering the single spray and the second single spray of the pharmaceutical solution to the patient results in a treatment selected from the group consisting of a reduction in the severity of the seizure, a reduction in the probability that the patient will experience a repeat seizure, an increase in the interval between a current seizure and a next seizure in the patient, a reduction in the frequency of seizure in the patient and combinations thereof.	*See* claims 1 and 6.
15. The method of claim 14, wherein the treatment achieves 96% of the bioavailability of an equivalent dose of diazepam administered intravenously.	*See* claim 14.

Claim Language	Exemplary Prior Art Citations
16. The method of claim 14, where the treatment achieves a Tmax of about 1.5 hours.	*See* claims 14 and 3.
17. The method of claim 14, wherein the pharmaceutical solution is substantially free of water.	*See* claims 14 and 4.
18. The method of claim 1, wherein administering the single spray of the pharmaceutical solution to the patient achieves 96% to 97% of the bioavailability of an equivalent dose of diazepam administered intravenously.	*See* claim 1.
19. The method of claim 14, wherein administering the single spray and the second single spray of the pharmaceutical solution to the patient achieves 96% to 97% of the bioavailability of an equivalent dose of diazepam administered intravenously.	*See* claim 14.
20. The method of claim 1, wherein administering the single spray of the pharmaceutical solution to the one nasal mucosal membrane of the patient results in treatment in less than about 5 minutes and treatment over about 24 hours.	*See* claim 1.
21. The method of claim 6, wherein administering the single spray and the second single spray of the pharmaceutical solution to the patient results in treatment in less than about 5 minutes and treatment over about 24 hours.	*See* claims 6 and 20.
22. The method of claim 10, wherein administering the single spray of the pharmaceutical solution to the patient results in treatment in less than about 5 minutes and treatment over about 24 hours.	*See* claims 10 and 20.
23. The method of claim 14, wherein administering the single spray and the second single spray of the pharmaceutical solution to the patient results in treatment in less than about 5 minutes and treatment over about 24 hours.	*See* claims 14 and 20.
24. The method of claim 1, wherein administering the single spray of the pharmaceutical solution to the one nasal mucosal membrane of the patient exhibits a half-life ($t_{1/2}$) of about 49.2 hours.	*See* claim 1.

Claim Language	Exemplary Prior Art Citations
25. The method of claim 6, wherein administering the single spray and the second single spray of the pharmaceutical solution to the patient exhibits a half-life ($t_{1/2}$) of about 49.2 hours.	*See* claims 6 and 24.
26. The method of claim 10, wherein administering the single spray of the pharmaceutical solution to the patient exhibits a half-life ($t_{1/2}$) of about 49.2 hours.	*See* claims 10 and 24.
27. The method of claim 14, wherein administering the single spray and the second single spray of the pharmaceutical solution to the patient exhibits a half-life ($t_{1/2}$) of about 49.2 hours.	*See* claims 14 and 24.
28. The method of claim 1, wherein dodecyl maltoside is n-dodecyl-β-D-maltoside.	*See* claim 1.
29. The method of claim 6, wherein dodecyl maltoside is n-dodecyl-β-D-maltoside.	*See* claim 6.
30. The method of claim 10, wherein dodecyl maltoside is n-dodecyl-β-D-maltoside.	*See* claim 10.
31. The method of claim 14, wherein dodecyl maltoside is n-dodecyl-β-D-maltoside.	*See* claim 14.

Exhibit H: Obviousness-Type Double Patenting Claim Chart for U.S. Patent No. 12,337,061

Claim Language	Exemplary Prior Art Citations
1. A method of treating bouts of intermittent and stereotypic episodes of increased seizure activity in an epilepsy patient that is distinguishable from other seizures suffered by the patient consisting of: administering a single spray of 100 μL of a stable pharmaceutical solution to a nostril of the patient, the pharmaceutical solution containing: 56.47 mg of vitamin E USP; 10 mg of diazepam; 0.25 mg of dodecyl maltoside; 10.50 mg of benzyl alcohol; and a sufficient quantity of ethanol; wherein administering the single spray of the pharmaceutical solution achieves 96% to 97% of the bioavailability of an equivalent dose of diazepam administered intravenously; wherein administering the single spray of the pharmaceutical solution is safe and effective in treating the bouts of intermittent and stereotypic episodes of increased seizure activity in the patient; and wherein administering the single spray of the pharmaceutical solution results in a treatment selected from the group consisting of a reduction in the severity of the seizure, a reduction in the probability that the patient will experience a repeat seizure, an increase in the interval between a current seizure and a next seizure in the patient, a reduction in the frequency of seizure in the patient and combinations thereof.	Claim 18 of the ’546 patent discloses a pharmaceutical solution for nasal administration consisting of about 56.47% (w/v) vitamin E, about 10.5% (w/v) benzyl alcohol, about 10% (w/v) diazepam, about 0.25% (w/v) dodecyl maltoside, and sufficient quantity of dehydrated ethanol. To the extent that the claims of the ’546 patent do not expressly recite a method of treating bouts of intermittent and stereotypic episodes of increased seizure activity in an epilepsy patient by administering a single spray of 100 μL of the recited formulation to one nasal mucosal membrane, or do not expressly recite the recited bioavailability range and treatment outcomes, such features were well-known and obvious in view of claim 18 of the ’546 patent and based on the prior art references cited in the obviousness chart for this limitation in the ’061 patent.
2. The method of claim 1, wherein the pharmaceutical solution is stable at 25° C. and 60% relative humidity for at least 3 months.	*See* claim 1.
3. The method of claim 1, wherein administering the single spray of the pharmaceutical solution results in treatment in less than about 5 minutes.	*See* claim 1.
4. The method of claim 3, wherein administering the single spray of the	*See* claim 3.

Claim Language	Exemplary Prior Art Citations
pharmaceutical solution results in treatment over about 24 hours.	
5. A method of treating bouts of intermittent and stereotypic episodes of increased seizure activity in an epilepsy patient that is distinguishable from other seizures suffered by the patient consisting of: administering a single spray of 100 μL of a stable pharmaceutical solution to a nostril of the patient and administering a second single spray of 100 μL of the pharmaceutical solution to a second nostril of the patient, each of the 100 μL of the pharmaceutical solution containing: 56.47 mg of vitamin E USP; 10 mg of diazepam; 0.25 mg of dodecyl maltoside; 10.50 mg of benzyl alcohol; and a sufficient quantity of ethanol; wherein administering the single spray and administering the second single spray of the pharmaceutical solution achieves 96% to 97% of the bioavailability of an equivalent dose of diazepam administered intravenously; wherein administering the single spray and administering the second single spray of the pharmaceutical solution is safe and effective in treating the bouts of intermittent and stereotypic episodes of increased seizure activity in the patient; and wherein administering the single spray and administering the second single spray of the pharmaceutical solution results in a treatment selected from the group consisting of a reduction in the severity of the seizure, a reduction in the probability that the patient will experience a repeat seizure, an increase in the interval between a current seizure and a next seizure in the patient, a reduction in the frequency of seizure in the patient and combinations thereof.	*See* claim 1.
6. The method of claim 5, wherein the pharmaceutical solution is stable at 25° C. and 60% relative humidity for at least 3 months.	*See* claims 5 and 2.

Claim Language	Exemplary Prior Art Citations
7. The method of claim 5, wherein administering the single spray and administering the second single spray of the pharmaceutical solution results in treatment in less than about 5 minutes.	*See* claims 5 and 3.
8. The method of claim 7, wherein administering the single spray and administering the second single spray of the pharmaceutical solution results in treatment over about 24 hours.	*See* claims 7 and 4.
9. The method of claim 1, wherein the single spray of 100 μL is administered to a nostril of the patient as a single metered spray.	*See* claim 1.
10. The method of claim 5, wherein the single spray of 100 μL and the second single spray of 100 μL are each administered to a nostril of the patient as a single metered spray.	*See* claims 5 and 1.
11. The method of claim 1, wherein the ethanol is dehydrated ethanol.	*See* claim 1.
12. The method of claim 5, wherein the ethanol is dehydrated ethanol.	*See* claims 5 and 11.
13. The method of claim 1, wherein the dodecyl maltoside is n-dodecyl-β-D-maltoside.	*See* claim 1.
14. The method of claim 5, wherein the dodecyl maltoside is n-dodecyl-β-D-maltoside.	*See* claim 1.
15. The method of claim 1, wherein the pharmaceutical solution exhibits an approximate area under a blood plasma concentration curve measuring total drug exposure across time ($AUC_{0-\infty}$) of 7338 hours*ng/ml.	*See* claim 1.
16. The method of claim 5, wherein the pharmaceutical solution exhibits an approximate area under a blood plasma concentration curve measuring total drug exposure across time ($AUC_{0-\infty}$) of 7338 hours*ng/mL.	*See* claims 5 and 15.
17. The method of claim 1, wherein the pharmaceutical solution exhibits an approximate C_{max} of 272 ng/mL.	*See* claim 1.
18. The method of claim 5, wherein the pharmaceutical solution exhibits an approximate C_{max} of 272 ng/mL.	*See* claims 5 and 17.

Claim Language	Exemplary Prior Art Citations
19. The method of claim 1, wherein the pharmaceutical solution exhibits an approximate T_{max} of 1.5 hours.	*See* claim 1.
20. The method of claim 5, wherein the pharmaceutical solution exhibits an approximate T_{max} of 1.5 hours.	*See* claims 5 and 19.
21. A method of treating bouts of intermittent and stereotypic episodes of increased seizure activity in an epilepsy patient that is distinguishable from other seizures suffered by the patient comprising: administering a single spray of 100 μL +/−5% of a stable pharmaceutical solution to a nostril of the patient, the pharmaceutical solution containing: 56.47 mg of vitamin E USP +/−5%; 10 mg of diazepam; 0.25 mg of dodecyl maltoside +/−5%; 10.50 mg of benzyl alcohol +/−5%; and a sufficient quantity of ethanol; wherein administering the single spray of the pharmaceutical solution achieves 92.5% to 107.5% of the bioavailability of an equivalent dose of diazepam administered intravenously; wherein administering the single spray of the pharmaceutical solution is safe and effective in treating the bouts of intermittent and stereotypic episodes of increased seizure activity in the patient; and wherein administering the single spray of the pharmaceutical solution results in a treatment selected from the group consisting of a reduction in the severity of the seizure, a reduction in the probability that the patient will experience a repeat seizure, an increase in the interval between a current seizure and a next seizure in the patient, a reduction in the frequency of seizure in the patient and combinations thereof.	*See* claim 1.
22. The method of claim 21, wherein the pharmaceutical solution is stable at 25° C. and 60% relative humidity for at least 3 months.	*See* claims 21 and 2.
23. The method of claim 21, wherein administering the single spray of the	*See* claims 21 and 3.

Claim Language	Exemplary Prior Art Citations
pharmaceutical solution results in treatment in less than about 5 minutes.	
24. The method of claim 21, wherein administering the single spray of the pharmaceutical solution results in treatment over about 24 hours.	*See* claims 21 and 4.
25. The method of claim 21, wherein the single spray of 100 μL is administered to a nostril of the patient as a single metered spray.	*See* claims 21 and 4.
26. The method of claim 21, wherein the ethanol is dehydrated ethanol.	*See* claims 21 and 11.
27. The method of claim 21, wherein the dodecyl maltoside is n-dodecyl-β-D-maltoside.	*See* claims 21 and 1.
28. The method of claim 21, wherein the pharmaceutical solution exhibits an approximate area under a blood plasma concentration curve measuring total drug exposure across time ($AUC_{0-\infty}$) of 7338 hours*ng/mL.	*See* claims 21 and 15.
29. The method of claim 21, wherein the pharmaceutical solution exhibits an approximate C_{max} of 272 ng/mL.	*See* claims 21 and 17.
30. The method of claim 21, wherein the pharmaceutical solution exhibits an approximate T_{max} of 1.5 hours.	*See* claims 21 and 19.
31. The method of claim 21, wherein the pharmaceutical solution exhibits a half-life of about 49.2 hours.	*See* claim 21.
32. The method of claim 21, wherein the absolute bioavailability is 96% to 97%.	*See* claims 21 and 1.
33. A method of treating bouts of intermittent and stereotypic episodes of increased seizure activity in an epilepsy patient that is distinguishable from other seizures suffered by the patient comprising: administering a single spray of 100 μL +/−5% of a stable pharmaceutical solution to a nostril of the patient and administering a second single spray of 100 μL +/−5% of the pharmaceutical solution to a second nostril of the patient, each of the 100 μL +/−5% of the pharmaceutical solution containing: 56.47 mg of vitamin E USP +/−5%;	*See* claims 1, 5, and 21. Claim 19 of the ’546 patent further discloses a pharmaceutical solution for nasal administration consisting of 5–15% (w/v) diazepam, 0.01–1% (w/v) dodecyl maltoside, 45–65% (w/v) vitamin E, 10–25% (w/v) ethanol, and 5–15% (w/v) benzyl alcohol. To the extent that the claims of the ’546 patent do not expressly recite a method of treating bouts of intermittent and stereotypic episodes of increased seizure activity in an

Claim Language	Exemplary Prior Art Citations
10 mg of diazepam; 10.50 mg of benzyl alcohol +/−5%; and a sufficient quantity of ethanol; wherein administering the single spray and administering the second single spray of the pharmaceutical solution achieves 92.5% to 107.5% of the bioavailability of an equivalent dose of diazepam administered intravenously; wherein administering the single spray and administering the second single spray of the pharmaceutical solution is safe and effective in treating the bouts of intermittent and stereotypic episodes of increased seizure activity in the patient; and wherein administering the single spray and administering the second single spray of the pharmaceutical solution results in a treatment selected from the group consisting of a reduction in the severity of the seizure, a reduction in the probability that the patient will experience a repeat seizure, an increase in the interval between a current seizure and a next seizure in the patient, a reduction in the frequency of seizure in the patient and combinations thereof.	epilepsy patient by administering a single spray of 100 μL of the recited formulation to one nasal mucosal membrane, or do not expressly recite the recited bioavailability range and treatment outcomes, such features were well-known and obvious in view of claims 18 and 19 of the ’546 patent and based on the prior art references cited in the obviousness chart for this limitation in the ’061 patent.
34. The method of claim 33, wherein the pharmaceutical solution is stable at 25° C. and 60% relative humidity for at least 3 months.	*See* claims 33 and 2.
35. The method of claim 33, wherein administering the single spray and the second single spray of the pharmaceutical solution results in treatment in less than about 5 minutes.	*See* claims 33 and 3.
36. The method of claim 33, wherein administering the single spray and the second single spray of the pharmaceutical solution results in treatment over about 24 hours.	*See* claims 33 and 4.
37. The method of claim 33, wherein the single spray of 100 μL +/−5% and the second single spray of 100 μL +/−5% are each administered to a nostril of the patient as a single metered spray.	*See* claims 33 and 5.
38. The method of claim 33, wherein the ethanol is dehydrated ethanol.	*See* claims 33 and 11.

Claim Language	Exemplary Prior Art Citations
39. The method of claim 33, wherein the dodecyl maltoside is n-dodecyl-β-D-maltoside.	*See* claims 33 and 1.
40. The method of claim 33, wherein the pharmaceutical solution exhibits an approximate T_{max} of 1.5 hours.	*See* claims 33 and 19.
41. The method of claim 33, wherein the pharmaceutical solution exhibits a half-life of about 49.2 hours.	*See* claims 33 and 31.
42. The method of claim 33, wherein the absolute bioavailability is 96% to 97%.	*See* claims 33 and 1.
43. A method of treating bouts of intermittent and stereotypic episodes of increased seizure activity in an epilepsy patient that is distinguishable from other seizures suffered by the patient comprising: the patient, each of the 100 μL +/−5% of the pharmaceutical solution containing: 56.47 mg of vitamin E USP +/−5%; 7.5 mg of diazepam; 0.25 mg of dodecyl maltoside +/−5%; 10.50 mg of benzyl alcohol +/−5%; and a sufficient quantity of ethanol; wherein administering the single spray and administering the second single spray of the pharmaceutical solution achieves 92.5% to 107.5% of the bioavailability of an equivalent dose of diazepam administered intravenously; wherein administering the single spray and administering the second single spray of the pharmaceutical solution is safe and effective in treating the bouts of intermittent and stereotypic episodes of increased seizure activity in the patient; and wherein administering the single spray and administering the second single spray of the pharmaceutical solution results in a treatment selected from the group consisting of a reduction in the severity of the seizure, a reduction in the probability that the patient will experience a repeat seizure, an increase in the interval between a current seizure and a next seizure in the patient, a reduction in the frequency of seizure in the patient and combinations thereof.	*See* claims 1, 5, and 21. Claim 19 of the ’546 patent further discloses a pharmaceutical solution for nasal administration consisting of 5–15% (w/v) diazepam, 0.01–1% (w/v) dodecyl maltoside, 45–65% (w/v) vitamin E, 10–25% (w/v) ethanol, and 5–15% (w/v) benzyl alcohol. To the extent that the claims of the ’546 patent do not expressly recite a method of treating bouts of intermittent and stereotypic episodes of increased seizure activity in an epilepsy patient by administering a single spray of 100 μL of the recited formulation to one nasal mucosal membrane, or do not expressly recite the recited bioavailability range and treatment outcomes, such features were well-known and obvious in view of claims 18 and 19 of the ’546 patent and based on the prior art references cited in the obviousness chart for this limitation in the ’061 patent.

Claim Language	Exemplary Prior Art Citations
44. The method of claim 43, wherein the pharmaceutical solution is stable at 25° C. and 60% relative humidity for at least 3 months.	*See* claims 43 and 2.
45. The method of claim 43, wherein administering the single spray and the second single spray of the pharmaceutical solution results in treatment in less than about 5 minutes.	*See* claims 43, 5, and 3.
46. The method of claim 43, wherein administering the single spray and the second single spray of the pharmaceutical solution results in treatment over about 24 hours.	*See* claims 43, 5, and 4.
47. The method of claim 43, wherein the single spray of 100 μL +/−5% and the second single spray of 100 μL +/−5% are each administered to a nostril of the patient as a single metered spray.	*See* claims 43 and 5.
48. The method of claim 43, wherein the ethanol is dehydrated ethanol.	*See* claims 43 and 11.
49. The method of claim 43, wherein the dodecyl maltoside is n-dodecyl-β-D-maltoside.	*See* claims 43 and 1.
50. The method of claim 43, wherein the pharmaceutical solution exhibits an approximate T_{max} of 1.5 hours.	*See* claims 43 and 19.
51. The method of claim 43, wherein the pharmaceutical solution exhibits a half-life of about 49.2 hours.	*See* claims 43 and 31.
52. The method of claim 43, wherein the absolute bioavailability is 96% to 97%.	*See* claims 43 and 1.
53. A method of treating bouts of intermittent and stereotypic episodes of increased seizure activity in an epilepsy patient that is distinguishable from other seizures suffered by the patient comprising: administering a single spray of 100 μL +/−5% of a stable pharmaceutical solution to a nostril of the patient, the pharmaceutical solution containing: 56.47 mg of vitamin E USP +/−5%; 5 mg of diazepam; 0.25 mg of dodecyl maltoside +/−5%; 10.50 mg of benzyl alcohol +/−5%; and a sufficient quantity of ethanol;	*See* claim 1. Claim 19 of the ’546 patent further discloses a pharmaceutical solution for nasal administration consisting of 5–15% (w/v) diazepam, 0.01–1% (w/v) dodecyl maltoside, 45–65% (w/v) vitamin E, 10–25% (w/v) ethanol, and 5–15% (w/v) benzyl alcohol. To the extent that the claims of the ’546 patent do not expressly recite a method of treating bouts of intermittent and stereotypic episodes of increased seizure activity in an epilepsy patient by administering a single spray of 100 μL of the recited formulation to

Claim Language	Exemplary Prior Art Citations
wherein administering the single spray of the pharmaceutical solution achieves 92.5% to 107.5% of the bioavailability of an equivalent dose of diazepam administered intravenously; wherein administering the single spray of the pharmaceutical solution is safe and effective in treating the bouts of intermittent and stereotypic episodes of increased seizure activity in the patient; and wherein administering the single spray of the pharmaceutical solution results in a treatment selected from the group consisting of a reduction in the severity of the seizure, a reduction in the probability that the patient will experience a repeat seizure, an increase in the interval between a current seizure and a next seizure in the patient, a reduction in the frequency of seizure in the patient and combinations thereof.	one nasal mucosal membrane, or do not expressly recite the recited bioavailability range and treatment outcomes, such features were well-known and obvious in view of claims 18 and 19 of the '546 patent and based on the prior art references cited in the obviousness chart for this limitation in the '061 patent.
54. The method of claim 53, wherein the pharmaceutical solution is stable at 25° C. and 60% relative humidity for at least 3 months.	*See* claims 53 and 2.
55. The method of claim 53, wherein administering the single spray of the pharmaceutical solution results in treatment in less than about 5 minutes.	*See* claims 53 and 3.
56. The method of claim 53, wherein administering the single spray of the pharmaceutical solution results in treatment over about 24 hours.	*See* claims 53 and 4.
57. The method of claim 53, wherein the single spray of 100 μL is administered to a nostril of the patient as a single metered spray.	*See* claims 53 and 1.
58. The method of claim 53, wherein the ethanol is dehydrated ethanol.	*See* claims 53 and 11.
59. The method of claim 53, wherein the dodecyl maltoside is n-dodecyl-β-D-maltoside.	*See* claims 53 and 1.
60. The method of claim 53, wherein the pharmaceutical solution exhibits an approximate T_{max} of 1.5 hours.	*See* claims 53 and 19.
61. The method of claim 53, wherein the pharmaceutical solution exhibits a half-life of about 49.2 hours.	*See* claims 53 and 31.

Claim Language	Exemplary Prior Art Citations
62. The method of claim 53, wherein the absolute bioavailability is 96% to 97%.	*See* claims 53 and 1.