

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PADAGIS US LLC
Petitioner,

v.

NEURELIS, INC.
Patent Owner.

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

**PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO.
11,241,414 UNDER 35 U.S.C. §§ 311–319 AND 37 C.F.R. § 42.100 *et seq.***

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PETITIONER’S EXHIBITS

<u>Exhibit No.</u>	<u>Exhibit Description</u>
1001	U.S. Patent No. 11,241,414, <i>Administration Of Benzodiazepine Compositions</i> , filed May 27, 2021 (“’414 Patent”)
1002	File History for 11,241,414, Ser. No. 17/332,800 (“’414 FH”)
1003	U.S. Patent No. 11,793,786, <i>Administration Of Benzodiazepine Compositions</i> , filed April 12, 2021 (“’786 Patent”)
1004	File History for 11,793,786 Patent, Ser. No. 17/228,514 (“’786 FH”)
1005	Non-Provisional Patent Application Serial No. 15/955,397, filed April 17, 2018 (“’397 Application”)
1006	File History for Non-Provisional Patent Application Serial No. 15/955,397, filed April 17, 2018 (“’397 FH”)
1007	File History for Non-Provisional Patent Application Serial No. 12/413,439, filed March 27, 2009 (“’439 FH”) Part 1: Pages 1-400 Part 2: Pages 401-800 Part 3: Pages 801-1200 Part 4: Pages 1201-1600 Part 5: Pages 1601-2000 Part 6: Pages 2001-2400 Part 7: Pages 2401-2800 Part 8: Pages 2801-3200 Part 9: Pages 3201-3488
1008	Provisional Patent Application No. 61/040,558, filed March 28, 2008 (“’558 Provisional”)
1009	Gwozdz et al., WO 2009/120933, <i>Pharmaceutical Solutions And Method For Solubilizing Therapeutic Agents</i> , published October 1, 2009, International Filing Date March 27, 2009 (PCT/US2009/038518) (“Gwozdz”)

Exhibit No.	Exhibit Description
1010	Meezan et al., U.S. Patent Application Publication No. US 2006/0046962, <i>Absorption Enhancers for Drug Administration</i> , Serial No. 11/127,786, published March 2, 2006 (“Meezan”)
1011	Ritschel, <i>Handbook of Basic Pharmacokinetics</i> , Chapter 36 (Bioavailability and Bioequivalence), Drug Intelligence Publications, Illinois, 1992 (“Ritschel”)
1012	Osborne et al., <i>Skin Penetration Enhancers Cited in the Technical Literature</i> , Pharmaceutical Technology, November 1997 (“Osborne”)
1013	Lindhardt et al., <i>Electroencephalographic effects and serum concentrations after intranasal and intravenous administration of diazepam to healthy volunteers</i> , Blackwell Science Ltd Br J Clin Pharmacol, 52, 521-527, 2001 (“Lindhardt”)
1014	Illum L, <i>Nasal drug delivery-possibilities, problems and solutions</i> , Journal of Controlled Release 87 (2003) 187198 (“Illum I”)
1015	Ivaturi et al., <i>Pharmacokinetics and tolerability of intranasal diazepam and midazolam in healthy adult volunteers</i> , Acta Neurol Scand. 2009 Nov;120(5):353-7. doi: 10.1111/j.1600-0404.2009.01170.x. Epub 2009 May 14 (“Ivaturi”)
1016	Rowe et al., editors, <i>Handbook of Pharmaceutical Excipients</i> , Fourth Edition (2003), Monographs for “Alcohol” (i.e., ethanol), “Alpha Tocopherol”, “Benzyl Alcohol”, “Glycerin”, “Olive Oil”, “Polyethylene Glycol”, “Propylene Glycol”, “Sesame Oil”, and “Triacetin”, American Pharmaceutical Association, Washington DC (“Rowe”)
1017	PDR 54th Edition 2000, DIASTAT® (diazepam rectal gel); MIACALCIN® (Calcitonin Nasal Spray); VALIUM® (diazepam injection), Physicians’ Desk Reference (“PDR”)
1018	Knoester PD, Jonker DM, Van Der Hoeven RT, et al. Pharmacokinetics and pharmacodynamics of midazolam administered as a concentrated intranasal spray. A study in

Exhibit No.	Exhibit Description
	healthy volunteers. Br J Clin Pharmacol. 2002; 53: 501-507 (“Knoester”)
1019	Florida Regional Common EMS Protocols Field Guide, Jones and Barlett Publishers, MA (2005) (“EMS”)
1020	Valium® Tablet Label, Roche, January 2008 (“Valium label”)
1021	Wolfe T, Macfarlane T. <i>Intranasal midazolam therapy for pediatric status epilepticus</i> . Am J Emerg Med 2006; 24:43-346 (“Wolfe”)
1022	Holsti M, Sill B, Firth S, et al., <i>Prehospital intranasal midazolam for the treatment of pediatric seizures</i> . Ped Emerg Care 2007; 23: 148-153 (“Holsti”)
1023	Greenblatt D, Gan L, Harmatz, et al. <i>Pharmacokinetics and pharmacodynamics of single-dose triazolam: EEG compared with digital symbol substitution test</i> . Br J Clin Pharmacol 2005; 60: 244-248 (“Greenblatt”)
1024	O’Regan M, Brown J, Clarke M. <i>Nasal rather than rectal benzodiazepines in the management of acute childhood seizures</i> . Develop Med and Child Neurol 1996; 38: 1037-1045 (“O’Regan”)
1025	Bhattacharyya M, Kalra V, Gulati S. <i>Intranasal midazolam vs rectal diazepam in acute childhood seizures</i> . Pediatric Neurology 2006; 34: 355-359 (“Bhattacharyya”)
1026	SIGMA Chemical Company Catalog (1988) (“Sigma Catalog”)
1027	Wermeling DP, et al., <i>Intranasal Delivery of Antiepileptic Medications for Treatment of Seizures, Neurotherapeutics: The Journal of the American Society for Experimental Neurotherapeutics</i> , Vol. 6, 352-353, April 2009 (“Wermeling I”)
1028	Hardman, et al., Editors, Goodman & Gilman’s, <i>The Pharmacological Basis of Therapeutics</i> , 10th Edition (2001) (“Goodman & Gilman”)

Exhibit No.	Exhibit Description
1029	Loftsson T, Gudmundsdottir H, Sigurjonsdittur JF, et al. Cyclodextrin solubilization of benzodiazepines: formulation of midazolam nasal spray. <i>Int J Pharm</i> 2001; 212:29-40 (“Loftsson”)
1030	Gudmundsdottir H, Sigurjonsdottir JF, Masson M, et al. <i>Intranasal administration of midazolam in a cyclodextrin based formulation: bioavailability and clinical evaluation in humans.</i> <i>Pharmazie</i> 2001; 56: 963-966 (“Gudmundsdottir”)
1031	Dale O., Nilsen T., Loftsson T. <i>Intranasal midazolam: a comparison of two delivery devices in human volunteers.</i> <i>J Pharmacy Pharmacol</i> 2006; 58: 1311-1318 (“Dale”)
1032	Burstein AH, Modica R, Hatton M, et al. <i>Pharmacokinetics and pharmacodynamics of midazolam after intranasal administration.</i> <i>J Clin Pharmacol</i> 1997; 37: 711-718 (“Burstein”)
1033	Wermeling, D, Record K, Kelly T, et al., <i>Pharmacokinetics and pharmacodynamics of a new intranasal midazolam formulation in healthy volunteers.</i> <i>Anesth Analg</i> 2006; 103: 344-349 (“Wermeling II”)
1034	Schols-Hendriks MWG, Lohman JJHM, Janknegt R, et al. <i>Absorption of clonazepam after intranasal and buccal administration.</i> <i>Br J Clin Pharmacol</i> , 1995; 39: 449-451 (“Schols-Hendricks”)
1035	Lau SWJ, Slattery JT. <i>Intl J Pharmaceutics. Absorption of diazepam and lorazepam following intranasal administration.</i> <i>Int J Pharmaceutics</i> 1989; 54: 171-174 (“Lau”)
1036	Wermeling DP, Miller JL, Archer SM, et al. <i>Bioavailability and pharmacokinetics of lorazepam after intranasal, intravenous, and intramuscular administration.</i> <i>J Clin Pharmacol</i> , 2001; 41: 1225-1231 (“Wermeling III”)
1037	Budavari, et al., Editors, <i>The Merck Index</i> , 12th Edition (1996) (“Merck Index”)
1038	USP 26/NF 21 2003, <i>The Official Compendia of Standards</i> , Ethanol, Copyright 2002 (“USP 26/ NF 21”)

Exhibit No.	Exhibit Description
1039	U.S. App. No. 12/413,439, filed March 27, 2009 (“’439 Application”)
1040	Final Written Decision issued in IPR 2019-00451 filed against U.S. Patent No. 9,763,876, August 6, 2020 (“IPR 2019-00451 Final Written Decision”)
1041	Lowenstein DH, Alldredge BK. <i>Status epilepticus</i> , N Eng J Med 1998; 338:970-976 (“Lowenstein I”)
1042	Lowenstein DH, Bleck T, Macdonald RL. <i>It’s time to revise the definition of status epilepticus</i> . Epilepsia 1999; 40:120-122 (“Lowenstein II”)
1043	Wang HC, Chang WN, Chang HW, et al., <i>Factors predictive of outcome in posttraumatic seizures</i> . J Trauma 2008; 64: 883-888 (“Wang”)
1044	Stavem K, Bjornaes H, Langmoen IA. <i>Long-term seizures and quality of life after epilepsy surgery compared with matched controls</i> . Neurosurgery 2008; 62: 326-334 (“Stavem”)
1045	Logroscino G, Hessdorffer DC, Cascino G, et al., <i>Time Trends in incidence, mortality, and case-fatality after first episode of status epilepticus</i> , Epilepsia 2001; 42:1031-1035 (“Logroscino”)
1046	Feen ES, Bershad EM, Suarez JI, <i>Status Epilepticus</i> , South Med J 2008; 101: 400-406 (“Feen”)
1047	Pang T, Hirsch L, <i>Treatment of convulsive and nonconvulsive status epilepticus</i> , Cur Treat Options Neurol 2005; 7:247-259 (“Pang”)
1048	Smith B, <i>Treatment of status epilepticus</i> , Neurol Clin 2001; 19:347-369 (“Smith”)
1049	Ericksson K, Kalviainen R. <i>Pharmacologic management of convulsive status epilepticus in childhood</i> , Expert Rev Neurotherapeutics 2005; 5:777-783 (“Ericksson”)
1050	Meierkord H, Engelsen B, Gocke K, et al., <i>EFNS guideline on the management of status epilepticus</i> , Eur J Neurol 2006; 13: 445-450 (“Meierkord”)
1051	Prasad K, Krishman P, Al-Roomi K, et al., <i>Anticonvulsant therapy for status epilepticus</i> , Br J Clin Pharmacol 2007; 63:640-647 (“Prasad”)

Exhibit No.	Exhibit Description
1052	Illum L., <i>Nasal Clearance in Health and Disease</i> , J Aerosol Med 2006; 19:92-99 (“Illum II”)
1053	Constantino HR, Illum L, Brandt G et al., <i>Intranasal delivery: Physicochemical and therapeutic aspects</i> , Intl J Pharmaceutics 2007; 337:1-24 (“Constantino”)
1054	Rudy AC, Coda BA, Archer SM, et al., <i>A multiple dose phase I study of intranasal hydromorphone hydrochloride in healthy volunteers</i> , Anesth Analg 2004; 99:1379-1386 (“Rudy”)
1055	Mittal P, Manohar R, Rawat A, <i>Comparative study of intranasal midazolam and intravenous diazepam sedation for procedures and seizures</i> , Ind J Pediatrics 2006; 73:975-78 (“Mittal”)
1056	Mahmoudian T, Zadeh M, <i>Comparison of intranasal midazolam with intravenous diazepam for treating acute seizures in children</i> , Epilepsy and Behavior 2004; 5:253-255 (“Mahmoudian”)
1057	Lahat E, Goldman M, Barr J, et al., <i>Comparison of intranasal midazolam with intravenous diazepam in treating febrile seizures in children: prospective randomized study</i> , BMJ 2000; 321:83-87 (“Lahat”)
1058	Sharma S, et al., <i>Permeation enhancers in the transmucosal delivery of macromolecules</i> , Pharmazie 2006; 61(6): 495-504 (“Sharma”)
1059	Ahsan F. et al., <i>Effects of the permeability enhancers, tetradecylmaltoside and dimethyl-β-cyclodextrin, on insulin movement across human bronchial epithelial cells</i> , Eur J Pharm Sciences 2003; 20:27-34 (“Ahsan”).
1060	U.S. Patent No. 5,661,130 to Meezan and Pillion (“Meezan II”)
1061	U.S. Patent No. 6,610,271 to Wermeling (“Wermeling IV”)
1062	Declaration of Dr. Maureen Donovan, Ph.D.
1063	Complaint filed in <i>Neurelis, Inc. v. Padagis LLC et al.</i> , Civil Action No. 1:24-cv-11637 (D. Mass) (complaint filed on June 25, 2024).
1064	U.S. Provisional Patent App. No. 61/040,281 (“’281 Provisional”)

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<u>Exhibit No.</u>	<u>Exhibit Description</u>
1065	Not Used
1066	Not Used
1067	Not Used
1068	Neurelis, Inc. v. Aquestive Therapeutics, Inc., No. 2021-1038, (Fed. Cir. Oct. 7, 2021)
1069	Chart comparing claims 1-18 of the '414 Patent to claims 1-16 and 24-36 of the '876 Patent

I. INTRODUCTION

Padagis US LLC (“Petitioner”) hereby respectfully requests *inter partes* review of claims 1-18 (“Challenged Claims”) of U.S. Patent No. 11,241,414 (“the ’414 Patent”) pursuant to 35 U.S.C. §§ 311-319.

Notably, the issues presented in this Petition are substantially the same as the issues the Board previously considered in IPR2019-00451 when issuing a Final Written Decision findings all claims of U.S. Patent No. 9,763,876 (“the ’876 Patent”) were unpatentable. *See* EX1040 at 69 (copy of final decision in IPR2019-00451, *Aquestive Therapeutics, Inc. v. Neurelis, Inc.*). The ’876 Patent and ’414 Patents both claim priority back to U.S. patent application no. 12/413,439 (“’439 Application”) through continuation or continuation-in-part priority claims. The ’876 Patent recites substantially the same limitations as the ’414 Patent. The primary difference between the ’876 Patent claims found to be unpatentable in IPR2019-00451 and the claims of the ’414 Patent is that the former are directed to a method of treatment using a specific pharmaceutical solution while the latter are to the pharmaceutical solution itself.

To illustrate, a comparison of claims 1 of the ’414 Patent to claims 1, 4 and 26 of the ’876 Patent is provided below:

<u>Claims 1, 4 and 26 of 9,763,876</u> <u>Found Unpatentable in IPR 2019-</u> <u>00451</u>	<u>Claim 1 of 11,241,414</u>
1. A method of treating a patient with a disorder which is treatable with a benzodiazepine drug, comprising: administering to one or more nasal mucosal membranes of a patient 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. 4. The method of claim 3, wherein the benzodiazepine drug is diazepam, or a pharmaceutically-acceptable salt thereof 26. The method of claim 25, wherein the solution contains about 0.01% to 1% (w/w) of dodecyl maltoside.	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.

See EX1069 (comparing claims 1-18 of the '414 Patent to claims 1-16 and 24-36 of the '876 Patent).

The present IPR relies on the same prior art and substantially same arguments that the Board considered already in IPR2019-00451 to find the claims there were unpatentable. The Board having already found a method of treatment using the claimed pharmaceutical formulation being obvious, there is no patentable distinction in claiming the pharmaceutical formulation itself. As such, Neurelis, Inc. (“Patent Owner”) is collaterally estopped from contesting the issues previously addressed in IPR2019-00451.

Even assuming Patent Owner is not collaterally estopped from contesting the patentability of the claims over the prior art cited in this Petition, the reasoning and analysis of the Board’s decision in IPR2019-00451 why the claim pharmaceutical compound is obvious would apply equally in the instant IPR.

For the reasons provided by the Board in IPR2019-00451 and as explained in detail below, there is a reasonable likelihood that claims 1-18 of the ’414 Patent are unpatentable, and the Board should institute IPR based on this Petition.

II. MANDATORY NOTICES

Pursuant to 37 C.F.R. § 42.8, Petitioner provides the following disclosures:

A. Real Party-In-Interest (37 C.F.R. § 42.8(b)(1))

The real parties-in-interest are Padagis US LLC, Padagis LLC, and Padagis Israel Pharmaceuticals Ltd.

B. Related Matters (37 C.F.R. § 42.8(b)(2))

- The '876 Patent, which is in the same family as the '414 Patent, was the subject of IPR2019-00451 which resulted in a Final Written Decision determining that claims 1-36 of the '876 Patent are unpatentable. EX1040.
- The '414 Patent is involved in district court litigation captioned *Neurelis, Inc. v. Padagis LLC et al.* Civil Action No. 1:24-cv-00562 (D. Del.) (complaint filed on May 8, 2024). See EX1063.

C. Lead and Backup Counsel (37 C.F.R. § 42.8(b)(3))

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Pursuant to 37 C.F.R. § 42.10(b), Powers of Attorney have been filed with this Petition.

D. Service Information (37 C.F.R. § 42.8(b)(4))

Petitioner consents to service by e-mail at the above e-mail addresses provided above for lead and backup counsel. Physical mailing service information is as follows:

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Suite 6400
Houston, Texas 77002

E. Payment of Fees (37 C.F.R. §§ 42.15(a) and 42.103(a))

All required fees have been paid with the filing of this Petition. Petitioner further authorizes the U.S. Patent & Trademark Office to charge Deposit Account No. 50-1662 for any fees, including the fee set forth in 37 C.F.R. § 42.15(a) for this Petition.

F. Certification of Word Count Under 37 C.F.R. § 42.24(d)

Petitioner certifies that the word count in this Petition, including all footnotes, is 10,995 words as counted by the word-processing program (Microsoft Word for Office 365) used to generate this Petition, where such word count excludes the table of contents, mandatory notices, certificate of service, list of exhibits, and this certificate of word count. This Petition is in compliance with the 14,000 word limit set forth in 37 C.F.R. § 42.24(a)(1)(i).

III. GROUNDS FOR STANDING UNDER 37 C.F.R. § 42.104(A)

Petitioner certifies that the '414 patent is available for *inter partes* review. Petitioner is not barred or estopped from requesting an *inter partes* review of the '414 patent claims on the grounds identified in this Petition. 37 C.F.R. § 42.104(a).

IV. IDENTIFICATION OF GROUNDS FOR WHICH REVIEW IS REQUESTED UNDER 37 C.F.R. § 42.104(B)(1)

Petitioner asserts that claims 1-18 of the '414 patent are unpatentable based on the following ground:

Ground 1: Claims 1-18 are obvious over Gwozdz¹ in view of Meezan².

V. PATENT OWNER IS COLLATERALLY ESTOPPED FROM RAISING ISSUES THAT WERE ADJUDICATED IN IPR2019-00451

“It is well established that collateral estoppel applies to IPR proceedings.” *Google LLC v. Hammond Dev. Int'l*, 54 F.4th 1377, 1381 (Fed. Cir. 2022); *see also Nestle USA, Inc. v. Steuben Foods, Inc.*, 884 F.3d 1350, 1352 (Fed. Cir. 2018). The party seeking to invoke collateral estoppel must show:

- (1) the issue is identical to one decided in the first action;
- (2) the issue was actually litigated in the first action;

¹ PCT Pub. No. WO 2009/120933 A2, published October 1, 2009 (Ex. 1009, “Gwozdz”).

² U.S. Pub. No. 2006/0046962 A1, published March 2, 2006 (Ex. 1010, “Meezan”).

(3) resolution of the issue was essential to a final judgment in the first action;
and

(4) the party against whom collateral estoppel is being asserted had a full and fair opportunity to litigate the issue in the first action.

Id. All four prongs of this test are indisputably met here in view of IPR2019-00451.

The Patent Owner in the instant IPR, Neurelis Inc., is the same Patent Owner that participated in IPR2019-00451 and there is little dispute that Patent Owner had a full and fair opportunity to litigate the issues in IPR2019-00451. The Board issued a final written decision in IPR2019-00451 regarding U.S. Patent No. 9,763,876 (“the ’876 Patent”), which is in the same family as the ’414 Patent. In the final written decision in IPR2019-00451, the PTAB determined that claims 1-16 and 24-36 are unpatentable over the combination of Gwozdz in view of Meezan³. EX1040. The Board’s decision was appealed by Patent Owner but affirmed by the Federal Circuit. *See* EX1068 (Fed Circuit affirmance of IPR2019-00451 decision). As such, the Board’s final decision in IPR2019-00451 provided final resolution of invalidity issues related to the Gwozdz and Meezan combination that was essential to the

³ In IPR2019-00451 the Board refers to Meezan as “Meezan ’962.” Both Meezan in this this IPR Petition and Meezan ’962 in IPR2019-00451 are the same reference, namely U.S. Patent Publication No. US 2006/0046962.

judgment. *XY, LLC v. Trans Ova Genetics, L.C.*, 890 F.3d 1282, 1294 (Fed. Cir. 2018) (“[A]n affirmance of an invalidity finding, whether from a district court or the Board, has a collateral estoppel effect on all pending or co-pending actions.”).

In addition, collateral estoppel applies even when claims are not identical so long as the issues are materially the same. *Nestle.*, 884 F.3d at 1352; *Finjan LLC v. SonicWall, Inc.*, 84 F.4th 963, 969 (Fed. Cir. 2023) (“collateral estoppel applies where the issues of patentability are identical, i.e., where the differences between the unadjudicated patent claims and adjudicated patent claims do not materially alter the question of invalidity.”) (internal quotations omitted).

Here, the question of patentability of claims 1-16 and 24-36 of the '876 Patent that was previously adjudicated and the patentability of claims 1-18 in the instant IPR are substantially the same. *See* EX1069. The primary difference between the '876 claims found unpatentable in IPR2019-00451 and the claims of the '414 Patent is that the former are directed to a method of treatment using a specific pharmaceutical solution while the latter are to the pharmaceutical solution itself. This difference does not materially alter the question of invalidity. Rather, if a method of treatment using a pharmaceutical solution is obvious, the pharmaceutical solution itself must likewise be obvious for substantially the same reasons.

There are a number of issues in the instant IPR that Patent Owner is precluded from contesting as they are materially identical to issues the Patent Owner actually

raised and were fully resolved by the Board in IPR2019-00451. In particular, Petitioner notes that the Patent Owner is precluded from contesting the following findings made by the Board in IPR2019-00451:

1. U.S. Prov. App. No. 61/040,558 (“the ’558 provisional”) “does not provide adequate written description support for the ‘alkyl glycoside’ limitation.” *See* EX1040 at p. 23 (finding that “after reviewing all of the evidence, we find that the ’558 provisional does not provide adequate written description support for the ‘alkyl glycoside’ limitation. Therefore, the claims of the ’876 patent are not entitled to the benefit of priority to the ’558 provisional.”)
2. Gwozdz is entitled to the filing date of the ’281 Provisional. *See* EX1040 at p. 14 (finding “Petitioner has shown that the claims of Gwozdz are supported by the Gwozdz provisional, ‘at least because Gwozdz’s claims are literally identical to the claims filed in [the] Gwozdz provisional.’”).)
3. “a person of ordinary skill in the art would have had reason to add alkyl glycoside as a penetration enhancer, as disclosed in Meezan ’962, with a formulation of benzodiazepine, tocopherol, ethanol, and benzyl alcohol, as disclosed in Gwozdz.” EX1040 at p 47.
4. “each limitation of claims 1–16 and 24–36 [of the ’876 Patent] are taught or suggested by the combination of Gwozdz and Meezan ’962 and further

that the skilled artisan would have had reason to make the suggested combination with a reasonable expectation of success.” EX1040 at p. 51 (emphasis added); *see also id.* at p. 54 (“On this record, we also find that the evidence of secondary considerations of non-obviousness is weak, at best. As discussed above, we find that Patent Owner has not established the requisite nexus between the challenged claims and any of the asserted secondary considerations”) (emphasis added); *see also* EX1069 (comparing claims of the ’414 Patent and the ’876 Patent).

The findings in IPR2019-00451 above are materially identical to issues to be determined in this IPR.

VI. THE CONTESTED PATENT

A. Overview of the ’414 Patent

The ’414 Patent describes pharmaceutical compositions (primarily solutions) for the intranasal administration of benzodiazepine drugs. ’414 Patent, Ex. 1001, 5:52-55. The ’414 Patent explains that the pharmaceutical composition for nasal administration comprises (1) a benzodiazepine drug; (2) one or more natural or synthetic tocopherols or tocotrienols in an amount of from about 30% to about 95% w/w; and (3) one or more alcohols or glycols in an amount of from about 10% to about 70% w/w. *Id.*, 5:55-64. As reflected in the claims of the ’414 Patent, the

pharmaceutical compositions (solutions) are focused on solutions consisting of diazepam (a benzodiazepine drug); 30% to 95% (w/w) of one or more natural or synthetic tocopherols or tocotrienols (including alpha-tocopherol, i.e., vitamin E); ethanol and benzyl alcohol in a combined amount of from 10% to 70% (w/w); and n-dodecyl beta-D-maltoside. *See id.*, claims 1 and 5.

B. Filing History and Priority Claims

The '414 Patent is a continuation of application No. 17/228,514, filed on April 12, 2021, now issued Patent No. 11,793,786 ("the '786 Patent"), which in turn is a continuation of application No. 15/955,397, filed on April 17, 2018, now abandoned ("the '397 Application"), which is a continuation of application No. 12/413,439, filed on March 27, 2009, also abandoned ("the '439 Application"), which in turn claims priority to U.S. provisional application No. 61/040,558 ("the '558 Provisional"), filed March 28, 2008.

C. Prosecution History of the '414 Patent

The '414 Patent was subject to minimal prosecution. During prosecution, the applicants submitted a Track 1 request to expedite prosecution of the '414 Patent (*see* '414 FH, Ex. 1002, pp. 264-65), which was granted by the Examiner (*see id.*, pp. 257-58). No substantive office actions were issued by the Examiner prior to the notice of allowance provided by the Examiner on December 13, 2021. *Id.* at pp. 22-28. 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). *Id.* at pp. 27-28. 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 the various reasons noted herein, this determination is incorrect, as 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. EX1062, ¶40, 46-52. Consequently, the earliest possible priority date for ’414 Patent claims is the filing of the ’439 Application on March 27, 2009.

D. Earliest Priority Date and Support for the ’414 Patent Claims

The claims of the ’414 Patent are entitled to an earliest effective filing date of no earlier than the filing date of the parent ’439 Application on March 27, 2009.

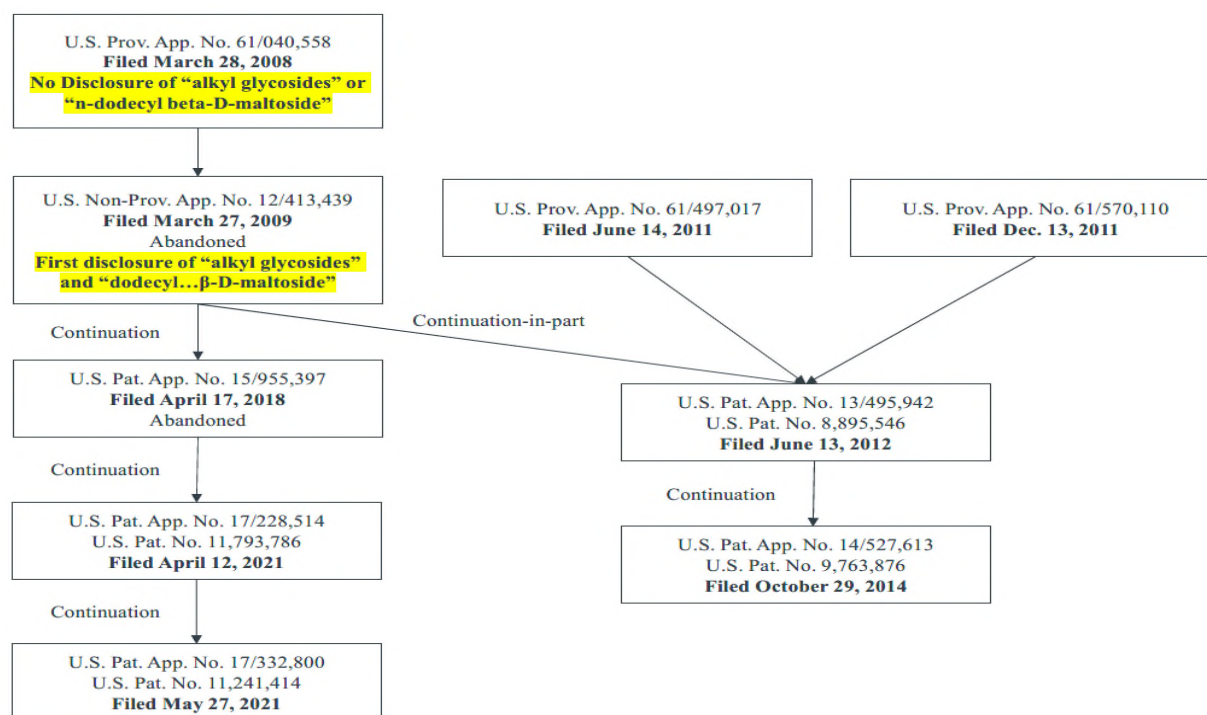
Every claim of the ’414 Patent requires the presence of an alkyl glycoside, specifically n-dodecyl beta-D-maltoside, as claims 1 and 11 (the only two independent claims) recite the requirement of “n-dodecyl beta-D-maltoside.” Consequently, for the ’414 Patent to be entitled to an effective filing date of the earliest priority application (i.e., the ’558 Provisional filed March 28, 2008), the ’558

Provisional must provide support for the claimed “n-dodecyl beta-D-maltoside” limitation. The ’558 Provisional provides no such support, and, consequently, the ’414 Patentee is entitled to an effective filing date no earlier than the ’439 Application.

In IPR2019-00451, the same question was at issue, namely, whether the “alkyl glycoside” limitation present in the claims of the ’876 Patent was supported by the ’558 Provisional. EX1040 at 13-14. Based on all the evidence submitted during the proceeding, the PTAB concluded that “the ’558 Provisional does not provide adequate written description support for the ‘alkyl glycoside’ limitation.” *Id.*, p. 23. (emphasis added). Patent Owner is collaterally estopped from contesting this finding as discussed previously. Even if collateral estoppel did not apply, the Board here should adopt the analysis and findings of the Final Decision in IPR2019-00451 on this issue.

The first mention in the patent family of the presence of alkyl glycosides in (or any species thereof, e.g., dodecyl maltoside) is in the ’439 Application, filed on March 27, 2009. *See, e.g.*, EX1039, ¶¶018, 043, 047, 056. Conversely, the ’558 Provisional does not mention, disclose, or provide any written support for alkyl glycosides (or any species thereof, e.g., dodecyl maltoside). There is not a single recitation of the terms “alkyl glycoside” or “maltoside” anywhere in the specification of the ’558 Provisional. The chart below developed by Dr. Donovan in

her expert report summarizes the filings of the various applications in the '414 Patent family, and illustrates the first disclosure of “alkyl glycosides”:



EX1062, ¶45.

In IPR 2019-00451, Patent Owner asserted that the claimed “alkyl glycoside” limitation was supported by the reference to the “SIGMA Catalog” provided in the ’558 Provisional because the SIGMA Catalog included a limited number of biological detergents, one category of which were non-ionic detergents, where alkyl glycosides were listed as non-ionic detergents. *See* IPR2019-00451, Paper No. 16 at 18-19.

However, this argument fails on its face, as the Patent Owner failed to acknowledge that “essential material” (i.e., material that is necessary to provide a

written description of the claimed invention) can only be incorporated by reference to a U.S. patent or a U.S. patent application publication. 37 C.F.R. §1.57(d). Written description support cannot be provided by incorporation by reference to non-patent literature. Thus, consistent with the requirements of 37 C.F.R. §1.57(d), the '414 Patent Owner cannot rely on the incorporation by reference of the Sigma Catalog in the '558 Provisional to assert that the “n-dodecyl beta-D-maltoside” limitation is supported by the disclosure '558 Provisional.

Moreover, as addressed in Dr. Donovan's declaration, the '558 Provisional discloses “enhancers” (i.e., “any material which acts to increase absorption across the mucosa and/or increases bioavailability”) but only generally and does not provide any guidance that would lead a POSA to the use of alkyl glycosides. EX1062, ¶¶47-52. Specifically, the '558 Provisional discloses at least fifteen different chemical classes of enhancers, one of which are the biological detergents listed in the 1998 SIGMA Catalog. *Id.*, ¶48 (citing ¶¶ [150]-[152] of the '558 Provisional). However, the SIGMA Catalog includes over 100 biological detergents on the pages cited of which only a very small percentage (i.e., only about a dozen) are alkyl glycosides. *Id.*, ¶49.

The '558 Provisional application does not identify with detail and particularity that it is incorporating the alkyl glycosides referred to in the Sigma Catalog, and a POSA looking at the more than 100 ionic and non-ionic compounds listed in the

Sigma Catalog would have no reason to select alkyl glycoside(s) (in particular n-dodecyl beta-D-maltoside) over other compounds disclosed in the Sigma Catalog to be used as the “enhancer” compound. *See id.*, ¶¶49-50. Based on this lack of guidance in the ’558 Provisional, a POSA would be forced to undergo undue experimentation to determine whether any of the alkyl glycosides are useful or preferred over any of the other hundreds of biological detergent candidates disclosed. *Id.*, ¶¶50-52.

Even considering the disclosure of the Sigma Catalog as a potential basis for support of the claimed “n-dodecyl beta-D-maltoside” (which is not appropriate under 37 C.F.R. §1.57(d)), the ’558 Provisional does not provide an enabling disclosure for the support of “n-dodecyl beta-D-maltoside.” *Id.*, ¶¶50-51. Consequently, the ’414 Patent is entitled to a priority date no earlier than the March 27, 2009, filing date of the ’439 Application.

E. Claim Construction of “Vitamin E”

Claim 10 of the ’414 Patent recites a solution consisting of “vitamin E” and other components. The ’414 Patent expressly defines “vitamin E.” EX1001, 30:7-10. Therefore, the Board should construe “vitamin E” as expressly defined to mean “any of the natural or synthetic tocopherols, tocotrienols, any isomers thereof, any esters thereof, any analogs or derivatives thereof, or any combinations thereof.” *Id.*

VII. STATE OF TECHNOLOGY AT THE TIME OF THE INVENTION

A. Summary

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. EX1027, p. 352; *see also* EX1019, p. 0030. Routes of administration employed in the field include intramuscular injection and transmucosal approaches such as rectal, nasal, and endotracheal administration, particularly when IV access has not yet been established. EX1045; EX1046; EX1047; EX1048; and EX1049. This is because patients experiencing epileptic seizures require prompt medical care. *See, e.g.,* EX1041; EX1042; EX1043; and EX1044.

Formulations for the intranasal administration of antiepileptic medications, including benzodiazepines, have been studied with epilepsy patients using various preparations. *See e.g.,* EX1021; EX1050; and EX1051. Under ideal conditions, most medication is absorbed from the nasal cavity and into the bloodstream within 15-20 minutes and diazepam is known to be well absorbed, with reported oral bioavailability values of 90% or greater. *See* EX1053; EX1011, p. 376; EX1028, p. 1948 (citing 100% $\pm$ 14% oral availability); and EX1020, p. 1 (citing >90% absorption after oral administration).

B. Product Design Considerations

A nasal spray is often preferred over injectable dosage forms to avoid the pain associated with injection by needle and to provide rapid relief. *See* EX1053; EX1054. Wermeling (reporting on the findings of Constantino et al. (EX1053)) 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
-

EX1027, p. 354. It was well-known that benzodiazepines have sufficient lipophilic character to readily cross biologic membranes (*id.*), meaning that a POSA would consider benzodiazepine drug compounds to be a logical choice for intranasal administration. *See* EX1062, ¶64.

Benzodiazepines also satisfy the potency requirement for potential nasal administration, as therapeutic doses are typically less than 20 mg. *See* EX1027, p. 354. Doses of drug compound “must have sufficient solubility to be administered in approximately 100 μ L to 200 μ L (1 spray per naris (nostril)) of solution.” *Id.*

Benzodiazepines alone do not have sufficient water solubility to formulate a nasal product, so a POSA will look to alternative formulation approaches, including non-aqueous solvents. *See* EX1062, ¶¶66 and 70.

A POSA would also be aware that viscosity enhancing agents such as methylcellulose can promote retention in the nasal cavity by slowing the ciliary clearance of mucus. *Id.*, ¶67. 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 Device™ (“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.*, EX1019, p. 0030 (5 mg doses of diazepam could be administered intranasally in emergent seizure patients); *see also* pp. 0029 and 0037-0039.

C. 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 (EX1024) documented the successful intranasal

administration of 0.2 mg/kg of midazolam (administering a midazolam injection solution intranasally). EX1024, p. 1044.

Additionally, others have compared intranasal midazolam to intravenous diazepam for reduction of seizure rates and time to cessation. *See* EX1055; EX1056; and EX1057. All 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. *See* EX1025.

Further, as noted by Dr. Donovan, the Florida Regional Common EMS Protocols Field Guide, Jones & Bartlett Publishers (2005) (EX1019), 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* EX1019, p. 54; EX1062, ¶68, 75. 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." EX1017, p. 2676. (Emphasis added). 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, a POSA would know and appreciate that the

medical literature provided numerous examples of the successful use and development of intranasal formulations containing various benzodiazepine compounds, including diazepam, for the successful treatment of acute seizures. See EX1062, ¶76.

VIII. SUMMARY OF PRIOR ART

A. Gwozdz (EX1009)

Gwozdz claims priority to U.S. Prov. App. No. 61/040,281 (hereinafter “the ’281 Provisional”, EX1064), filed March 28, 2008. In IPR2019-00451, the Board determined Gwozdz was entitled to the date of the ’281 Provisional. EX1040 at 13-14 (“Gwozdz is entitled to the filing date of the Gwozdz provisional.”). Patent Owner is collaterally estopped from contesting this finding as discussed previously. Even if collateral estoppel did not apply, the Board here should adopt the findings of the Final Decision in IPR2019-00451 on this issue.

Consistent with the standards outlined in *Dynamic Drinkware, LLC v. Nat’l Graphics, Inc.*, 800 F.3d 1375 (Fed. Cir. 2015), Gwozdz qualifies as prior art based on the filing date of the ’281 Provisional, because the thirteen claims recited in Gwozdz are identical to the thirteen claims in the ’281 Provisional and thus at least one claim in Gwozdz is supported by the ’281 Provisional. See EX1062, ¶¶79-80.

In addition, all of the disclosure Petitioner relies on from Gwozdz is supported by the ’281 Provisional. The table below includes the citations from Gwozdz cited

in this Petition and the corresponding disclosure in the '281 Provisional that supports the cited disclosure in Gwozdz.

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

Therefore, the claims and specification of Gwozdz are supported by the '281 Provisional, and therefore Gwozdz is entitled to the March 28, 2008, filing date of the '281 Provisional. As such, based on the earliest possible effective filing date for the '414 Patent (i.e., March 27, 2009) as discussed above, and based on the filing date of the '281 Provisional (March 28, 2008), Gwozdz constitutes prior art against the '414 Patent under at 35 U.S.C. § 102(e)(1) (pre-AIA).

Moreover, in IPR2019-00451, the Board previously summarized the disclosure of Gwozdz and thus Petitioner does not repeat the same here. EX1040 at 23-24. Petitioner addresses all the relevant disclosure of Gwozdz in detail with respect to the claim limitations in its analysis herein.

B. Meezan (EX1010)

Meezan published more than one year prior to the earliest possible priority date for the '414 Patent (i.e., March 27, 2009), and constitutes prior art under §102(b).

In IPR2019-00451, the Board previously summarized the disclosure of Meezan and thus Petitioner does not repeat the same here. EX1040 at 25 (referred to as Meezan '962). Petitioner addresses all the relevant disclosure of Meezan in detail with respect to the claim limitations in its analysis herein.

IX. LEVEL OF SKILL IN THE ART

A person of ordinary skill in the art ("POSA") at the time of the earliest effective filing date of the '414 Patent would have been a pharmaceutical scientist, chemist, or biologist involved in the research and development of pharmaceutical formulations and/or delivery, and would have at least a Bachelor's degree with at least 5 years of experience, or a Master's, Ph.D. or Pharm.D. degree with several years of experience. In addition, 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.

This petition is supported by the declaration of Dr. Maureen Donovan, Ph.D., who qualifies as a POSA under the qualifications outlined above. *See* EX1062.

X. GWOZDZ IN VIEW OF MEEZAN RENDERS OBVIOUS CLAIMS 1-18 OF THE '414 PATENT

Gwozdz in view of Meezan renders obvious at least claims 1-18 for at least the reasons described below.

In addition, in IPR2019-00451, the Board has already previously determined the combination of Gwozdz and Meezan teaches the subject matter of the pharmaceutical solution recited in the claims of the '414 Patent with a motivation to combine and a reasonable expectation of success to do so:

In sum, we find that the combination of Gwozdz and Meezan '962 teaches or suggests each and every element of claim 1–16 and 24–36 [of the '876 Patent]. We find that an ordinarily skilled artisan would have been motivated to combine Gwozdz with Meezan '962, and would have had a reasonable expectation of success in achieving the claimed invention. On this record, we also find that the evidence of secondary considerations of non-obviousness is weak, at best. As discussed above, we find that Patent Owner has not established the requisite nexus between the challenged claims and any of the asserted secondary considerations.

EX1040 at 54. As previously discussed, the subject matter of the claims 1-16 and 24-36 of the '876 Patent at issue in IPR2019-00451 are materially the same as the subject matter of claims 1-18 of the '414 Patent challenged in this IPR. See EX1069 (comparing claims of the '414 Patent and '876 Patent). In particular, claims 1, 4 and 26 of the '876 Patent recite substantially the same subject matter as recited in claim 1 of the '414 Patent.

While Petitioner sets forth a detailed explanation on how the prior art renders claims 1-18 of the '414 Patent obvious, Patent Owner is collaterally estopped from contesting obviousness of the claimed pharmaceutical solution recited in claims 1-18 due to the identity of these issues with those already adjudicated in IPR2019-00451.

A. Motivation to Combine and Expectation of Success

In view of the teachings of the prior art, and the background knowledge of a POSA discussed above, a POSA was motivated to combine the teachings of Gwozdz and Meezan prior to the filing of the '414 Patent to pursue the claimed compositions. The '414 Patent admits and acknowledges the known problem in the art regarding the inability to administer benzodiazepine drugs (e.g., diazepam) due to the limited solubility of the benzodiazepine drug compounds. The '414 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” as well as other shortcomings. EX1001, 1:47-51. In view of these shortcomings, a POSA would have been motivated to improve the solubility of benzodiazepine drugs to allow for the development of additional dosage forms that would be an improvement over oral, intravenous, and rectal dosage forms.

Gwozdz provides guidance regarding how to solubilize poorly water-soluble compounds (such as diazepam), and would have been a primary reference that a POSA would look to for design strategies to overcome the shortcomings of oral, intravenous, and rectal benzodiazepine dosage forms. EX1062, ¶94-96. 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.” EX1009, 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.*, 9:19-22. A POSA would understand that Gwozdz provides guidance on strategies to improve the solubility of benzodiazepine drugs to develop new dosage forms, including nasally administered formulations that improves over oral, intravenous, and rectal dosage forms EX1062, ¶96.

Moreover, a motivation existed to combine the teachings of Meezan related to alkyl glycosides with the pharmaceutical solutions described in Gwozdz. Gwozdz teaches that the pharmaceutical solutions described therein may further incorporate additional pharmaceutically acceptable additives, including, “acidifying, alkalizing, buffering, chelating, complexing and solubilizing agents, antioxidants and antimicrobial preservatives, penetration enhancers, humectants, suspending and/or viscosity modifying agents, tonicity and wetting or other biocompatible materials” to improve the efficacy. *Id.*, 10:12-16; EX1062, ¶97. Meezan 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.” EX1010, ¶0004. Thus, while Gwozdz was focused on pharmaceutical solutions developed to improve the solubility of drugs with solubility issues (primarily by the use of solvent systems containing alcohols in combination with tocopherol compounds), Meezan presented an additional and unique formulation strategy to increase absorption and bioavailability, namely by the incorporation of compounds that increase the absorption (i.e., absorption enhancers) and bioavailability of drug compounds. EX1062, ¶97. Based on this, a POSA was motivated to apply the teachings of Meezan related to alkyl glycosides to the pharmaceutical solutions of Gwozdz. *Id.*

Finally, a reasonable expectation existed that the Gwozdz formulations could be successfully developed to improve the solubility of benzodiazepine drugs (including diazepam), and that the alkyl glycoside compounds of Meezan (including, e.g., dodecyl beta-D-maltoside) could be successfully incorporated into the Gwozdz pharmaceutical solution. 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.” EX1009, 7:12-14. Based on this disclosure, a POSA would have at least a reasonable expectation that the Gwozdz formulations could successfully improve the solubility of benzodiazepine drug compounds, particularly diazepam. EX1062, ¶198.

The following sections address specific motivations and expectations from combining the teachings of Gwozdz and Meezan that contribute to the finding that claims 1-18 of the ’414 Patent are obvious over the prior art.

1. The Combination of Ethanol and Benzyl Alcohol and Diazepam for Use in Treating Seizures in Humans was Well Known and a Motivation Existed to Include Tocopherols

Prior to the filing of the ’414 Patent, a POSA was aware of many examples of diazepam being formulated with alcohol solvents, such as benzyl alcohol and

ethanol. EX1062, ¶100. Specifically, two known commercial diazepam products, DiastatTM and ValiumTM, were both developed by combining diazepam with ethanol and benzyl alcohol. *See* EX1017, pp. 1012, 2676. While both are injectable formulations, it was also known that the ValiumTM injection (again, containing diazepam, ethanol, and benzyl alcohol) could be used intranasally with the MAD device, and was known in the art to treat acute seizures. *See* EX1019, pp. 54-55, 69-71. 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* EX1016, p. 54, Table III; EX1037, p. 1162. Consequently, when considering alcohol solvents to be formulated with diazepam, a POSA would have known that diazepam had been successfully administered via intranasal administration when combined with ethanol and benzyl alcohol. EX1062, ¶¶100-101.

In addition to the teachings in the art related to formulating diazepam with ethanol and benzyl alcohol for nasal formulations, Gwozdz expressly teaches using tocopherol in combination with one or more alcohols, including 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.” EX1009, 7:3-8. Again, a POSA

knew that the combination of ethanol and benzyl alcohol was effective to intranasally administer diazepam (i.e., in the form of Valium™) as disclosed in the Florida EMS manual. *See* EX1019, pp. 54-55, 69-71; EX1062, ¶100-102.

Based on Gwozdz's teaching that the combination of a tocopherol with one or more alcohols (i.e., ethanol and benzyl alcohol) provides increased bioavailability for hydrophobic or lipophilic drug compound (e.g., poorly water soluble drug compounds such as diazepam) a POSA was motivated to utilize the combination of ethanol, benzyl alcohol, and tocopherols together for the solubilization of diazepam, and would reasonably expect that the combination could be used to nasally administer diazepam. EX1062, ¶102.

2. A Motivation Existed to Include Alkyl Glycosides in the Gwozdz Formulation as a POSA Would Expect Improved Bioavailability

Beyond the motivation to formulate diazepam in the combination of ethanol, benzyl alcohol, and a tocopherol (as established by Gwozdz), a motivation also existed to incorporate an alkyl glycoside into the formulation. EX1062, ¶103. This motivation is supported by the express disclosure of Gwozdz, which discusses using additional excipients to improve delivery and absorption of the drug. EX1009, 10:14. Based on this express disclosure, a POSA would not only have been motivated to include additional excipients to improve absorption but would then consider which absorption enhancer(s) to use. EX1062, ¶103.

As an initial matter, a POSA would focus on (1) absorption enhancing compounds known to be used in intranasal formulations; and (2) compounds known to be compatible with other components of the Gwozdz formulation (e.g., ethanol and benzyl alcohol). See EX1062, ¶103. A POSA would have known that alkyl glycosides were one class of absorption enhancers that had been successfully utilized in intranasal formulations, including the administration of insulin and glucagon via the nasal route. EX1062, ¶104. 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 such as diazepam, as the prior art established that even large drug molecules (e.g., glucagon and insulin) showed improved bioavailability when nasally administered with alkyl glycosides. *Id.*

Larger molecules inherently have a more difficult time crossing the cell membrane compared to smaller molecules. EX1062, ¶105. Thus, if a compound is shown to increase penetration and absorption for a large molecule, it will be expected to also increase penetration and absorption for a small molecule, simply because molecular size can be one of the primary constraints for passing through and between epithelial cells. *Id.* This understanding is consistent with the teachings of Meezan, teaching that alkyl glycosides will increase the bioavailability of small molecules, including those having molecular weights less than 1.5 kDaltons. EX1010, ¶ [0130]. Diazepam is a small molecule, having a molecular weight of 284.74 Daltons (i.e.,

0.28474 kDaltons). See EX1017, p. 2677. Thus, based on the knowledge in the art, and the express disclosure of Meezan, a POSA would be motivated and expect that incorporating an alkyl glycoside into the Gwozdz intranasal formulation containing diazepam, ethanol, benzyl alcohol, and a tocopherol compound would increase nasal absorption and bioavailability of diazepam. EX1062, ¶106.

Further, the motivation to include an alkyl glycoside in the Gwozdz formulation is further supported by the fact that alkyl glycosides were shown to be successfully utilized in non-aqueous solvent systems, including alcohol-based solvent systems. *Id.*, ¶107-109 (citing EX1010, ¶74).

Based on these considerations and teachings, a POSA was motivated to include an alkyl glycoside in the intranasal formulation of Gwozdz containing diazepam, ethanol, benzyl alcohol, and a tocopherol, as doing so would be expected to enhance absorption/bioavailability of diazepam, and alkyl glycosides were known to be compatible with alcohol-based solvent systems. *Id.*, ¶108-109.

3. A POSA Was Motivated to Include Benzyl Alcohol in the Intranasal Spray of Gwozdz Despite Any Potential Irritation

It was known in the art that ValiumTM injection (containing ethanol and benzyl alcohol) could be administered intranasally for the acute treatment of seizure. See EX1019, pp. pp. 54-55, 69-71. There were reports of benzyl alcohol potentially causing nasal mucosa irritation (see EX1061, 6:31-39), but even if a POSA were to

accept that benzyl alcohol may cause this irritation, it would be an acceptable design choice for the treatment of acute life-threatening indications, such as epileptic seizures. EX1062, ¶110. Additionally, a POSA would also know that benzyl alcohol provides other advantageous properties to the formulation, including its function as an antimicrobial preservative. *Id.* (citing EX1016, p. 53). Consequently, despite any potential impact the benzyl alcohol may have on nasal mucosa, a POSA would have been nonetheless motivated to include it in the formulation of Gwozdz. *Id.*

4. Patent Owner Did Not Establish Criticality or Unexpected Results for the Claimed Components and Amounts

The '414 Patent specification and prosecution history, as well as the specifications and prosecution histories of the applications to which the '414 Patent claims priority, do not provide any evidence of criticality or unexpected results with regard to the claimed types and amounts of alcohols, tocopherols, benzodiazepines, or alkyl glycosides. *Id.*, ¶111.

The '414 Patent does not include any data or evidence suggesting that the claimed pharmaceutical solution consisting of diazepam, one or more natural or synthetic tocopherols or tocotrienols, ethanol, benzyl alcohol, and n-dodecyl beta-D-maltoside provides any results that a POSA would consider surprising or unexpected. *Id.*, ¶112-113. In fact, the '414 Patent does not include any data whatsoever for the claimed formulation. Rather, all of the examples provided in the

'414 Patent specification are directed to (1) diazepam solutions containing diazepam, Vitamin E, and dehydrated ethanol (no benzyl alcohol) (*see* EX1001, 42:57 to 43:33), and further containing an alkyl glycoside “such as dodecyl maltoside, tetradecyl maltoside, sucrose dodecanoate, sucrose monostearate, sucrose distearate, and/or combinations of two or more thereof” (*see id.*, 53:30-42), though the '414 Patent does not specify which alkyl glycoside was included or in what amount; and (2) diazepam suspensions containing diazepam, Vitamin E polyethylene glycol succinate NF, methylparaben NF, propylparaben NF, propylene glycol USP, povidone USP/NF, and purified water USP/EP (*see id.*, 43:35 to 44:26). None of the formulations described in the aforementioned examples include all of the claimed components in the claimed amounts. Consequently, none of this disclosure provides a POSA with any evidence of potential surprising and unexpected results for the claimed formulation, and there is no evidence of criticality or unexpected results for the claimed components and amounts. *Id.*

B. Application of the Combined Teachings of Gwozdz and Meezan to claims 1-18 of the '414 Patent

Claim 1 [preamble]: “1. A *pharmaceutical solution for nasal administration consisting of:*”

Gwozdz discloses pharmaceutical solutions for nasal administration. *See* EX1009, at 4:24-26 (disclosing that “the present invention relates to methods of

treatment of a patient with these pharmaceutical solutions.”) *Id.*; *see also* EX1062, ¶118.

Gwozdz continues, “[p]harmaceutical 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.... Use of a pharmaceutical solution of the present invention, however, provides for improved ability to dissolve hydrophilic 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.*, 9:19 to 10:2; EX1062, ¶119.

In view of the foregoing, a POSA would understand that Gwozdz is “preferably utilized to deliver drugs to the nasal mucosa via the nasal route, which provides faster achievement of systemic therapeutic agent concentrations.” *Id.* (citing EX1009, at 9:19-25).

Similarly, POSA would understand Meezan also discloses “a pharmaceutical solution for nasal administration.” EX1062, ¶120. In particular, 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...” EX1010, ¶[0008]; *see also Id.*, ¶[0049] (describing a

therapeutic composition with non-toxic, pharmaceutically acceptable carriers in solid, semisolid, or liquid form). EX1062, ¶120.

Finally, as noted by Dr. Donovan, “Gwozdz and Meezan render obvious a pharmaceutical solution for nasal administration “consisting of” (i.e., containing only) the claimed benzodiazepine drug, one or more natural or synthetic tocopherols or tocotrienols, ethanol, benzyl alcohol, and an alkyl glycoside.” EX1062, ¶121.

Claim 1(a): “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...benzodiazepines such as Diazepam....” Gwozdz, EX1009, 8:6-18; *See also* EX1062, ¶123 (concluding that “Gwozdz discloses various benzodiazepine drug compounds that may be used in the formulations, including diazepam.”).

In addition, a POSA would understand that “the teachings of Meezan are applicable to small molecule drug compounds, such as diazepam.” EX1062, ¶124.

Claim 1(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);

Gwozdz discloses “a pharmaceutical solution is formed by dissolving a therapeutic agent in a tocopherol and/or a tocotrienol...” EX1009, at 5:12-14; *see also Id.*, 5:33-6:2 (providing 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 tocopherols or vitamin E.”); EX1062, ¶126; *see Iron Grip Barbell Co. v. USA Sports, Inc.*, 392 F.3d 1317, 1322 (Fed. Cir. 2004) (overlap in ranges is *prima facie* obviousness)⁴

Regarding the claimed feature wherein “amount from 30% to 95% (w/w),” Gwozdz discloses “the tocopherol(s) and/or tocotrienol(s) is in an amount from about 30% to about 99% (w/w)”. EX1009, at 4:18-19; 7:8-10; *see also* 7:20-25 (60-99% or approximately 70-90% alpha-tocopherol). As explained by Dr. Donovan,

there is no criticality associated with the claimed concentration of tocopherols (see *supra* at ¶¶ 116-118). Due to the lack of criticality of the ingredients in the solution, a POSA would routinely experiment with varying amounts and concentrations of tocopherols to optimize the formulation, with an expectation of success. This predictable experimentation would result in concentrations falling in the claimed range of about 30% to about 95%.

EX1062, ¶127.

Accordingly, as concluded by Dr. Donovan, “Gwozdz discloses and renders obvious the use of alpha-tocopherol (i.e., a ‘natural or synthetic tocopherol or tocotrienol’) at concentrations within the claimed concentration range of ‘from about 30% to about 95% (w/w).’” EX1062, ¶127-128.

⁴ This case law applies to all of the various ranges recited in the claims of the ’414 Patent.

Claim 1(c): “(c) ethanol and benzyl alcohol in a combined amount from 10% to about 70% (w/w);”

Gwozdz discloses “a pharmaceutical solution is formed by dissolving a therapeutic agent in a tocopherol and/or a tocotrienol and an alcohol...” EX1009, 5:12-14. Regarding the alcohol, Gwozdz describes “[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.*, 6:16-19 (emphasis added); *see also* EX1062, ¶130.

Gwozdz continues, “[i]n some embodiments, the alcohol(s) and/or glycol(s) is in an amount from about 1% to about 70% (w/w).” *Id.*, 4:17-21; 7:8-11; *see also* 7:20-24 (1-40% or approximately 10-30% ethanol). Accordingly, a POSA would understand that Gwozdz renders obvious the requirements for the inclusion of ethanol and benzyl alcohol “in a combined amount from about 10% to about 70% (w/w).” As explained by Dr. Donovan,

there is no criticality associated with the claimed concentration of alcohols (for both the ethanol and benzyl alcohol amounts) (*see supra* at ¶¶ 116-118). Due to the lack of criticality of the ingredients in the solution, a POSA would routinely experiment with varying amounts and concentrations of ethanol and benzyl alcohol to optimize the formulation, with an expectation of success. This predictable experimentation would result in a combined amount of ethanol and benzyl alcohol of about 10% to about 70% (w/w).

EX1062, ¶131.

Accordingly, as concluded by Dr. Donovan, “Gwozdz discloses and renders obvious the use of “ethanol and benzyl alcohol in a combined amount from 10% to about 70% (w/w).” EX1062, ¶¶131.

Claim 1(d): “*n*-dodecyl beta-D-maltoside”

A POSA would look to optimize the bioavailability of Gwozdz formulation and based on Meezan’s teachings would have been motivated to add alkyl glycoside to do so. EX1062, ¶133. As discussed above, Gwozdz teaches its “invention relates to methods of treatment of a patient with these pharmaceutical solutions.” EX1009, 4:24-26. Further, Gwozdz discloses that “[p]harmaceutical 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.” *Id.*, 9:19-22; EX1062, ¶134.

A POSA would seek out absorption enhancing excipients (generally described by Gwozdz, EX1009, 10:11-16), which are known to be useful in intranasal formulations, and “would [be] motivated to modify Gwozdz’s solution with Meezan’s teaching of absorption enhancers.” EX1062, ¶135.

Meezan specifically teaches an alkyl glycoside amount of about 0.25%. *See, e.g.*, EX1010, ¶¶ [0150]- [0151]; *see also* Fig. 1, ¶¶[0158]- [0159], Table I; EX1062, ¶135. Meezan also discloses alkyl glycosides, including dodecyl maltoside. *See Id.* ¶¶ [0056], [0058], and [0061]; EX1062, ¶136.

Accordingly, as observed by Dr. Donovan, “based on Meezan’s teaching of 0.25% alkyl glycoside, including dodecyl maltoside, and the fact that the amount and identity of the alkyl glycoside is not critical, a POSA would routinely select dodecyl maltoside to add to Gwozdz’s solution.” EX1062, ¶137.

Since each of the limitations of claim 1 is disclosed by the combination of Gwozdz and Meezan, claim 1 is obvious over this combination. EX1062, ¶138-139.

Claim 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 about 1 to about 20% (w/v).*”

As discussed above, Gwozdz in view of Meezan renders obvious the pharmaceutical solution of claim 1.

With respect to claim 2, Gwozdz discloses that diazepam can be present in an amount “approaching the 10% level” because “[d]iazepam is soluble to greater than or equal to 8%” in some tocopherol/alcohol combinations and that “[d]iazepam is soluble at greater than or equal to 9%” in other tocopherol/alcohol combinations. See EX1009, 7:12-19.

Dr. Donovan notes:

the percentages in Gwozdz recited for diazepam appear to be percentages based on weight (w/w), given that the other percentages reported for the tocopherols and alcohols are reported in % w/w. See *id.*, 7:9-16. However, based on the specific gravities of the three ingredients that constitute nearly all of the solution (i.e., tocopherol, ethanol, and benzyl alcohol (n-dodecyl beta-D-maltoside only constitutes a small percentage)³, the differences between measurements

of “% (w/v)” and “% (w/w)” (and even % (v/v)) should be small enough as to be insignificant to my discussion here as well as to the arguments laid out in the Petition. Therefore, Gwozdz discloses diazepam concentrations of 8-10% (w/w), which a POSA would expect to approximate (and, at a minimum, render obvious) a concentration of ~8-10% w/v. Based on this, it is my opinion that Gwozdz discloses a diazepam concentration of ~8-10% w/v, which meets the claimed requirement of “a concentration from about 1 to about 20% (w/v).”

EX1062, ¶142; *see also id.* at FN 3 (listing specific gravities: (i) ethanol at 20°C = 0.8119-0.8139, and dehydrated ethanol at 20°C = 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 20°C = 1.0454 (*id.* at p. 54; *see also* Table I on p. 53).

Accordingly, claim 2 is obvious over Gwozdz in view of Meezan. EX1062, ¶143

Claim 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.*”

As discussed above, Gwozdz in view of Meezan renders obvious the pharmaceutical solution of claim 1.

Dr. Donovan notes that “[a] POSA knows that the claimed range of ‘from 10 mg/mL to 250 mg/mL’ is equivalent to 1-25% (w/v).” EX1062, ¶145.

In view of the foregoing, claim 3 is obvious over the combination of Gwozdz in view of Meezan for similar reasons as presented against claim 2. *See* claim 2

analysis *supra*; see also EX1062, ¶145 (showing Diazepam concentrations of ~8-10% (w/v) are within the range of “from 10 mg/mL to 250 mg/mL”).

Accordingly, claim 3 is obvious over Gwozdz in view of Meezan. EX1062, ¶146.

Claim 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.*”

As discussed above, Gwozdz in view of Meezan renders obvious the pharmaceutical solution of claim 3.

Dr. Donovan notes that “[a] POSA knows that the claimed range of ‘from 20 mg/mL to 50 mg/mL’ is equivalent to 2-5% (w/v).” EX1062, ¶148.

As discussed in claim 2 above, Gwozdz and Meezan disclose and render obvious the inclusion of diazepam at a concentration of ~8-10% (w/v). See claim 2 analysis *supra*. Additionally, Dr. Donovan states “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 2-5% (w/v), simply by reducing the amount of diazepam added to the solvent system.” EX1062, ¶148.

Accordingly, claim 4 is obvious over Gwozdz in view of Meezan. EX1062, ¶149.

Claim 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.*”

As discussed above, Gwozdz in view of Meezan renders obvious the pharmaceutical solution of claim 1.

Gwozdz discloses that, “the tocopherol(s) and/or tocotrienol(s) employed is alpha-tocopherol” which is one of the options recited in claim 5. EX1009, 6:13-15; EX1062, ¶152.

Accordingly, claim 5 is obvious over Gwozdz in view of Meezan. EX1062, ¶153.

Claim 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).*”

As discussed above, Gwozdz in view of Meezan renders obvious the pharmaceutical solution of claim 1.

Gwozdz discloses the tocopherol in an amount of, e.g., 70-90%. EX1009, 7:22-25. As discussed by Dr. Donovan, “there is no criticality or unexpected effects associated with the amount of tocopherol. Consequently, a POSA would routinely experiment with different amounts, especially in view of Gwozdz’s teachings that the tocopherol:ethanol ratio may be approximately 95:5, 90:10, 85:15, 80:20, 75:25, 70:30, 65:35, or 60:40.” *Id.*, 7:25-28.” EX1062, ¶155 citing EX1009, 7:25-28.

As such, “a POSA would arrive at amounts in the disclosed range (70%-90%), including at the lower end of the range (i.e., 70-85%) which falls within the claimed range of about 45% to about 85%.” EX1062, ¶156.

Accordingly, claim 6 is obvious over Gwozdz in view of Meezan. EX1062, ¶157.

Claim 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 60% to 75% (w/w).*”

As discussed above, Gwozdz in view of Meezan renders obvious the pharmaceutical solution of claim 6.

Claim 7 is obvious over the combination of Gwozdz in view of Meezan for similar reasons as presented against claim 6. *See* claim 6 analysis *supra*. EX1062, ¶159.

Moreover, a POSA would routinely experiment with different amounts, especially in view of Gwozdz’s teachings that the tocopherol:ethanol ratio may be approximately 95:5, 90:10, 85:15, 80:20, 75:25, 70:30, 65:35, or 60:40. EX1062, ¶159 (citing EX1009, 7:25-28). Dr. Donovan concludes “as a result of this routine and predictable experimentation, a POSA would arrive at amounts in the disclosed range (70%-90% (w/w)), including at the lower end of this range (i.e., 70-75% (w/w)), which falls within the claimed range of 60% to 75% (w/w).” EX1062, ¶160.

Accordingly, claim 7 is obvious over Gwozdz in view of Meezan. EX1062, ¶161.

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

As discussed above, Gwozdz in view of Meezan renders obvious the pharmaceutical solution of claim 1.

As set out in the analysis of claim 1, Gwozdz discloses ethanol and benzyl alcohol as two of the alcohol compounds that may be utilized in the solution. EX1009, 6:16-19; *See* analysis of Claim 1(c) *supra* (describing that Gwozdz discloses that the alcohols can be present in the amount 1-70% (w/w), with ethanol specifically being called out in amounts of 10-30% (w/w)); EX1062, ¶163.

Moreover, Dr. Donovan states:

there is no criticality or unexpected effects associated with the amount or type of alcohol(s), including the ethanol and benzyl alcohol. Consequently, a POSA would routinely experiment with different amounts, especially in view of Gwozdz’s teachings that the tocopherol:ethanol ratio may be approximately 95:5, 90:10, 85:15, 80:20, 75:25, 70:30, 65:35, or 60:40.

EX1062, ¶163.

Dr. Donovan concludes that through routine experimentation, “a POSA would arrive at amounts of ethanol and benzyl alcohol that fall within the ranges recited in Claim 8 (i.e., “a combined amount from 15% to 55% (w/w)”), while also falling

within the total alcohol range of “about 10% to about 70%” required by Claim 1 (which I addressed previously).” EX1062, ¶164.

Accordingly, claim 8 is obvious over Gwozdz in view of Meezan. EX1062, ¶165.

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

As discussed above, Gwozdz in view of Meezan renders obvious the pharmaceutical solution of claim 8.

Claim 9 is obvious over the combination of Gwozdz in view of Meezan for similar reasons as presented against claim 8. *See* claim 8 analysis *supra*. EX1062, ¶167.

Again, as noted by Dr. Donovan, through “the routine and predictable experimentation I noted in my claim 8 analysis, a POSA would arrive at amounts of ethanol and benzyl alcohol that fall within the ranges recited in claim 9 (i.e., “a combined amount from 25% to 40% (w/w)”) while also falling within the total alcohol range of “from 10% to 70%” required by claim 1 (which I addressed previously).” *Id.*

Accordingly, claim 9 is obvious over Gwozdz in view of Meezan. EX1062, ¶168.

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

As discussed above, Gwozdz in view of Meezan renders obvious the pharmaceutical solution of claim 1.

As addressed in the claim 1 analysis *supra*, Gwozdz and Meezan render obvious a pharmaceutical solution consisting of diazepam, one or more natural or synthetic tocopherols or tocotrienols, ethanol, benzyl alcohol, and n-dodecyl beta-D-maltoside. *See* claim 1 analysis *supra*. EX1062, ¶171.

Regarding vitamin E – Gwozdz states “[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.” *Id.*, 5:33-6:2; EX1062, ¶172-173.

Accordingly, claim 10 is obvious over Gwozdz in view of Meezan. EX1062, ¶174.

Claim 11 [preamble]: “***11. A pharmaceutical solution for nasal administration consisting of:***”

Claim 11 [preamble] is obvious over the combination of Gwozdz in view of Meezan for similar reasons as presented against claim 1 [preamble]. *See* claim 1 [preamble] analysis *supra*; see also EX1062, ¶175.

Accordingly, claim 11 [preamble] is obvious over Gwozdz in view of Meezan. EX1062, ¶174.

Claim 11(a): “***diazepam or a pharmaceutically acceptable salt thereof;***”

Claim 11(a) is obvious over the combination of Gwozdz in view of Meezan for similar reasons as presented against claim 1(a). *See* claim 1(a) analysis *supra*. EX1062, ¶176.

Accordingly, claim 11(a) is obvious over Gwozdz in view of Meezan. *Id.*

Claim 11(b): “*one or more natural or synthetic α -tocopherols, or any combinations thereof, in an amount from 30% to 95% (w/w);*

Claim 11(b) is obvious over the combination of Gwozdz in view of Meezan for similar reasons as presented against claim 1(b), establishing the obviousness of one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from 30% to 95% (w/w). *See* claim 1(b) analysis *supra*. EX1062, ¶177. Additionally, Gwozdz discloses that, “the tocopherol(s) and/or tocotrienol(s) employed is alpha-tocopherol.” EX1009, 6:13-15; EX1062, ¶177.

Dr. Donovan further states:

there is no criticality associated with the claimed concentration of tocopherols (*see supra* at ¶¶ 111-113). Due to the lack of criticality of the ingredients in the solution, a POSA would routinely experiment with varying amounts and concentrations of tocopherols to optimize the formulation, with an expectation of success. This predictable experimentation would result in concentrations of alpha-tocopherol falling in the claimed range of from 30% to 95% (w/w).

EX1062, ¶178.

Accordingly, claim 11(b) is obvious over Gwozdz in view of Meezan. EX1062, ¶179-180.

Claim 11(c): “ethanol and benzyl alcohol in a combined amount from 10% to 70% (w/w);”

Claim 11(c) is obvious over the combination of Gwozdz in view of Meezan for similar reasons as presented against claim 1(c). See claim 1(c) analysis *supra*. EX1062, ¶181.

Accordingly, claim 11(c) is obvious over Gwozdz in view of Meezan. *Id.*

Claim 11(d): “n-dodecyl beta-D-maltoside”

Claim 11(d) is obvious over the combination of Gwozdz in view of Meezan for similar reasons as presented against claim 1(d). See claim 1(d) analysis *supra*. EX1062, ¶182.

Since each of the limitations of claim 11 is disclosed by the combination of Gwozdz and Meezan, claim 11 is obvious over this combination. EX1062, ¶182-183.

Claim 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).”

As discussed above, Gwozdz in view of Meezan renders obvious the pharmaceutical solution of claim 11.

Claim 12 is obvious over the combination of Gwozdz in view of Meezan for similar reasons as presented against claim 2. See claim 2 analysis *supra*. EX1062, ¶185.

Accordingly, claim 12 is obvious over Gwozdz in view of Meezan. *Id.*, ¶186

Claim 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.*”

As discussed above, Gwozdz in view of Meezan renders obvious the pharmaceutical solution of claim 11.

Claim 13 is obvious over the combination of Gwozdz in view of Meezan for similar reasons as presented against claim 3. See claim 3 analysis *supra*. EX1062, ¶188.

Accordingly, claim 13 is obvious over Gwozdz in view of Meezan. EX1062, ¶189.

Claim 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.*”

As discussed above, Gwozdz in view of Meezan renders obvious the pharmaceutical solution of claim 13.

Claim 14 is obvious over the combination of Gwozdz in view of Meezan for similar reasons as presented against claim 4. See claim 4 analysis *supra*. EX1062, ¶191.

Accordingly, claim 14 is obvious over Gwozdz in view of Meezan. *Id.*, ¶192.

Claim 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).*”

As discussed above, Gwozdz in view of Meezan renders obvious the pharmaceutical solution of claim 11.

Claim 15 is obvious over the combination of Gwozdz in view of Meezan for similar reasons as presented against claim 6. *See* claim 6 analysis *supra*. EX1062, ¶194.

Accordingly, claim 15 is obvious over Gwozdz in view of Meezan. *Id.*, ¶195.

Claim 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).*”

As discussed above, Gwozdz in view of Meezan renders obvious the pharmaceutical solution of claim 15.

Claim 16 is obvious over the combination of Gwozdz in view of Meezan for similar reasons as presented against claim 7. *See* claim 7 analysis *supra*. EX1062, ¶197.

Accordingly, claim 16 is obvious over Gwozdz in view of Meezan. EX1062, ¶198.

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

As discussed above, Gwozdz in view of Meezan renders obvious the pharmaceutical solution of claim 11.

Claim 17 is obvious over the combination of Gwozdz in view of Meezan for similar reasons as presented against claim 8. *See* claim 8 analysis *supra*. EX1062, ¶200.

Accordingly, claim 17 is obvious over Gwozdz in view of Meezan. EX1062, ¶201.

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

As discussed above, Gwozdz in view of Meezan renders obvious the pharmaceutical solution of claim 17.

Claim 18 is obvious over the combination of Gwozdz in view of Meezan for similar reasons as presented against claim 9. *See* claim 9 analysis *supra*. EX1062, ¶203.

Accordingly, claim 18 is obvious over Gwozdz in view of Meezan. EX1062, ¶204.

XI. THE BOARD SHOULD NOT EXERCISE ITS DISCRETION TO DENY INSTITUTION

A. 35 U.S.C. § 325(d)

When evaluating a petition under § 325(d), the Board looks to the factors set out in *Advanced Bionics. Advanced Bionics LLC v. MED-EL Elektromedizinische Geräte GmbH*, IPR2019-01469, Paper 6 at 8 (PTAB Feb. 13, 2020) (precedential).

While Meezan and Gwozdz were cited on an IDS during prosecution, and Gwozdz was referenced by the Examiner in the notice of allowance, the examiner did not issue any rejection based on them or address either of their teachings cited in this IPR petition, particularly as combined herein. Indeed, the Examiner did not issue any rejections at all. In addition, Petition provides the testimony of Dr. Donovan to explain how a POSA would view the teachings of these references. *See* Ex.1062. Therefore, part one of the *Advanced Bionics* test favors institution, as the arguments and evidence set forth herein were not considered by the Examiner even if the individual references were previously cited.

Further, under part two of *Advanced Bionics*, then the examiner clearly erred in a manner material to the patentability in light of the Board's decision in IP2019-00451 that the '558 provisional does not provide adequate written description support for "alkyl glycoside." *See* EX1040 at p. 23 (finding that "after reviewing all of the evidence, we find that the '558 provisional does not provide adequate written description support for the 'alkyl glycoside' limitation. Therefore, the claims of the '876 patent are not entitled to the benefit of priority to the '558 provisional.").

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 '558 priority application. Ex. 1002 at pp. 27-28. The Board's

decision in IPR2019-00451 demonstrates that this finding by the Examiner was incorrect.

Moreover, based on this erroneously found 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.* Thus, the Examiner materially erred in the priority analysis and in disqualifying Gwozdz as prior art.

In addition to the Board’s finding in IPR2019-00451, Petitioner further explains in Section VI(D) why the Examiner’s determination is incorrect, as 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. EX1062, ¶40, 46-52. Consequently, the earliest possible priority date for '414 Patent claims is the filing of the '439 Application on March 27, 2009, which does not disqualify Gwozdz as prior art.

As discussed in this petition, the proposed combinations teach all the claim limitations. The Examiner materially erred in finding the '414 Patent has priority to the '558 Provisional application and thus refusing to consider Gwozdz as prior art. Perhaps most important, the Board decision in IPR2019-00451 demonstrates that the

examiner materially erred in allowing the claims of the '414 Patent over the teachings of Gwozdz and Meezan.

B. *Fintiv*

Apple, Inc. v. Fintiv, Inc., IPR2020-00019, Paper 11 (Mar. 20, 2020) (precedential) favors institution because this Petition presents compelling evidence of unpatentability. Furthermore, Petitioner stipulates that if the Board institutes this IPR 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).

XII. CONCLUSION

Petitioner requests this petition for *inter partes* review be granted and that the Challenged Claims be cancelled as unpatentable under 35 U.S.C. § 318(b).

Petition for Inter Partes Review of
U.S. Patent No. 11,241,414

Dated: January 17, 2025

Respectfully submitted,

/James P. Murphy/

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e)(4)(i) *et seq.* and 42.105(b), the undersigned certifies that on January 17, 2025, complete copies of this Petition for *Inter Partes* Review including all supporting exhibits and Petitioner's Power of Attorney are being served by Federal Express® on the following counsel of record for U.S. Patent 11,241,414:

Marissa Kuzirian
DLA Piper LLP (US)
1650 Market Street, Suite 5000
Philadelphia, PA 19103

In addition, a notification of the filing of this IPR petition and accompanying exhibits is being sent via email to Patent Owner's counsel of record in the underlying litigation asserting the '414 Patent styled *Neurelis, Inc. v. Padagis LLC et al.* Civil Action No. 1:24-cv-00562 (D. Del.).

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