

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PADAGIS US LLC,

Petitioner

v.

NEURELIS, INC.,

Patent Owner.

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

EXPERT DECLARATION OF DR. MARC BROWN

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I. INTRODUCTION

1. My name is Marc Brown, Ph.D., and I declare as follows:

2. I am a citizen of the United Kingdom and am over 18 years of age. I have personal knowledge of the matters stated in this declaration.

3. I have been asked to provide technical assistance in the *inter partes* reviews of three patents from the same family: U.S. Patent No. 11,241,414 (which I may abbreviate as “the ’414 Patent”), U.S. Patent No. 11,793,786 (which I may abbreviate as “the ’786 Patent”), and U.S. Patent No. 8,895,546 (which I may abbreviate as “the ’546 Patent”). I may refer to these patents collectively as the “Challenged Patents.” The *inter partes* review petitions were filed by Padagis US LLC, which I may refer to as “Padagis” or “Petitioner.” This declaration is a statement of my opinions on issues related to the patentability of claims of the ’786 Patent (which I may refer to as the “Challenged Patent”). I am being compensated at my normal rate of £600 per hour for my analysis, plus reimbursement for expenses. My compensation does not depend on the content of my opinions or the outcome of these proceedings.

4. This declaration contains statements of my opinions formed to date and the bases and reasons for those opinions. I may offer additional opinions based on

further review of materials in this case, including opinions and testimony of other expert witnesses.

II. EDUCATION AND PROFESSIONAL EXPERIENCE

5. I have summarised in this section my educational background, career history, publications, and other relevant qualifications. My full curriculum vitae has been provided as Exhibit 2049.

6. I graduated from Loughborough University of Technology in 1990 with a B.Sc. (Hons) in Medicinal and Pharmaceutical Chemistry, remaining at Loughborough to undertake a Ph.D. in drug-protein interactions, which I completed in 1993.

7. In 1993 I was employed as a Research Fellow in the Department of Pharmacy, King's College London, and in 1994 I was appointed as a member of academic staff in Pharmaceutics and Drug Delivery. I remained at KCL until 2006.

8. From 1995-1996 I was seconded to Hyal Pharmaceutical Corporation, Toronto, Canada as Director of Pharmaceutical Development to help get their lead product Solaraze, a topical treatment of actinic keratosis, to market.

9. In 1999, as a result of my academic collaborations with industry, I co-founded a spin-out company named MedPharm Ltd. MedPharm is a contract research organization specialising in the formulation of topical products for the skin,

airway, nail, eye and other mucosal membranes. My main responsibilities at MedPharm included designing and executing pharmaceutical development programs, technical trouble shooting, attending and contributing to meetings with FDA, MHRA, EMA etc., as part of the regulatory team and preparing non-clinical, clinical and CMC sections of regulatory submissions. I also provided technical and intellectual property support to commercial partnering activities. I remained as CSO, Chair of the Scientific Advisory Committee, and Board Member until I sold my final tranche of shares in 2023.

10. From 2006-2018 I was employed as a F/T and then P/T Chair in Pharmaceutics at the Department of Pharmacy, University of Hertfordshire.

11. From 2010-2013 I was a Member of the Wellcome Trust Technology Transfer Challenge Committee.

12. In 2011, I was appointed as a Visiting Professor of Pharmaceutics, School of Pharmacy, University of Reading.

13. From 2011-2015 I was an Honorary Professor of Pharmaceutics, Dermatology and Genetic Medicine Division of Molecular Medicine, University of Dundee.

14. In 2018, I was appointed as a Visiting Professor of Pharmaceutics, Institute of Pharmaceutical Sciences, KCL.

15. In 2018, I founded MLBT Investments and Consultancy, which focuses on providing consultancy services and investments in the Pharmaceutical Development realm, catering to both start-ups and established pharmaceutical companies and investment institutions.

16. In 2018, I was appointed as a Visiting Professor of Toxicology, University of Hertfordshire.

17. In 2019, I was appointed as a Visiting Professor of Pharmaceutics, De Montfort University.

18. In 2022, I was awarded Professor Emeritus, University of Hertfordshire.

19. From 2022-2024 I was Chief Scientific Officer and Chair of the Scientific Advisory Board for Mosanna Therapeutics AG which is a Swiss Biotech company based in Basel currently in clinical evaluation of MOS-118 in the form of a locally delivered nasal spray to treat Metabolic Obstructive Sleep Apnoea. In 2024 I was part of the executive team to secure \$80 million of series A investment to take the product to late-stage clinical investigation.

20. In 2024, I co-founded Heparin Therapeutics Ltd, which is a UK based pre-seed funded company developing respiratory formulation for the treatment of airway disease.

21. I have been directly involved in over 50 products that have gained regulatory approval in the U.S., Europe, and Japan.

22. During my career, both academically and commercially, I have worked extensively on nasal drug delivery and in the formulation development of benzodiazepines including sprays.

23. I have given over 70 invited lectures and co-authored over 200 publications and 30 patents describing my research in drug delivery and pharmaceuticals.

24. I have supervised over 45 Ph.D. students in the field of pharmaceuticals.

25. I have acted as a witness in ten Court and USPTO patent disputes.

26. I was named on the Medicine Maker Power list of 2023 and 2024 for my work on the development and commercialisation of small molecular weight drug products.

27. I have CChem FRSC Membership of the Royal Society of Chemistry.

28. Having this knowledge and experience, I am well-qualified to offer the opinions I express in this declaration.

III. THE CHALLENGED CLAIMS FROM THE '786 PATENT

29. In the subsections below, I have copied the language from the challenged claims. Some of the claim elements have been further sub-divided for ease of reference.

Claim Element	Claim Language from '786 Patent
1(Preamble)	1. A pharmaceutical solution for nasal administration consisting of:
1(a)	a therapeutically effective amount of diazepam or a pharmaceutically acceptable salt thereof;
1(b)	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);
1(c)	one or more alcohols in an amount from 10% to 70% (w/w), wherein the one or more alcohols comprises benzyl alcohol; and
1(d)	n-dodecyl beta-D-maltoside.
2	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	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	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	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).

Claim Element	Claim Language from '786 Patent
6	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	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	8. The pharmaceutical solution of claim 1, wherein the one or more alcohols are in an amount from 15% to 55% (w/w).
9	9. The pharmaceutical solution of claim 8, wherein the one or more alcohols are in an amount from 25% to 40% (w/w).
10	10. The pharmaceutical solution of claim 1, wherein the solution consists of diazepam, vitamin E, benzyl alcohol, and n-dodecyl beta-D-maltoside.
11(preamble)	11. A pharmaceutical solution for nasal administration consisting of:
11(a)	a therapeutically effective amount of diazepam or a pharmaceutically acceptable salt thereof;
11(b)	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);
11(c)	one of more alcohols in an amount from 10% to 70% (w/w)), wherein the one or more alcohols comprises benzyl alcohol;
11(d)	and n-dodecyl beta-D-maltoside.
12	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	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.

Claim Element	Claim Language from '786 Patent
14	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	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	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	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	18. The pharmaceutical solution of claim 11, wherein the one or more alcohols are in an amount from 15% to 55% (w/w).
19	19. The pharmaceutical solution of claim 18, wherein the one or more alcohols are in an amount from 25% to 40% (w/w).
20	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	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	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	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	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).

Claim Element	Claim Language from '786 Patent
25	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	26. The pharmaceutical solution of claim 1, wherein the α -tocopherol is Vitamin E USP.
27	27. The pharmaceutical solution of claim 11, wherein the α -tocopherol is Vitamin E USP.

IV. SCOPE OF WORK AND MATERIALS REVIEWED

30. I have been asked to review the Challenged Patents and their prosecution histories, to provide an understanding of the technology relevant to the Challenged Patents, to review certain prior art references, to analyse whether or not those references disclose or teach limitations of claims from the Challenged Patent, and to assess whether the combinations of references as a whole render obvious any of the challenged claims.

31. The opinions stated in this declaration are from the perspective of a Person of Ordinary Skill in the Art (which I refer to as a “skilled artisan”) as of March 28, 2008, whose qualifications and abilities are described below. I understand that Petitioner and Patent Owner may have a dispute as to whether the claims of the Challenged Patent are entitled to a priority date in 2008 or 2009. Unless otherwise noted, my opinions expressed in this report remain unchanged regardless of the date used.

32. In forming my opinions, I have reviewed the Challenged Patents, their prosecution histories, the materials cited in the List of Exhibits, the expert declarations of Dr. Donovan, the materials cited in her declarations, and the materials cited throughout my declaration. I have also relied on my academic and professional experience in reaching the opinions expressed in this declaration.

V. LIST OF EXHIBITS

33. In forming my opinions, I have reviewed the materials cited throughout my declaration, including the List of Exhibits below.

A. LIST OF EXHIBITS SUBMITTED BY PETITIONER FOR IPR2025-00466

Exhibit	Description of Exhibits
1001	U.S. Patent No. 11,793,786, <i>Administration Of Benzodiazepine Compositions</i> , filed April 12, 2021 (“786 Patent”)
1002	File History for 11,793,786 Patent, Ser. No. 17/228,514 (“786 FH”)
1003	U.S. Patent No. 11,241,414, <i>Administration of Benzodiazepine Compositions</i> , filed May 27, 2021 (“414 Patent”)
1004	File History for 11,241,414, Ser. No. 17/332,800 (“414 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”)

Exhibit	Description of Exhibits
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”)
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</i>

Exhibit	Description of Exhibits
	<i>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 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”)

Exhibit	Description of Exhibits
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</i> , Neurotherapeutics: The Journal of the American Society for Experimental Neurotherapeutics, Vol. 6, 352-353, April 2009 (“Wermeling I”)
1028	Hardman, et al., Editors, Goodman & Gilman’s, The Pharmacological Basis of Therapeutics, 10th Edition (2001) (“Goodman & Gilman”)

Exhibit	Description of Exhibits
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</i> . <i>Absorption of diazepam and lorazepam following intranasal administration</i> . <i>Intl 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</i>

Exhibit	Description of Exhibits
	<i>intramuscular administration</i> . J Clin Pharmacol, 2001; 41: 1225-1231 (“Wermeling III”)
1037	Budavari, et al., Editors, The Merck Index, 12th Edition (1996) (“Merck Index”)
1038	USP 26/NF 21 2003, The Official Compendia of Standards, Ethanol, Copyright 2002 (“USP 26/ NF 21”)
1039	U.S. App. No. 12/413,439, filed March 27, 2009 (“’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”)

Exhibit	Description of Exhibits
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”)
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”)

Exhibit	Description of Exhibits
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”)
1065	U.S. Publication No. 2008/0279784 to Cartt et al. (“Cartt”)

Exhibit	Description of Exhibits
1066	USP 23/NF 18 1995, The Official Compendia of Standards, Vitamin E, Copyright 1994 (“USP 23/NF 18”)
1067	U.S. Provisional Patent App. No. 60/916,550 (“’550 Provisional”)
1068	Neurelis, Inc. v. Aquestive Therapeutics, Inc., No. 2021-1038, (Fed. Cir. Oct. 7, 2021)
1069	Chart comparing claims 1-27 of the ’786 Patent to claims 1-36 of the ’876 Patent

B. LIST OF EXHIBITS SUBMITTED BY PATENT OWNER FOR IPR2025-00466

Exhibit	Description of Exhibits
2001	<i>Clinical Superiority Findings</i> , U.S. Food & Drug Admin. (Dec. 18, 2024) https://www.fda.gov/industry/designating-orphan-product-drugs-and-biological-products/clinical-superiority-findings
2002	Scheduling Order entered in <i>Neurelis, Inc. v. Padagis LLC</i> , 1:24-cv-00562, D.I. 20 (D. Del. Aug. 28, 2024)
2003	Preliminary Invalidity Contentions served in <i>Neurelis, Inc. v. Padagis LLC</i> , 1:24-cv-00562 (D. Del. Dec. 20, 2024)
2004	Markman Order entered in <i>Gilead Sciences, Inc. v. Lupin Ltd.</i> , 1:22-cv-00615-MN, D.I. 280 (D. Del. Feb. 21, 2025)
2005	Markman Order entered in <i>Spinal Generations, LLC v. Depuy Synthes, Inc.</i> , 1:22-cv-01368 (MN), D.I. 147 (D. Del. Oct. 16, 2024)
2006	Orange Book Listing for U.S. Patent No. 11,793,786

Exhibit	Description of Exhibits
2007	Declaration of Nicholas A. Peppas, Sc.D., dated December 6, 2018 in <i>Aquestive Therapeutics, Inc. v. Hale Biopharma Ventures, LLC</i> , IPR2019-00451, Exhibit 1041 (Jan. 29, 2019)
2008	Declaration of Daniel P. Wermeling, Pharm.D., dated January 27, 2020 in <i>Aquestive Therapeutics, Inc. v. Hale Biopharma Ventures, LLC</i> , IPR2019-00451, Exhibit 1150 (Jan. 28, 2020)
2009	Application No. 18/782,666 (“’666 Application”)
2010	Information Disclosure Statements filed with the Application No. 18/782,666 (“’666 Application”) Prosecution History
2011	Sai H. S. Boddu, Sneha Kumar, A Short Review on the Intranasal Delivery of Diazepam for Treating Acute Repetitive Seizures. <i>Pharmaceutics</i> 2020; 12, 1167
2012	Cornett et al., VALTOCO® (Diazepam Nasal Spray) for the Acute Treatment of Intermittent Stereotypic Episodes of Frequent Seizure Activity, <i>Neurology International</i> 2021; 13:64–78
2013	Scheduling Oral Order entered in <i>Neurelis, Inc. v. Padagis LLC</i> , 1:24-cv-00562, D.I. 47 (D. Del. March 11, 2025) Order Granting Stipulation to Extend Certain Fact Discovery Deadlines entered in <i>Neurelis, Inc. v. Padagis LLC</i> , 1:24-cv-00562, D.I. 65 (D. Del. May 15, 2025)
2014	Jacqueline A. French, Timothy A. Pedley, <i>Initial Management of Epilepsy</i> , <i>New England Journal of Medicine</i> 2008; 359:166-76 (“French & Pedley 2008”)
2015	Penovich et al., <i>Burden of Seizure Clusters on Patients With Epilepsy and Caregivers</i> , <i>The Neurologist</i> 2017; 22: 207-214

Exhibit	Description of Exhibits
2016	Cloyd et al., <i>Overcoming the Challenges of Developing an Intranasal Diazepam Rescue Therapy for the Treatment of Seizure Clusters</i> , <i>Epilepsia</i> 2021; 62:846-856
2017	Hogan, R.E., et al., <i>Bioavailability and Safety of Diazepam Intranasal Solution Compared to Oral and Rectal Diazepam in Healthy Volunteers</i> , <i>Epilepsia</i> , 61:455-464 (Feb. 2020)
2018	Lindsay M. Higdon and Michael R. Sperling, <i>A Review of a Diazepam Nasal Spray for the Treatment Of Acute Seizure Clusters and Prolonged Seizures</i> , <i>J Expert Review of Neurotherapeutics</i> 2021; 21(11):1207-1212
2019	Bechgaard et al., <i>Solubilization of Various Benzodiazepines for Intranasal Administration, a Pilot Study</i> , <i>Pharmaceutical Development and Technology</i> 1997; 2(3):293-296
2020	Gizurarson, S., et al., <i>Intranasal Administration of Diazepam Aiming at the Treatment of Acute Seizures: Clinical Trials in Healthy Volunteers</i> , <i>Biol. Pharm. Bull.</i> , 22(4):425-427 (Apr. 1999)
2021	Ivaturi, V.D., et al., <i>Bioavailability and Tolerability of Intranasal Diazepam in Healthy Adult Volunteers</i> , <i>Epilepsy Res.</i> , 84:120-126 (2009)
2022	Schrier, L., et al., <i>Pharmacokinetics and Pharmacodynamics of a New Highly Concentrated Intranasal Midazolam Formulation for Conscious Sedation</i> , <i>Brit. J. Clin. Pharmacol.</i> , 83:721-731 (Apr. 2017)
2023	Penovich et al., <i>Benzodiazepines for the Treatment of Seizure Clusters</i> , <i>CNS Drugs</i> 2024; 38:125-140
2024	Kapoor et al., <i>A Review of Intranasal Formulations for the Treatment of Seizure Emergencies</i> , <i>Journal of Controlled Release</i> 2016; 237: 147-159

Exhibit	Description of Exhibits
2025	Rabinowicz et al., <i>Improvement of Intranasal Drug Delivery with Intravail® Alkylsaccharide Excipient as a Mucosal Absorption Enhancer Aiding in the Treatment of Conditions of the Central Nervous System</i> , Drugs in R&D 2021; 21:361-369
2026	Acorda Therapeutics, Letter to Plumiaz Clinical Trial Participants, May 20, 2016
2027	U.S. Patent No. 6,193,985 (“Sonne”)
2039	Redline Comparison between U.S. Patent No. 11,793,786 and U.S. Patent No. 11,241,414
2048	Redline Comparison between U.S. Patent Application No. 15/955,397 and U.S. Patent Application No. 17/228,514
2049	Marc Brown <i>Curriculum Vitae</i>
2050	Joint Claim Construction Brief, <i>Neurelis, Inc. v. Padagis LLC et al.</i> , 1:24-cv-00562, D.I. 87 (D. Del. August 15, 2025) (“Joint CC Brief”)
2051	Andrew Streitwieser, <i>Introduction to Organic Chemistry</i> (4th ed. 1992) (“Streitwieser”)
2052	David W. Oxtoby et al., <i>Principles of Modern Chemistry</i> (4th ed. 1999) (“Oxtoby”)
2053	European Pharmacopoeia 6.0, Vol 2 (6th ed. 2007) (“PhEur 6.0”)
2054	Panayiotis P. Constantinides et al., <i>Advances in the Use of Tocols as Drug Delivery Vehicles</i> , 23 Pharm Res. 243 (2006) (“Constantinides-2006”)
2055	Rowe, Sheskey, & Owen, <i>Handbook of Pharmaceutical Excipients</i> , (6th ed. 2009) (“Rowe-2009”)

Exhibit	Description of Exhibits
2056	Afaf Kamal-Eldin, <i>Effect of Fatty Acids and Tocopherols on the Oxidative Stability of Vegetable Oils</i> , 108 Eur. J. of Lipid Sci. & Tech. 1051 (2006) (“Kamal-Eldin-2006”)
2057	Branka Rozman & Mirjana Gašperlin, <i>Stability of Vitamins C and E in Topical Microemulsions for Combined Antioxidant Therapy</i> , 14 Drug Delivery 235 (2008) (“Rozman-2007”)
2058	Afaf Kamai-Eldin & Lars-Ake Appelqvist, <i>The Chemistry and Antioxidant Properties of Tocopherols and Tocotrienols</i> , 31 Lipids 671 (1996) (“Kamai-Eldin-1996”)
2059	March 2009 FDA Inactive Ingredient Database
2060	Redline Comparison between U.S. Patent Application No. 12/413/439 and U.S. Patent Application No. 15/955,397
2061	David Ward, <i>Optimizing Nasal Products for Systemic Delivery</i> , 106 ONdrugDelivery 56 (2020) (“Ward-2020”)
2062	C. Holvoet et al., <i>Inclusion Complexation of Diazepam with Different Cyclodextrins in Formulations for Parenteral Use</i> , 60 Pharmazie 598 (2005) (“Holvoet-2005”)
2063	Sila-On et al., <i>Influence of Incorporation Methods on Partitioning Behavior of Lipophilic Drugs into Various Phases of a Parenteral Lipid Emulsion</i> , 9 PharmSciTech 684 (2008) (“Sila-On-2008”)
2064	D. J. Van Drooge et al., <i>Incorporation of Lipophilic Drugs in Sugar Glasses by Lyophilization using a Mixture of Water and Tertiary Butyl Alcohol as Solvent</i> , 93 J. of Pharm. Sci. 713 (2004) (“Van Drooge-2004”)
2065	L. M. A. Monzon & L. M. Yudi, <i>Voltammetric Analysis of Lipophilicity of Benzodiazepine Derivatives at the Water 1,2-</i>

Exhibit	Description of Exhibits
	<i>dichloroethan Interface</i> , 495 J. of Electroanalytical Chem. 146 (2001) (“Monzon-2001”)
2066	M. Molero-Monfort et al., <i>Retention-activity Relationship Studies of Benzodiazepines by Micellar Liquid Chromatography</i> , 13 Biomed. Chromatography 394 (1999) (“Molero-Monfort-1999”)
2067	M. Molero-Monfort et al., <i>Micellar Liquid Chromatography for Prediction of Drug Transport</i> , 870 J. of Chromatography 1 (2000) (“Molero-Monfort-2000”)
2068	Neurelis Patent Family Tree
2069	Declaration of Mareen Donovan, Ph.D. in Support of Defendants’ Responsive Claim Construction Brief, <i>Neurelis, Inc. v. Padagis LLC et al.</i> , 1:24-cv-562, D.I. 88-28 (D. Del. August 22, 2025) (“Donovan-CC Decl.”)
2070	Certified transcription of December 10-11, 2025, Volume I and II Deposition of Maureen Donovan, Ph.D. in <i>Padagis US LLC vs. Neurelis, Inc.</i> , IPR2025-00464, IPR2025-00465, IPR2025-00466 (“Donovan Transcript”)
2071	<i>What is Log P and How Does It Predict Chemical Behavior?</i> , Biology Insights, (August 16, 2025), https://biologyinsights.com/what-is-log-p-and-how-does-it-predict-chemical-behavior/ (“Log P”)

VI. SUMMARY OF CONCLUSIONS

34. After reviewing the materials identified in the List of Exhibits, I have concluded the following:

- Each of the parent applications to the Challenged Patent, including Provisional Application No. 61/040,558, expressly or inherently discloses each limitation of the challenged claims.
- A skilled artisan would not have found any of the challenged claims obvious over the combination of Gwozdz-PCT (EX1009) and Meezan (EX1010), or over the three-way combination of Gwozdz-PCT, Meezan, and Cartt-784 (EX1065).

VII. LEGAL STANDARDS

35. I am not a legal expert. In presenting my opinions, I have been informed of, and applied, the legal standards provided to me by counsel in arriving at the opinions set forth in this declaration.

A. LEVEL OF ORDINARY SKILL IN THE ART

36. When interpreting a patent, I understand that it is important to identify the relevant art pertaining to the patent-in-suit as well as the level of ordinary skill in that art at the time of the claimed invention. The “art” is the field of technology to which the patent is related.

37. I have been instructed by counsel that the person of ordinary skill in the art (“skilled artisan”) is a hypothetical person who is presumed to know the relevant prior art. I understand that the actual inventor’s skill can be considered but is not determinative of the level of ordinary skill. I further understand that the factors that may be considered in determining the level of skill include: the types of problems encountered in the art; prior art solutions to those problems; rapidity with which

innovations are made; sophistication of the technology; and educational level of active workers in the field. I understand that not all such factors may be present in every case, and one or more of them may predominate.

B. LEGAL STANDARD FOR CLAIM CONSTRUCTION

38. I understand that the first step in determining whether a patent claim would have been obvious is to ascertain how a skilled artisan would have understood the claim terms.

39. I have been instructed by counsel on the law regarding claim construction and patent claims, and I understand that a patent may include two types of claims: independent claims and dependent claims. An independent claim stands alone and includes only the limitations it recites. A dependent claim can depend from an independent claim, or it can further depend from another dependent claim. I understand that a dependent claim includes all the limitations that it recites, in addition to all the limitations recited in the claim(s) from which it depends.

40. It is my understanding that in proceedings before the USPTO, the claims of a patent are to be construed under what is referred to as the “*Phillips* standard.” I understand that this means that claim terms of a patent are given the meaning the terms would have to a skilled artisan.

41. I understand that to determine how a skilled artisan would understand a claim term, one should look to those sources available that show what the skilled artisan would have understood the disputed claim language to mean. Such sources include the words of the claims themselves, the remainder of the patent’s description, the prosecution history of the patent (all considered “intrinsic” evidence),¹ and “extrinsic” evidence concerning relevant scientific principles, the meaning of technical terms, the technical literature on established and emerging relevant technologies, and the state of the art at the time of the invention.

42. I understand that, in construing a claim term, one looks primarily to the intrinsic patent evidence, including the words of the claims themselves, the remainder of the patent, and the patent’s prosecution history.

43. I understand that extrinsic evidence, which is evidence external to the patent and the prosecution history, may also be useful in interpreting patent claims when the intrinsic evidence itself is insufficient.

44. I understand that words or terms should be given their ordinary and accepted meaning unless it appears that the inventors were using them to mean

¹ I understand that the “prosecution history” (also referred to as the “file wrapper”) contains the filings at the USPTO that led up to the patent at issue, such as the original application, office actions, and response to office actions.

something else. In making this determination, the claims, the remainder of the patent, and the prosecution history are of paramount importance. Additionally, the patent and its prosecution history must be consulted to confirm whether the patentee has acted as its own lexicographer (i.e., provided its own special meaning to any disputed terms), or intentionally disclaimed, disavowed, or surrendered any claim scope.

C. LEGAL STANDARD FOR PRIOR ART

45. I understand that a patent or other publication must first qualify as prior art before it can be used to invalidate a patent claim. That is, in some sense it must be earlier than the priority date of the challenged claims.

46. I understand that for a prior art reference to be considered for obviousness, the reference must be “analogous.” I understand that the comparison for purposes of determining “analogous” is between the asserted prior art reference and the Challenged Patent. I have been further informed that for a prior art reference to be considered “analogous” to the Challenged Patent and thus available as prior art for obviousness, at least one of the following conditions must be met: (1) the reference is from the same field of endeavour as the Challenged Patent, even if it addresses a different problem; or (2) the reference is reasonably pertinent to the

particular problem the Challenged Patent is concerned with, even if it is not within the same field of endeavour.

D. LEGAL STANDARD FOR VALIDITY

47. I have been informed that the United States patent law statutes state that issued patent claims are presumed to be valid. I understand that in this *inter partes* review proceeding, a Petitioner has the burden of proving that the claims of a Challenged Patent are unpatentable in light of the prior art by a preponderance of the evidence. I understand that a preponderance of the evidence is evidence sufficient to show that a fact is more likely true than not true.

1. Anticipation, Express, and Inherent Disclosures

48. Dr. Donovan does not contend that any of the challenged claims are anticipated. Anticipation requires the party challenging the patent to prove that all of the limitations of a challenged claim were present in a single prior art reference. The claims may be disclosed expressly or they may be disclosed inherently, but must be in such a way that a skilled artisan could make and use the claimed invention without undue experimentation.

49. I understand that for a limitation to be “disclosed inherently” (that is, inherent) in a prior art reference, that requires a showing that the missing descriptive

matter is *necessarily* present in the allegedly anticipating reference (even if not expressly stated), and that it would have been so recognised by a skilled artisan.

2. Obviousness

50. Dr. Donovan has not presented any opinions that any of the challenged claims are anticipated over prior art. Rather, she provides obviousness contentions.

51. I have been informed that another way for a party challenging a patent to demonstrate invalidity of a challenged claim is to demonstrate that the challenged claim would have been obvious. That is, even though an invention may not have been identically disclosed or described in a single, unmodified prior-art reference, in order to be patentable, the challenged claim must also not have been obvious to a skilled artisan as of the priority date. I have been informed that an obviousness inquiry must not be conducted from the hindsight of a “today” perspective, but must instead be conducted from the viewpoint of a skilled artisan as of the priority date (sometimes referred to as “effective filing date”) of the patent claim.

52. Dr. Donovan contends that “claims 1-27 of the ’786 Patent are entitled to an effective filing date of no earlier than March 27, 2009, and in certain circumstances, may only be entitled to an effective filing date later than March 27,

2009.”² At no point in her declaration, however, does she actually offer an opinion as to what that “later” priority date might be, or which claims might be entitled to only that later date. Accordingly, for purposes of conducting an obviousness analysis, I have used the priority date of March 27, 2009, because if the challenged claims are in fact entitled to priority to March 28, 2008 (corresponding with the filing of 61/040,558), then Gwozdz-PCT would not qualify as prior art and there would be no obviousness assertions.

53. In determining whether a claimed invention would have been obvious, I have been informed that I should consider: the level of ordinary skill in the field of the invention that someone would have had at the time the invention was made; with the scope and content of the prior art; any differences between the prior art and the claimed invention; and any objective evidence of non-obviousness. I understand that it is important that hindsight must not be used in an obviousness analysis, and that one must consider only what was known at the time of the priority date of the Challenged Patent. For example, I understand that reliance on knowledge that is gleaned only from reading the Challenged Patent constitutes impermissible hindsight. I have been informed by counsel that one should not rely on the

² EX1062 (Donovan-786 Decl.) ¶54.

Challenged Patent itself as a roadmap for putting together the pieces of the jigsaw puzzle to arrive at the claimed invention. I understand that impermissible hindsight must be avoided.

54. I have been informed that when analysing prior-art references for purposes of an obviousness analysis, it is important to consider the prior-art references as a whole, for everything they teach. I have been informed that courts have summarised this tenet of patent law as, “One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention.” I have been informed that considering the references as a whole for everything they teach, rather than picking and choosing amongst isolated passages, helps avoid hindsight in an obviousness analysis.

55. I have also been informed that the existence of each and every element of the claimed invention in the prior art does not necessarily prove obviousness. Most, if not all, inventions rely on building blocks of prior art. For example, I have been informed that just because possible arrangements existed in the prior art does not provide a reason why a skilled artisan would modify or substitute one arrangement for another. It does not suffice for elements of a claim to simply be known in prior art; rather, a reason to modify or substitute must exist. Stated another way, I have been informed that obviousness concerns not only whether a skilled

artisan not only could have made the claimed invention, but instead concerns whether the skilled artisan would have been motivated to make the combinations or modifications of prior art to arrive at the claimed invention. In other words, the skilled artisan must have been able to make the claimed invention, and also must have had a reason to do so.

56. I understand that in considering whether a claimed invention is obvious, one must consider whether, at the time of the claimed invention, there was a reason that would have prompted a person having ordinary skill in the field of the invention to combine the known elements in the prior art in a way the claimed invention does, taking into account such factors as (1) whether the claimed invention was merely the predictable result of using prior art elements according to their known function(s); (2) whether the claimed invention provides an obvious solution to a known problem in the relevant field; (3) whether the prior art teaches or suggests the desirability of combining elements claimed in the invention; (4) whether the prior art teaches away from combining elements in the claimed invention; (5) whether it would have been “obvious to try” the combinations of elements, such as when there is a design incentive or market pressure to solve a problem and there are a finite number of identified, predictable solutions (i.e., the prior art suggests what should be tried and why it would work).

57. In order to find an invention obvious, one must find a reasonable expectation of success. For example, I understand that the mere fact that certain possible arrangements existed in the prior art does not provide a reason that a skilled artisan would have substituted one arrangement in one reference with another arrangement in another reference, or that the skilled artisan would have reasonably expected the substitution to work.

58. I understand that in determining whether the claimed invention is obvious, objective indications that may shed light on whether or not the claimed invention is obvious include: (a) whether the claimed invention was commercially successful as a result of the merits of the claimed invention (rather than the result of design needs or market-pressure advertising or similar activities); (b) whether the claimed invention satisfied a long-felt need; (c) whether others had tried and failed to make the claimed invention; (d) whether others invented the claimed invention at roughly the same time; (e) whether others copied the claimed invention; (f) whether there were changes or related technologies or market needs contemporaneous with the claimed invention; (g) whether the claimed invention achieved unexpected results; (h) whether others in the field praised the claimed invention; (i) whether persons having ordinary skill in the art of the invention expressed surprise or disbelief regarding the claimed invention; (j) whether others sought or obtained

rights to the patent from the patent holder; and (k) whether the inventor proceeded contrary to accepted wisdom in the field. I understand that there must be a nexus between any such objective indications and the claimed invention.

E. LEGAL STANDARD FOR WRITTEN DESCRIPTION

59. I have been informed that in determining whether a patent claim has written description, one must look at the disclosure of that patent as originally filed (including claims, specification, and drawings) and ascertain whether it supports each limitation of that claim. I understand that it is not enough for the disclosure to merely render the claim obvious, but instead that the disclosure must expressly disclose or inherently (i.e., show it is necessarily present) disclose all limitations of the claim. I have been informed that the disclosure must convey with reasonable clarity to a skilled artisan that the inventor was in possession of the invention.

VIII. LEVEL OF ORDINARY SKILL IN THE ART

60. As described in the Legal Standards section, I have been provided the legal standards for determining the qualifications of a Person of Ordinary Skill in the Art (“skilled artisan”). Dr. Donovan contends the following regarding a skilled artisan (which she abbreviates as a “POSA” or Person of Skill in the Art):

It is my opinion that as of the earliest priority date that the ’786 Patent as a whole is entitled to (i.e., no earlier than March 27, 2009, as discussed in ¶¶ XX-XX, [*sic*] above), a POSA would have been a pharmaceutical scientist, chemist, or biologist

involved in the research and development of pharmaceutical formulations and/or delivery, and would have at least a Bachelor's degree with at least 5 years of experience, or a Master's, Ph.D. or Pharm.D. degree with several years of experience. In addition, it is my opinion that a POSA would have had knowledge of benzodiazepine structure and function, and would further have knowledge and practical experience working with intranasal and transmembrane formulations, including knowledge of the physiology and anatomy of the nasal cavity, with relevant experience in developing intranasal formulations.³

61. I understand that Neurelis has contended that the level of a skilled artisan is as follows:

[T]he skilled artisan holds a Master's degree with many years of experience, or a Ph.D. or Pharm.D degree with several years of experience or its equivalent experience in the field of pharmaceutical research and development. The skilled artisan would have knowledge of benzodiazepine structure and function, including physiochemical characteristics of benzodiazepines generally. The skilled artisan would further have knowledge and practical experience developing and working with intranasal formulations, including knowledge of the physiology and anatomy of the nasal cavity and methods of administering drugs intranasally. The skilled artisan also would have knowledge concerning clinical aspects of bioavailability, tolerability, and patient acceptability of intranasal formulations and the difficulty of administering drugs by other routes during an event like a seizure.⁴

³ EX1062 (Donovan-786 Decl.) ¶20.

⁴ EX2050 (Joint CC Brief) at 22.

62. I was a person of at least ordinary skill as of 2008, and I remain so today. Regardless of which definition for a skilled artisan is used, the opinions in my declaration are unchanged.

IX. TECHNOLOGY BACKGROUND AND STATE OF THE ART

63. In the subsections below, I describe some basic principles of chemistry and biochemistry.

A. CHEMICAL COMPOUNDS AND THEIR STRUCTURES

1. Organic Chemical Compounds

64. A chemical compound is a substance made up of two or more atoms that are chemically bonded together. The structure and atoms that compose the compound help define that compound's functional characteristics.

65. Organic compounds are structured around carbon-carbon (C–C) and carbon-hydrogen (C–H) bonds, although they may include other elements, particularly oxygen, nitrogen, and sulphur. A carbon atom's ability to form up to four covalent bonds with other atoms allows for a vast diversity of structures: straight chains, branched chains, cyclic compounds, and aromatic rings (containing C–C double bonds).⁵

⁵ See, e.g., EX2051 (Streitwieser) at 2.

66. Although chemical compounds are three-dimensional objects, they are often represented by a two-dimensional skeletal structure, which is a shorthand way of identifying the atoms and bonds. Such representations of carbon-based molecules show a series of atoms bonded together. Such skeletal structures can depict chains, branches, and rings of carbon and other atoms.⁶ The following representations are common in skeletal structures:

- A carbon atom is represented by a vertex, where two lines interact or terminate.
- Hydrogen atoms that are attached to carbons are not shown, as they are implied for any carbon with less than four depicted bonds.
- A vertex without any labels represents a carbon atom bonded to other constituents and the number of hydrogens needed to satisfy the octet rule (i.e., eight electrons surrounding the carbon). Accordingly, a carbon bonded to four other carbons would not have any hydrogens.

For example, two depictions of *n*-pentane (C₅H₁₂) are shown below. A figure with all of the carbons and hydrogens labelled is shown on the left, and a skeletal structure of *n*-pentane is shown on the right:

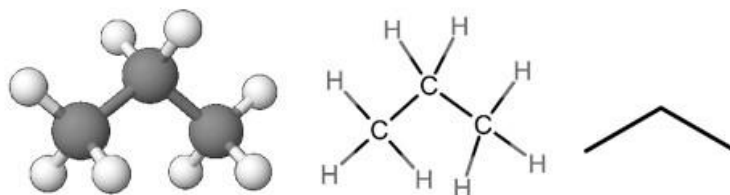


⁶ See, e.g., EX2051 (Streitwieser) at 2.

67. In skeletal structures, certain common elements or groups of elements (sometimes called “functional groups”) are indicated by shorthand. “X” typically represents a halogen atom or another group that donates only one electron (such as —OH). “R” typically represents an alkyl group (forming a carbon-carbon bond), such as $\text{H}_3\text{C(H}_2\text{)C—}$, $\text{Cl(H}_2\text{)C—}$, $\text{H}_3\text{C(O=)C—}$. Functional groups include hydroxyl (—OH), carboxyl (—COOH), amino (—NH_2), aldehyde (—CHO), and ketone (—C=O).⁷

2. Alkanes, Alkyl Groups, and Isomers

68. Organic compounds can be categorised by their composition and structure. For example, *alkanes* are a type of hydrocarbon compound that are made entirely of carbon (C) and hydrogen (H) atoms, and in which all the carbon-carbon bonds are single bonds. A three-carbon alkane is propane (C_3H_8). It can be depicted in a three-dimensional fashion (showing the three carbon atoms in grey and the eight hydrogen atoms in white), in shorthand fashion, or in skeletal fashion:



⁷ See, e.g., EX2051 (Streitwieser) at 2.

When an alkane is not a standalone molecule, but is instead bonded to other chemical components as a group, the “group name is derived by replacing the *-ane* of the corresponding alkane by the suffix *-yl*.”⁸

69. Alkanes of four or more carbons can form different *isomers*. One textbook describes isomers as follows:

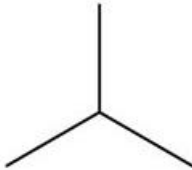
There are two **isomeric** compounds having the formula C_4H_{10} . **Isomers** are defined as compounds that have identical formulas but differ in the nature or sequence of bonding of their atoms or in the arrangement of their atoms in space. ... In general, isomers have different physical and chemical properties.⁹

These different arrangements lead to not only distinct physical and chemical properties (e.g., boiling point and melting point), but also distinct biological activity, even though the number and type of atoms are the same. For example, cisplatin is an important chemotherapy drug, but its isomer (transplatin) has no known pharmaceutical uses.

70. A simpler example is butane (C_4H_{10}), which is a four-carbon alkane that can exist as two isomers:

⁸ EX2051 (Streitwieser) at 10.

⁹ EX2051 (Streitwieser) at 11 (emphasis in original).

	
<i>n</i> -butane	<i>iso</i> -butane

Both isomers have the same number of carbons and hydrogens, but they have different structures. The “*n*-” nomenclature refers to the “normal” or ***linear*** isomer: “Straight-chain alkanes are called **normal alkanes**, or simply ***n*-alkanes**, to distinguish them from the branched alkanes.”¹⁰ For *n*-alkanes, all carbons form a continuous, unbranched (i.e., linear) chain. A general chemistry textbook describes *n*-alkanes as follows: “The most prevalent hydrocarbons in petroleum are the straight-chain alkanes (also called normal alkanes, or *n*-alkanes), which consist of chains of carbon atoms bonded to one another by single bonds” and which “have the generic formula C_nH_{2n+2} .”¹¹ In contrast to *n*-alkanes, the other category of isomer is ***branched***.

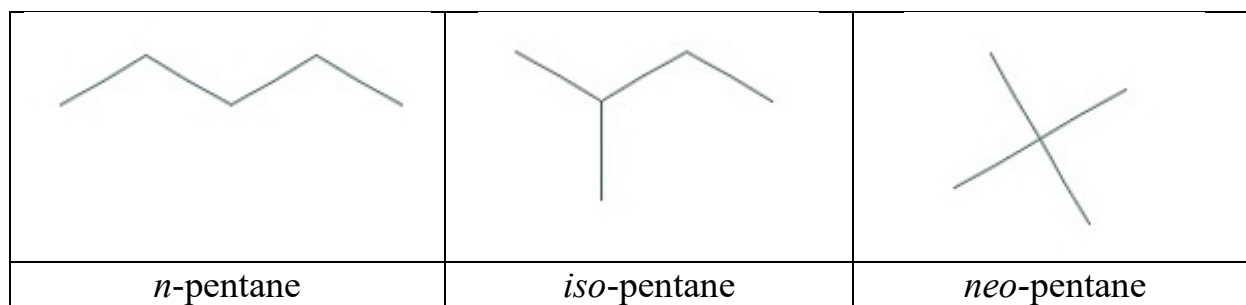
Branched-chain alkanes are hydrocarbons that contain only C—C and C—H single bonds but in which the carbon atoms are no longer arranged in a straight chain. One or more carbon atoms in each molecule are bonded to three or four other carbon atoms

¹⁰ EX2051 (Streitwieser) at 9 (emphasis in original).

¹¹ EX2052 (Oxtoby) at 8.

rather than to only one or two as in the normal alkanes or cycloalkanes.¹²

71. Butane can exist as only the two isomers above. But as the number of carbons in the molecule increases, the number of isomers grows. Thus, larger alkanes can adopt many different types of branched structures. Consider, for example, the number of isomers in pentane (C_5H_{12}), which has one linear isomer and two branched isomers:¹³



72. Alkanes can possess almost arbitrarily large numbers of carbon atoms. For example, octane is an 8-carbon alkane (C_8H_{18}), dodecane is a 12-carbon alkane ($C_{12}H_{26}$), tetradecane is a 14-carbon alkane ($C_{14}H_{30}$), and tetracosane is a 24-carbon alkane ($C_{24}H_{50}$). Larger alkanes can exist in many more isomeric structures than smaller alkanes like butane and pentane—“[w]ith more carbons the number of possible isomers increases rapidly. . . . [T]here are 5 possible hexanes, 9 heptanes,

¹² EX2052 (Oxtoby) at 9.

¹³ EX2051 (Streitwieser) at 11.

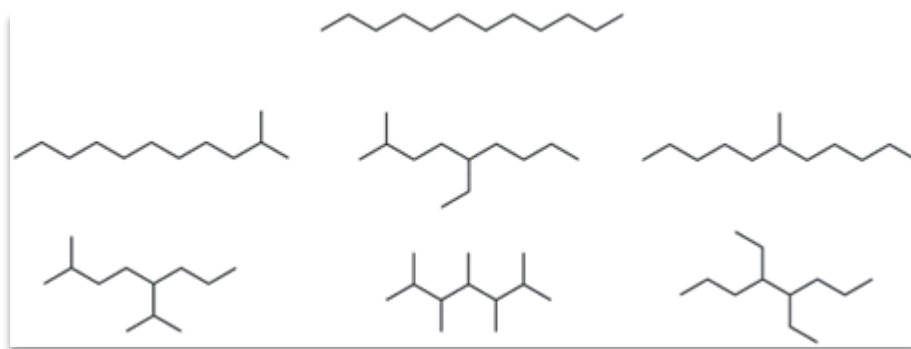
and 75 decanes, and with larger alkanes the number of isomers becomes astronomic.”¹⁴ Dodecane (C_{12}) can adopt 355 different isomeric structures, and eicosane (C_{20}) can adopt 366,319 different isomeric structures.¹⁵

TABLE 3.3 Number of Isomers of C_nH_{2n+2}	
<i>n</i>	Number of Isomers
4	2
5	3
6	5
7	9
8	18
9	35
10	75
12	355
15	4,347
20	366,319

In the figure below a handful of the 355 isomers that dodecane ($C_{12}H_{26}$) can adopt is presented:

¹⁴ EX2051 (Streitwieser) at 11.

¹⁵ EX2051 (Streitwieser) at 11.



n-dodecane is the linear isomer depicted at the top of this figure, but dodecane can adopt 354 other isomeric forms, only a few of which are depicted above. Other than *n*-dodecane, every other isomer of dodecane is branched in one or more locations.

73. When an alkane is chemically connected to another chemically distinct portion of a molecule (often called a *moiety*), the alkane is then termed an “alkyl” group. For example, when connected to another moiety, butane becomes “butyl”; octane becomes “octyl”; dodecane becomes “dodecyl”; tetradecane becomes “tetradecyl”; and tetracosane becomes “tetracosanyl.”¹⁶ The alkyl can be bonded to the moiety not only at a terminal carbon of the alkyl group, but also at various other carbon atoms.

3. Saccharides and Glycosides

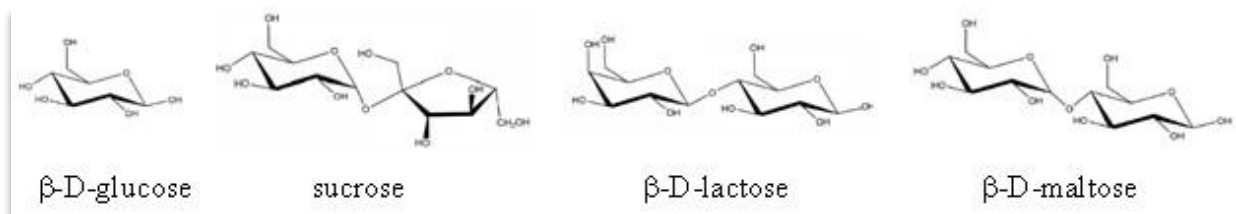
74. There are many types of chemical compounds other than alkanes. Another type of compound relevant to my opinions in this matter are carbohydrates.

¹⁶ EX2051 (Streitwieser) at 10.

These are chemical compounds containing carbon, oxygen, and hydrogen in various ratios.

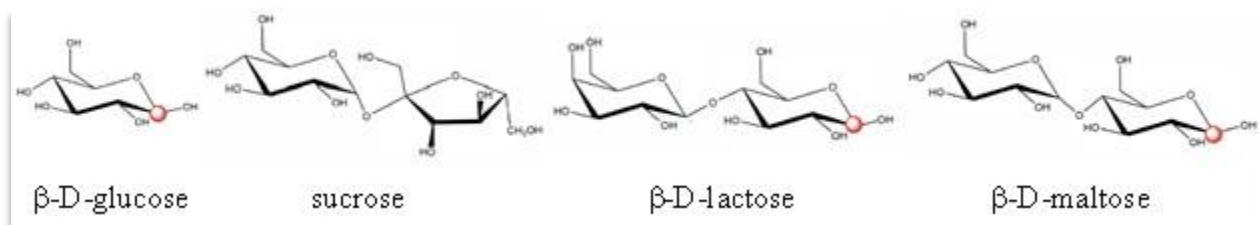
a. Saccharides

75. One category of carbohydrates is commonly called “sugars,” or “saccharides.” There are a vast number of known saccharides. A simple sugar molecule with one unit (monosaccharide) has the chemical formula of $C_6H_{12}O_6$. The most abundant monosaccharide is glucose, though there are numerous isomers (including stereoisomers) of glucose. A few common disaccharides (two sugar units) are sucrose, lactose, and maltose. Their structures are depicted below:



Some less common saccharides include maltotrioside, maltotetroside, trehaloside, palatinose, and isomaltamine, among countless others.

76. Like alkanes, saccharides isomerize, possessing the ability to take on multiple different structural forms while maintaining the same chemical composition. Relevant here, saccharides have different *anomers*.

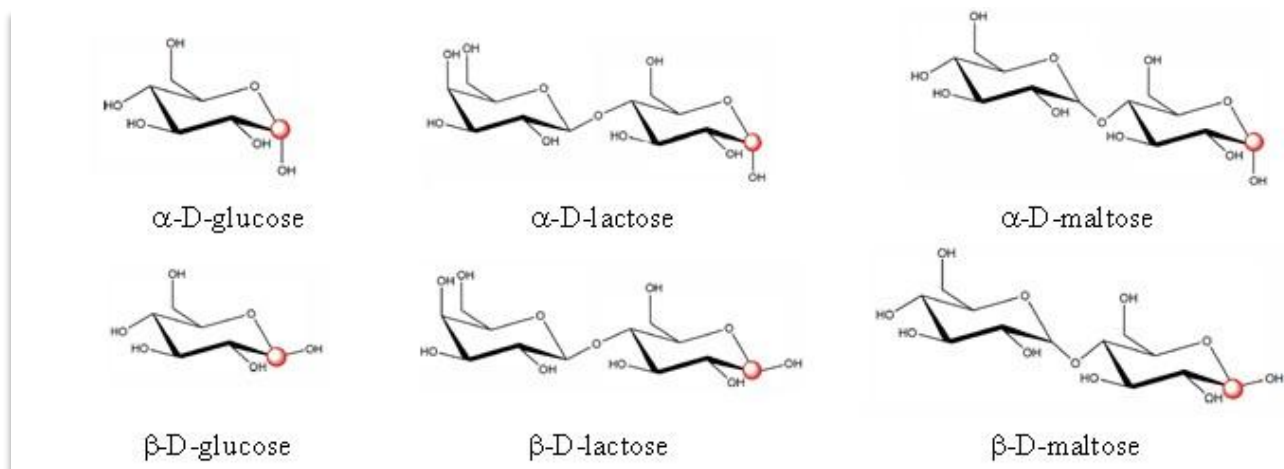


Anomers are isomers of a saccharide that differ in the 3-dimensional configuration of a particular carbon atom, called the “anomeric carbon.” The anomeric carbon in glucose, lactose, and maltose (sucrose has no free anomeric carbon) is indicated above.¹⁷

77. The distinction between anomers is the configuration of the -OH group in relation to the -CH₂OH group on the saccharide ring. If those two groups are on opposite “faces” of the ring (i.e., the *trans* configuration), then the saccharide is termed the α -anomer. If those two groups are on the same “face” of the ring (i.e., the *cis* configuration), then the saccharide is termed the β -anomer.¹⁸ Those two configurations for glucose, lactose, and maltose are depicted below:

¹⁷ EX2051 (Streitwieser) at 11-13.

¹⁸ EX2051 (Streitwieser) at 13.



b. Glycosides

78. When a saccharide is chemically connected to another chemically distinct moiety, the resulting molecule is often termed a “**glycoside**.” For example, when connected to another moiety, glucose becomes “glucoside”; sucrose becomes “sucroside”; lactose becomes “lactoside”; and maltose becomes “maltoside.”

79. A glycoside has two main parts: the sugar part, which is typically a cyclic monosaccharide; and the non-sugar part, which can be an organic molecule, like an alkane. The bond between those two moieties can involve various chemistries (e.g., ether, ester, amide, ureide, etc.), and it usually involves the anomeric carbon of the sugar. An “alkyl glycoside” represents a broad genus of potential chemical compounds, including accounting for the following variations:

- The saccharide or glycoside moiety (e.g., single-unit sugars such as glucose, fructose, and galactose, or two-unit sugars such as maltose, etc.);

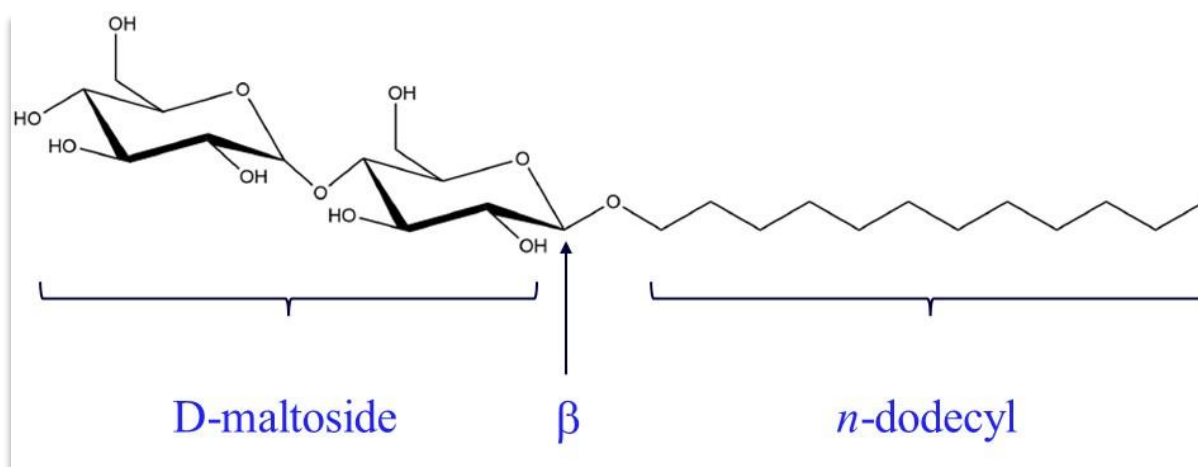
- The stereochemistry of the saccharide or glycoside (e.g., D or L);
- The anomeric structure of the saccharide or glycoside (e.g., α or β);
- Substitution of heteroatoms (e.g., sulphur) in the saccharide or glycoside;
- The alkyl chain (its size and its isomeric structure, i.e., the number of carbon atoms, and whether they are linear or branched);
- Which carbon of the alkyl chain is connected to the glycoside or saccharide moiety; and
- The linking chemistry between the moieties (e.g., glycosidic, thioglycosidic, ester, ureide, amide, etc.).

80. When a molecule is constructed of these various parts, chemists will give a common name to it, as well as identifying it by formal IUPAC¹⁹ nomenclature. The common name usually links the various characteristics I have discussed in the preceding paragraphs.

c. *n*-dodecyl- β -D-maltoside

81. Relevant to my opinions in this matter, the compound *n*-dodecyl- β -D-maltoside (also known as lauryl-beta-D-maltoside) refers to a particular chemical compound having a specific chemical structure and resulting functional characteristics. The structure of *n*-dodecyl- β -D-maltoside is depicted below, with the structural characteristics corresponding to the name of the compound indicated:

¹⁹ “IUPAC” is the International Union of Pure and Applied Chemistry. This organization promulgates formal rules for naming chemical compounds.

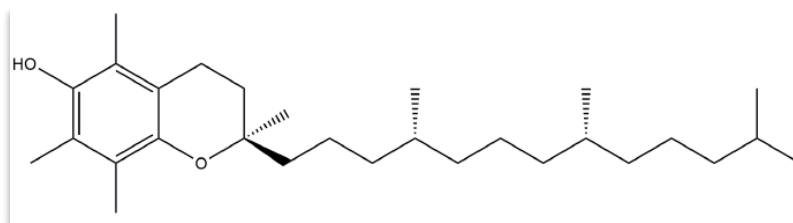


As shown above, the *n*-dodecyl is a linear chain. Considering only the dodecyl moiety on its own, there are 354 other chemical compounds (isomers) qualifying as dodecyl- β -D-maltoside. Considering the other isomeric permutations—such as the multiple types of maltoside (e.g., L-maltoside or D-maltoside), the glycosidic linkages (e.g., α or β), and which carbon of the dodecyl moiety is bonded to the maltoside—the number of chemical compounds qualifying as dodecyl maltoside is much greater.

B. TOCOPHEROLS AND TOCOTRIENOLS

82. Tocopherols and tocotrienols are 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. There are multiple isomers and multiple esters of each of these compounds.²⁰ The structure of α -tocopherol appears below:



83. The PhEur 6.0 (published in January 2008), describes α -tocopherol as a clear, colourless or yellowish-brown, viscous, oily liquid²¹ that is unstable when exposed to alkalis, light, oxygen, and contact with iron or lead.²² By 2009, α -tocopherol was referred as “RR- α -tocopherol” in the British Pharmacopeia, “tocopherol” in the Japanese Pharmacopeia, “RRR- α -tocopherol” in the European Pharmacopeia and as Vitamin E in the USP.

84. Functionally, Vitamin E USP is mainly used as an antioxidant, by inhibiting oxidation by scavenging peroxy radicals, especially at low concentrations, but it can also function as a therapeutic agent.²³ This excipient is

²⁰ EX1008 ('558 Provisional) ¶116.

²¹ EX2053 (PhEur 6.0) at 10.

²² EX2054 (Constantinides-2006) at 1; EX2055 (Rowe-2009) at 9.

²³ EX1008 ('558 Provisional) ¶117.

highly lipophilic, being practically insoluble in water, but it is freely soluble in acetone, chloroform, ethanol (95%), ether, and vegetable oils.²⁴ Therefore, it can act as a solvent for poorly water-soluble drugs.²⁵

85. When present in high concentrations, tocopherols gradually lose their activity, due to their participation in side reactions that boost the initiation rate of new oxidation chains (pro-oxidant effect). This effect is greater for α -tocopherol, when compared to other homologues like γ -tocopherol.²⁶

86. In addition, tocopherols are susceptible to photo-oxidation upon UV exposure which results in the formation of tocopheroxyl radicals²⁷; alkaline conditions accelerate hydrolysis-and oxidation-type loss and polarity with the pro-oxidant effect being higher in aqueous media, when compared to other solvents (e.g., dimethyl sulfoxide, acetonitrile, hexane).²⁸ As such due to these inherent

²⁴ EX2055 (Rowe-2009) at 9.

²⁵ EX2055 (Rowe-2009) at 9.

²⁶ EX2056 (Kamal-Eldin-2006) at 6.

²⁷ EX2057 (Rozman-2007) at 8.

²⁸ EX2058 (Kamai-Eldin-1996) at 17.

instabilities, tocopherols should be stored in airtight containers under inert gas, in a cool, dry place, and protected from light.²⁹

87. Such properties and instabilities are also an important consideration when developing the composition of formulations containing tocopherols.

88. According to the FDA Inactive Ingredient Database published in March 2009, there were no nasal products containing this excipient as of 2009.³⁰ The following levels were listed for other dosage forms/delivery routes:

- Intravenous lyophilized powder for liposomal suspension – 0.06%
- Oral capsule – 0.50 mg
- Oral soft gelatine capsule – 5 mg
- Oral tablet – 0.30 mg
- Topical ointment – 2.0 and 0.3%
- Intravenous concentrate solution – 0.07%

C. ALCOHOLS

89. Alcohols are organic compounds that possess a hydroxyl (–OH) functional group wherein the oxygen atom is covalently bound to a carbon atom. Most alcohols are water-soluble liquids. Their water-solubility is due to polar

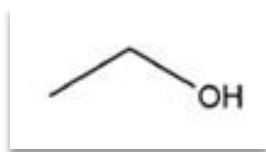
²⁹ EX2055 (Rowe-2009) at 9.

³⁰ EX2059 (March 2009 FDA IID) at 7.

interactions between water molecules and the –OH group. Some well-known alcohols include ethanol, propanol, butanol, pentanol, and benzyl alcohol.³¹

1. Ethanol

90. Ethanol (or “ethyl alcohol”) has a chemical formula of C₂H₅OH. It is a liquid at room temperature, with a boiling point of about 78°C at 1 atmosphere.³² Ethanol is a clear, colourless, mobile, and volatile liquid with a slight, characteristic odour and burning taste. Ethanol is readily miscible with water, meaning it will form a homogeneous solution at any relative concentration of water and ethanol. Most ethanol that is synthesised commercially is created by fermentation of feedstock by microorganisms (e.g., barley by yeast). The structure of ethanol is:



91. Industrial ethanol can be purchased in various grades, having more or less of various other substances dissolved in it. In the USP 26 (2003), the term “dehydrated alcohol” refers to ethanol $\geq 99.5\%$ v/v, whilst the term “alcohol” without

³¹ EX1009 ('558 Provisional) ¶12.

³² EX1016 (2003 Handbook of Pharm. Excipients) at 14.

other qualification refers to ethanol 94.9–96.0% v/v.³³ The remaining percentage of the composition in both instances is mostly water, with other compounds present in trace amounts.³⁴

92. This excipient was widely used in pharmaceutical and cosmetic products as of 2008. Functionally, ethanol was primarily used as a solvent. But it also could be used as a disinfectant and as an antimicrobial preservative. According to the Handbook of Pharmaceutical Excipients (July 2009), ethanol could be used up to 60-90% as a solvent in topical products, up to 10% as an antimicrobial preservative, and up to 60-90% as a disinfectant.³⁵

93. Dehydrated alcohol USP (i.e., dehydrated ethanol) was an excipient present in FDA-approved nasal products by 2008, more specifically in Nasacort HFA (a triamcinolone acetonide metered aqueous solution spray) in a concentration of 0.7%. According to the FDA IID published on March 2009, dehydrated alcohol USP was approved by the nasal route in the following concentrations: aerosol: up to

³³ EX1038 (USP 26/NF 21) at 4.

³⁴ EX2055 (Rowe-2009) at 5.

³⁵ EX2055 (Rowe-2009) at 5.

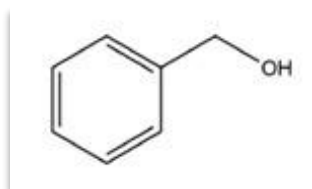
2.0%; spray: 10-198.8 mg/mL maximum potency unit dose (i.e., up to 20 % w/w).³⁶

In the FDA IID (2009) the levels for other topical delivery routes were as follows:³⁷

- Rectal gel – 11.22%
- Topical aerosol – 60.39%
- Topical aerosol foam – 60.43%
- Topical gel – 94.78%
- Topical lotion – 8.80%
- Topical solutions – up to 96.67%

2. Benzyl alcohol

94. Benzyl alcohol is a clear, colourless, oily liquid with a faint aromatic odour and a sharp, burning taste. Its chemical formula is C_7H_7OH . Functionally, this excipient was used as an antimicrobial preservative and disinfectant as well as solvent.³⁸ Its structure is:



³⁶ EX2059 (March 2009 FDA IID) at 6.

³⁷ EX2059 (March 2009 FDA IID) at 6.

³⁸ EX1016 (Rowe) at 9.

D. SOLUTIONS AND SUSPENSIONS

95. When two substances are mixed together, various processes can occur.

Three examples include the creation of a solution, a suspension, and an emulsion.

1. Solutions

96. A ***solution*** is a mixture of two or more substances where the substances are mixed homogenously with each other. I will focus my discussion on the dissolution of a solid substance in a liquid substance, although other types of solutions (e.g., solids in solids) are possible. A solution is comprised of one substance (for purposes of this discussion a solid, called the “solute”) dissolved in the other substance (for purposes of this discussion a liquid, called the “solvent”).

97. Solubility is a measure of how much of the solute can dissolve in a given quantity of the solvent to form a solution. Solubility is not absolute; once a threshold is reached, no more solute will dissolve in the solvent at a given temperature or pressure—for example, at room temperature.

98. Solubility of a particular solute in a particular solvent depends primarily on the compatibility between the two substances. The guiding principle is often stated as “like dissolves like.” This adage captures well the concept that a solute that is chemically similar to a particular solvent will likely dissolve well in that solvent, and vice-versa. Substances are often very roughly divided into two broad

categories: “hydrophilic” and “lipophilic.” The former “water-loving” substances tend to dissolve well in aqueous solvents (typically water or aqueous buffers), but not in nonaqueous solvents like fats and oils. The latter “fat-loving” substances tend to dissolve well in fats and oils, but not in aqueous solvents.

2. Suspensions

99. In contrast to a solution, where the mixture of two substances is homogenous, a *suspension* is a mixture of two substances (for my purposes here, a solid and a liquid) that is heterogeneous. Particles of the solid are large enough that they remain separate from the liquid carrier and mixed into it. Due to gravity and other forces, the particles over time can settle out of the carrier and aggregate.

100. Many drugs have poor water solubility (i.e., are lipophilic). Formulating them as suspensions can allow the drug to be delivered in particulate form.

3. Emulsions

101. An emulsion is a type of heterogenous mixture of one liquid into another liquid. While to the naked eye it may appear homogeneous, at the microscopic level an emulsion shows very small droplets of one liquid within the other. In this respect an emulsion is something like a suspension. Over time the liquids can separate into layers. The emulsion typically is formed by agitation. For

example, a vinaigrette involves an aqueous (vinegar) layer and an oil layer. They can be temporarily emulsified by agitation, but over time they will tend to separate.

102. An emulsion can be stabilised by an “emulsifier,” which can interact with both liquids in the emulsion and form an interface layer between the droplets of one liquid and the other liquid. Mayonnaise is an example of a stabilised emulsion, where oil and an acidic aqueous component are stabilised by substances present in egg yolks.

103. Emulsions can have drawbacks in the context of pharmaceutical use. For instance, they may be difficult to create. They can be unstable, separating into their constituent parts. Additionally, they can leave an oily film on the surface to which they are applied. Emulsions contain an aqueous component and consequently can be difficult to render and maintain as sterile.³⁹

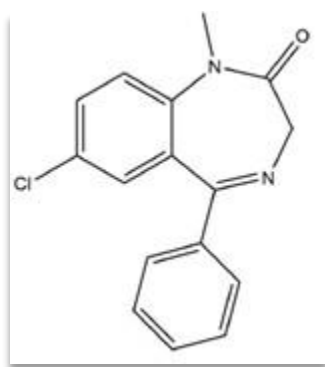
E. BENZODIAZEPINES, INCLUDING DIAZEPAM

104. Benzodiazepines are a family of chemically related drug compounds that, by 2008, had been observed to possess sedative, tranquilizing, and muscle-relaxing properties. They had long been used to treat symptoms of anxiety, especially the drug product Valium®, comprising the drug substance diazepam.

³⁹ See EX1009 (Gwozdz-PCT) at 1:35-2:1.

Benzodiazepines were also a treatment option for seizures, particularly those caused by epilepsy, when administered by IV or by rectal suppository.

105. Diazepam (1,7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepine-2-one) is a type of benzodiazepine that displays anticonvulsant, anxiolytic, sedative, muscle-relaxant, and amnesic pharmacological effects.⁴⁰ The structure of diazepam is:



106. Diazepam is one of the most stable substituted 1,4-benzodiazepines, although it undergoes hydrolysis in aqueous solution.⁴¹ Certain physicochemical properties of diazepam known by 2008 are shown below:

Category	Characteristic	Reference
Appearance	Colourless crystalline compound	General
Molecular Formula	C ₁₆ H ₁₃ ClN ₂ O	

⁴⁰ EX2062 (Holvoet-2005) at 1.

⁴¹ EX2062 (Holvoet-2005) at 1.

Molecular Weight	284.74 g/mol	EX2063 ⁴² .
pH (1% solution)	6.5	
Aqueous solubility (n=3):	0.051 ± 0.000 mg/mL	
Oil solubility (n=3):	13.718 ± 0.046 mg/g	
Oil-water Partition Coefficient (n=3):	2.23 ± 0.03	

107. “Log P” is a commonly-used measure of the lipophilicity of a drug, derived from how well the drug dissolves in relatively nonpolar octanol versus how well it dissolves in water. A Log P value of 0 indicates that a compound is equally partitioned between the lipid and aqueous phases, meaning it is neutral in terms of lipophilicity or hydrophilicity. A Log P value of greater than 0 indicates that a compound is lipophilic and a Log P value less than 0 indicates that a compound is hydrophilic.⁴³ Reported Log P values for diazepam prior to 2008 vary across studies, ranging from 2.82⁴⁴ to 3.67.⁴⁵ Other published values include 3.18⁴⁶ and 2.96.⁴⁷

⁴² EX2063 (Sila-On-2008) at 3.

⁴³ EX2071 (LogP) at 1, 4-5.

⁴⁴ EX2064 (Van Drooge-2004) at 5.

⁴⁵ EX2065 (Monzon-2001) at 3.

⁴⁶ EX2066 (Molero-Monfort-1999) at 2.

⁴⁷ EX2067 (Molero-Monfort-2000) at 4.

Considering this variability, and applying a cutoff of ± 0.5 units relative to the observed extremes, a person of ordinary skill would consider a Log P between 2.32 and 4.17 similar to diazepam.

108. Diazepam is a highly lipophilic molecule, therefore according to the literature published before 2008, liquid formulation strategies (all dosage forms) involved the use of cosolvents, pH adjustment, complexation with cyclodextrins, or the use of solid suspensions and dispersions.⁴⁸

F. BIOAVAILABILITY

109. Bioavailability refers to the proportion of an administered drug that reaches the systemic circulation in its active form and is available to exert its therapeutic effect. For a drug to exert its desired therapeutic effect, it must find its way to the location in the body where that effect can manifest. The most direct way to achieve this is to infuse the drug intravenously into the body's systemic blood circulation. This route of administration provides what is usually defined as absolute or 100% bioavailability. IV infusion is complicated by the need to have medical assistance and training to provide it, plus the time it takes to administer.

⁴⁸ EX2062 (Holvoet-2005) at 1; EX2064 (Van Drooge-2004) at 6-7.

Extravascular routes of administration, such as oral, topical, or intranasal, are far more convenient and often can be used in non-medical settings.

110. When a drug is administered by an extravascular route such as this, not all of it ends up in the subject's bloodstream. Bioavailability is usually expressed as a percentage, where 100% is equivalent to intravenous infusion. For extravascular administration routes, some portion of the drug is lost to various processes. For example, the drug must avoid being degraded by enzymatic or chemical processes, both before and after it enters the systemic circulation. Once in circulation, the body's clearance mechanisms (principally, metabolism in the liver and excretion by the kidneys) will begin removing some portion of it from the body.

111. Importantly, the drug must cross one or more biological membranes. If administered orally, the drug must cross the lumen in the gut. If administered topically, the drug must cross the layered barriers the skin provides. If administered intranasally, the drug must cross the nasal mucosal membrane. Whatever portion of the drug that fails to cross the biological membrane will be excreted, degraded, or washed away and thus unable to cause the desired biological effect.

112. A drug's tendency to cross biological membranes depends on several factors, one of which is its inherent lipophilicity. All else equal, at least up to a point,

a more lipophilic drug will have a greater tendency to cross a biological membrane than a less lipophilic drug.

113. Dr. Donovan states that “it was well-known that benzodiazepines have sufficient lipophilic character to readily cross biologic membranes.”⁴⁹ From that proposition, Dr. Donovan concludes that “benzodiazepines would be considered a logical choice for intranasal administration.”⁵⁰ Thus, under Dr. Donovan’s analysis, the limiting property for benzodiazepines was solubility, and that once sufficient solubility could be achieved, then bioavailability would follow, at least when administered intranasally.

X. OVERVIEW OF THE CHALLENGED PATENT FAMILY

A. SUBJECT MATTER OF THE ’786 PATENT

114. The ’786 Patent claims pharmaceutical solutions of diazepam for nasal administration. Claim 1 is shown below:⁵¹

⁴⁹ EX1062 (Donovan-786 Decl.) ¶65 (citing EX1027 (Wermeling I) at 354).

⁵⁰ EX1062 (Donovan-786 Decl.) ¶65.

⁵¹ EX1001(’786 Patent) at claim 1.

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.

Vitamin E and other tocopherols and tocotrienols provide solubility for diazepam and are highly tolerable, but alone, they were considered too viscous for a nasal spray. Consequently, when Vitamin E had been used as a carrier in the prior art, it was typically as a component of suspensions and emulsions. In contrast, alcohols had low viscosity and good capacity to dissolve diazepam (thus thinning the solution) but were considered undesirable for intranasal use due to their tendency to cause irritation and intolerability.⁵²

⁵² EX2027 (Sonne) at 3:60-67 (discussing viscosity issues with tocopherols and irritation issues with alcohol as a co-solvent).

115. The '786 Patent provides a pharmaceutical solution containing both tocopherols/tocotrienols (e.g., Vitamin E) and alcohols (e.g., ethanol and benzyl alcohol), which maintain diazepam solubility with appropriate viscosity.⁵³ The ethanol and benzyl alcohol surprisingly are used in relatively large amounts without irritating the patient's nasal mucosae.⁵⁴

116. The combination of these components embodied in the challenged claims of the '786 Patent provides a pharmaceutical solution for nasal administration of diazepam that Neurelis provides to patients as Valtoco®, which can be readily provided outside of the hospital setting:

Diazepam may also be administered by another person (e.g. an acquaintance or associate, a family member or a health care professional) to the patient while the patient is in a state of seizure. Thus, one of the advantages of the formulations according to the present invention is the ability to administer them in an acute therapeutic environment to treat the seizure victim, for example, nasally. Among the beneficial therapeutic effects that may be imparted by acute dosing of benzodiazepine anticonvulsants, such as nasal dosing, are: 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

⁵³ EX1001 ('786 Patent) at 35:27-37.

⁵⁴ EX1001 ('786 Patent) at 30:49-54.

seizure. Thus, the diazepam formulations of the invention, and in particular nasal formulations, provide fast onset of therapeutic benefit—in some instances less than about 30 minutes, less than about 15 minutes, less than about 10 minutes, and in some cases less than about 5 minutes. The diazepam formulations of the invention, and in particular nasal formulations, also provide convenient administration of a therapeutically beneficial drug to a patient that does not require intravenous drug administration or rectal drug administration.⁵⁵

117. Valtoco® was approved in January 2020 and was awarded Orphan Drug Exclusivity because it possesses clinical superiority and provides “a major contribution to patient care.”⁵⁶ This superiority has met with industry praise and has supported substantial commercial success.

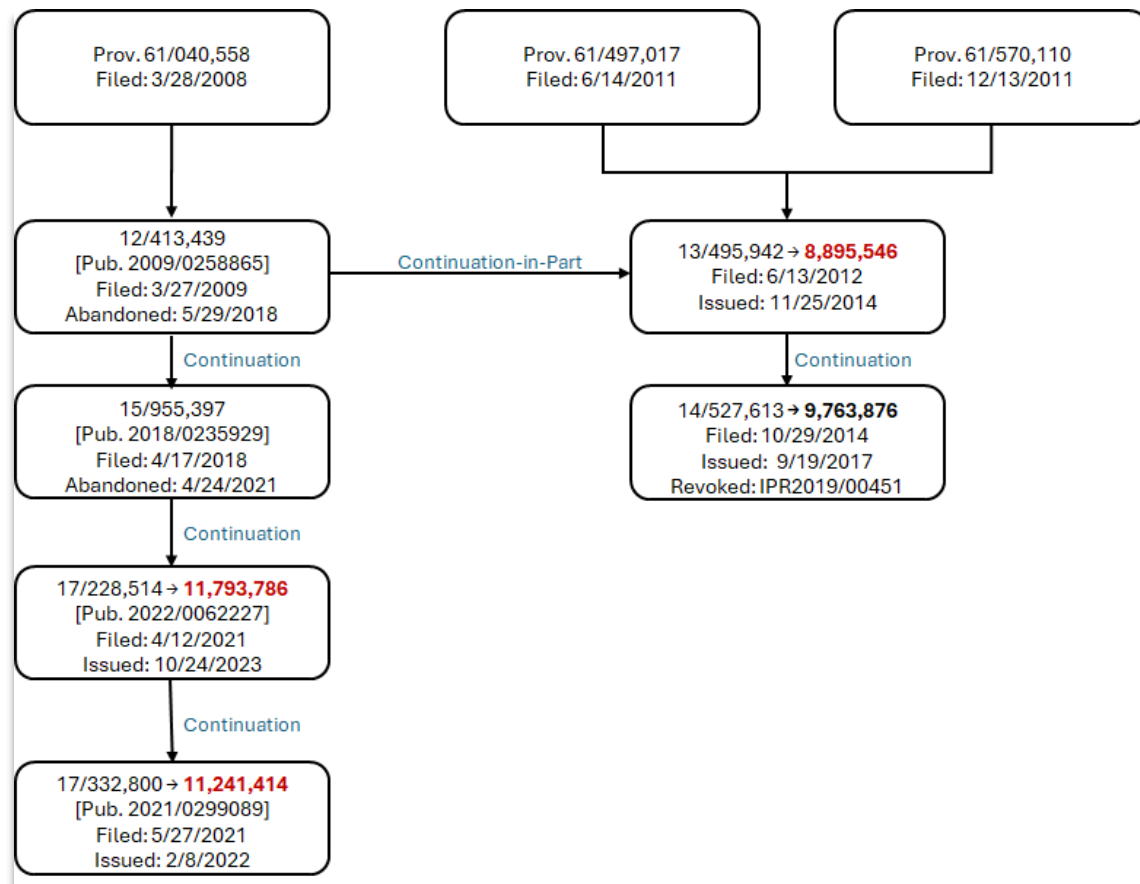
B. FAMILY TREE

118. I understand that the family tree below depicts the challenged patents, and the patent applications to which they claim priority.⁵⁷

⁵⁵ EX1001 ('786 Patent) at 18:64-19:22.

⁵⁶ EX2001 (FDA Clinical Superiority Findings) at 1, 4.

⁵⁷ EX2068 (Neurelis Patent Family Tree).



C. PROSECUTION HISTORY OF THE '786 PATENT

119. I have reviewed the prosecution history of the '786 Patent.

120. The '786 Patent issued from a U.S. application No. 17/228,514, ("the '514 Application,") that claims priority, through an intervening continuation, to the '439 Application, filed March 27, 2009, and to the '558 Provisional, filed March 28, 2008. The other non-provisional applications to which the '786 Patent claims priority are U.S. Application No. 12/413,439 ("the '439 Application") and U.S. application No. 15/955,397, ("the '397 Application").

121. Almost immediately after filing the '514 Application, Neurelis submitted all the art on which this Petition relies (specifically including Meezan and Gwozdz-PCT).⁵⁸ Neurelis also submitted the entire record from the 451 IPR on which the Petition relies.⁵⁹

122. Every claim of the '786 Patent requires *n*-dodecyl- β -D-maltoside.⁶⁰

123. Furthermore, Examiner Milligan also issued a rejection of the then-pending claims during prosecution of the '786 Patent based on Meezan (EX1010), on which this Petition relies, and Sonne (U.S. 6,193,985).⁶¹ Following that rejection, Neurelis's counsel discussed these matters with the Examiner, including discussing the withdrawal of the '876 Patent due to the 451 IPR.⁶² Neurelis overcame the obviousness rejection based in part on Meezan,⁶³ and the Examiner withdrew it, allowing the claims.⁶⁴

⁵⁸ EX1002 ('786 FH) at 487-515.

⁵⁹ EX1002 ('786 FH) at 374-94.

⁶⁰ EX1001 ('786 Patent) at 36-37.

⁶¹ EX1002 ('786 FH) at 66.

⁶² EX1002 ('786 FH) at 59.

⁶³ EX1002 ('786 FH) at 43-46.

⁶⁴ EX1002 ('786 FH) at 20-22.

D. PRIORITY DATE OF THE CHALLENGED CLAIMS

124. I have been asked to review the '786 Patent, and its earlier filed parent applications,⁶⁵ from the perspective of a skilled artisan and analyse whether each of the claim limitations of the '786 Patent is disclosed (either expressly or inherently) in those earlier filed parent applications.

1. Summary of Non-Provisional Applications

125. As shown in the Family Tree above,⁶⁶ the '786 Patent traces priority to two non-provisional applications: 15/955,397 (published as 2018/0235929); and 12/413,439 (published as 2009/0258865). The following redline comparisons were made:

Starting Document	Ending Document	Redline Comparison
U.S. Patent App. 15/955,397, as published at 2018/0235929 (EX1005)	U.S. Patent App. 17/228,514 (issued as the '786 patent), as published at 2022/0062227	EX2048
U.S. Patent App. 12/413/439, as published at 2009/0258865 (EX1039)	U.S. Patent App. 15/955,397, as published at 2018/0235929 (EX1005)	EX2060

⁶⁵ EX2068 (Neurelis Patent Family Tree).

⁶⁶ EX2068 (Neurelis Patent Family Tree).

126. After reviewing each of the above comparisons and figures across the non-provisional applications, I have determined that their specifications are substantively identical. Accordingly, in analysing the support for the claim limitations, I will primarily cite to App. No. 12/413,439 (published at 2009/0258865), which is the publication of the first non-provisional, but my analysis applies equally to App. No. 15/955,397 (published at 2018/0235929).

2. Comparison of Challenged Claims of '786 Patent to Earlier Applications

127. Dr. Donovan does not contend that any of the non-provisional parent applications fail to provide written description support for the challenged claims. Rather, she asserts a lack of support only in the 61/040,558 Provisional. For example, Dr. Donovan states that “the first mention, disclosure, and written support of alkyl glycosides, specifically n-dodecyl beta-D-maltoside is in the '439 Application, filed on March 27, 2009. *See, e.g., '439 Application, Ex. 1039, ¶¶ 018, 043, 047, 056.*”⁶⁷ I have been asked to independently analyse the disclosures of the 61/040,558 Provisional and the non-provisional applications. While I disagree with Dr. Donovan concerning the 61/040,558 Provisional, I do agree with her that the

⁶⁷ EX1062 (Donovan-786 Decl.) ¶46.

'439 and other non-provisional applications disclose the subject matter of each of the challenged claims.

a. Independent Claim 1

128. I have concluded that Claim 1 of the '786 Patent is supported in each of the parent applications, including the 61/040,558 Provisional.

i. Claim 1 (Preamble): “A pharmaceutical solution for nasal administration consisting of:”

129. The non-provisional applications disclose this preamble. For example, they recite:

“In some embodiments, the pharmaceutical composition for nasal administration comprises”⁶⁸

130. The 61/040,558 Provisional also discloses this preamble. For example, the Provisional states:

“A pharmaceutical composition for nasal administration comprising”⁶⁹

“In some embodiments, the pharmaceutical composition for nasal administration comprises”⁷⁰

⁶⁸ EX1039 ('439 Application) ¶[010]; *see also* EX1005 ('397 Application) ¶[0010]; EX1001 ('786 Patent) at 2:10-11.

⁶⁹ EX1008 ('558 Application) at claim 1.

⁷⁰ EX1008 ('558 Application) ¶[009].

“A pharmaceutical composition comprising diazepam is prepared. It is formulated as a solution to be delivered via a nasal delivery device.”⁷¹

ii. Claim 1(a): “a therapeutically effective amount of diazepam or a pharmaceutically acceptable salt thereof;”

131. The non-provisional applications disclose this element. For example, they recite:

“In some embodiments, the benzodiazepine drug is diazepam, or a pharmaceutically-acceptable salt thereof.”⁷²

132. The 61/040,558 Provisional also discloses this element. For example, the Provisional states:

“a benzodiazepine drug”⁷³

“In some embodiments, the benzodiazepine drug is diazepam, or a pharmaceutically-acceptable salt thereof”⁷⁴

iii. Claim 1(b): “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,

⁷¹ EX1008 ('558 Application) ¶[173].

⁷² EX1039 ('439 Application) ¶[011]; *see also* EX1005 ('397 Application) ¶[0011]; EX1001 ('786 Patent) at 2:39-41.

⁷³ EX1008 ('558 Application) at claim 1(b).

⁷⁴ EX1008 ('558 Application) ¶[010].

tocophersolan, any isomers thereof, any esters thereof, and any combinations thereof, in an amount from 30% to 95% (w/w);”

133. The non-provisional applications disclose this element. For example, they recite:

“one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w)”⁷⁵

“In some embodiments, 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, any isomers thereof, any esters thereof, any analogs or derivatives thereof, and any combinations thereof”⁷⁶

134. The 61/040,558 Provisional also discloses this element. For example, the Provisional states:

“one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w)”⁷⁷

“In some embodiments, the one or more natural or synthetic tocopherols or tocotrienols are selected from the group

⁷⁵ EX1039 ('439 Application) ¶[010]; *see also* EX1005 ('397 Application) ¶[0010]; EX1001 ('786 Patent) at 2:12-14.

⁷⁶ EX1039 ('439 Application) ¶[012]; *see also* EX1005 ('397 Application) ¶[0012]; EX1001 ('786 Patent) at 2:49-55.

⁷⁷ EX1008 ('558 Application) ¶[009], claim 1.

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, any analogs or derivatives thereof, and any combinations thereof”⁷⁸

“The pharmaceutical composition 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, any isomers thereof, any esters thereof, any analogs or derivatives thereof, and any combinations thereof”⁷⁹

iv. Claim 1(c): “one or more alcohols in an amount from 10% to 70% (w/w), wherein the one or more alcohols comprises benzyl alcohol;”

135. The non-provisional applications disclose this element. For example, they recite:

“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)”⁸⁰

“In some embodiments, one or more alcohols are selected from the group consisting of: ethanol, propyl alcohol, butyl alcohol,

⁷⁸ EX1008 ('558 Application) ¶[011].

⁷⁹ EX1008 ('558 Application) at claim 7.

⁸⁰ EX1039 ('439 Application) ¶[010]; *see also* EX1005 ('397 Application) ¶[0013], ¶[0037]; EX1001 ('786 Patent) at 2:14-16.

pentanol, benzyl alcohol, any isomers thereof, or any combinations thereof”⁸¹

“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.”⁸²

136. The 61/040,558 Provisional also discloses this element. For example, the Provisional states:

“one or more alcohols or glycols, or any combinations thereof, in an amount from about 5% to about 70% (w/w)”⁸³

“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.”⁸⁴

“In some embodiments, the one or more alcohols are selected from the group consisting of: ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, any isomers thereof, and any combinations thereof”⁸⁵

⁸¹ EX1039 ('439 Application) ¶[013]; *see also* EX1005 ('397 Application) ¶[0013]; EX1001 ('786 Patent) at 2:63-66, 6:66-7:2.

⁸² EX1039 ('439 Application) ¶[0134]; *see also* EX1005 ('397 Application) ¶[0134]; EX1001 ('786 Patent) at 30:55-58.

⁸³ EX1008 ('558 Application) ¶[009], claim 2.

⁸⁴ EX1008 ('558 Application) ¶[120].

⁸⁵ EX1008 ('558 Application) ¶[020].

v. Claim 1(d): “and n-dodecyl beta-D-maltoside”

137. The non-provisional applications disclose this element. For example, they recite:

“In some embodiments, the drug delivery system of the invention by advantageously comprise an absorption enhancer. The term ‘enhancer’, means any material which acts to increase absorption across the mucosa and/or increase bioavailability....in some embodiments, enhancing agents that are appropriate include chelating agents (EGTA, EDTA, alginates), surface active agents (especially non-ionic materials), acyl glycerols, fatty acids and salts, tyloxapol and biological detergents listed in the SIGMA Catalog, 1988, page 316-321 (which is incorporated herein by reference).”⁸⁶

“Exemplary alkyl glycosides that may be employed include octyl-, nonyl-, decyl-, undecyl-, dodecyl, tridecyl, tetradecyl, pentadecyl, octadecyl α - or β -D-maltoside, -glucoside or sucroside. In some embodiments, the preferred glycosides include maltose, sucrose or glucose linked by glycosidic linkage to an alkyl chain of 9, 10, 12, 14, 16, 18 or 20 carbon atoms”⁸⁷

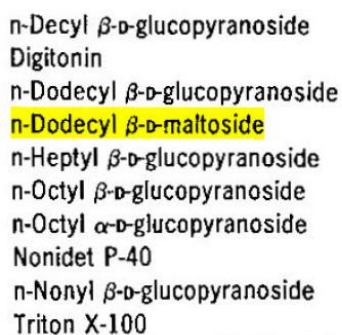
“Alkyl glycosides that are particularly considered useful in embodiments of the invention include those marketed under the name Intravail® by Aegis Therapeutics, LLC, San Diego, CA”⁸⁸

⁸⁶ EX1039 (’439 Application) ¶¶[0172]-[0174] (emphasis added); *see also* EX1005 (’397 Application) ¶[0172], ¶[0174] (emphasis added); EX1001 (’786 Patent) at 37:16-47 (emphasis added).

⁸⁷ *See, e.g.*, EX1039 (’439 Application) ¶[056], ¶[0136]; EX1005 (’397 Application) ¶[056], ¶[0130]; EX1001 (’786 Patent) at 13:43-49, 31:17-23.

⁸⁸ EX1039 (’439 Application) ¶[0136]; EX1005 (’397 Application) ¶[0136]; EX1001 (’786 Patent) at 31:28-31; *see also* EX2061 (Ward) at 4.

The Sigma Catalogue discloses this element:⁸⁹



n-Decyl β-D-glucopyranoside
Digitonin
n-Dodecyl β-D-glucopyranoside
n-Dodecyl β-D-maltoside
n-Heptyl β-D-glucopyranoside
n-Octyl β-D-glucopyranoside
n-Octyl α-D-glucopyranoside
Nonidet P-40
n-Nonyl β-D-glucopyranoside
Triton X-100

138. The 61/040,558 Provisional also discloses this element. For example, the Provisional states:

“The composition of one of claims 1-16, further comprising at least one additional ingredient selected from the group consisting of . . . enhancers”⁹⁰

“The method of claim 18, wherein the composition comprises at least one additional ingredient selected from the group consisting of . . . enhancers”⁹¹

“In some embodiments, the drug delivery system of the invention by advantageously comprise an absorption enhancer. The term ‘enhancer’, means any material which acts to increase absorption across the mucosa and/or increase bioavailability....in some embodiments, enhancing agents that are appropriate include chelating agents (EGTA, EDTA, alginates), surface active agents (especially non-ionic materials), acyl glycerols, fatty acids and

⁸⁹ EX1026 (Sigma Catalog) at 19 (page 316 of the original document) (annotation added).

⁹⁰ EX1008 (’558 Application) at claim 17.

⁹¹ EX1008 (’558 Application) at claim 35.

salts, tyloxapol and biological detergents listed in the SIGMA Catalog, 1988, page 316-321 (which is incorporated herein by reference).”⁹²

b. Claim 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).”

139. The non-provisional applications disclose this claim. For example, they recite:

“In some embodiments, the benzodiazepine drug is present in a carrier system in a concentration from about 10 mg/mL to about 250 mg/mL.”⁹³

“In some embodiments, the benzodiazepine drug is selected from the group consisting of: alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepam, demoxazepam, diazepam, flumazenil, flurazepam, halazepam, midazolam, nordazepam, medazepam, nitrazepam, oxazepam, medazepam, lorazepam, prazepam, quazepam, triazolam, temazepam, loprazolam, any pharmaceutically-acceptable salts thereof, and any combinations thereof.”⁹⁴

⁹² EX1008 (’558 Application) ¶[150], ¶[152] (emphasis added).

⁹³ EX1039 (’439 Application) ¶[014]; *see also* EX1005 (’397 Application) ¶[0014]; EX1001 (’786 Patent) at 4:45-47.

⁹⁴ EX1039 (’439 Application) ¶[011] (emphasis added); *see also* EX1005 (’397 Application) ¶[0011] (emphasis added); EX1001 (’786 Patent) at 4:4-11 (emphasis added).

The claimed concentration “from 1 to 20% (w/v)” is approximately equivalent to 10 mg/mL to 200 mg/mL.⁹⁵

140. The 61/040,558 Provisional also discloses this claim. For example, the Provisional states:

“The pharmaceutical composition of claim 1, wherein the benzodiazepine drug is present in the pharmaceutical composition in a concentration from about 10 mg/mL to about 250 mg/mL.”⁹⁶

“In some embodiments, the benzodiazepine drug is present in a carrier system in a concentration from about 10 mg/mL to about 250 mg/mL.”⁹⁷

“In some embodiments, the benzodiazepine drug is selected from the group consisting of: alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepam, demoxazepam, diazepam, flumazenil, flurazepam, halazepam, midazolam, nordazepam, medazepam, nitrazepam, oxazepam, medazepam, lorazepam, prazepam, quazepam, triazolam, temazepam, loprazolam, any pharmaceutically-acceptable salts thereof, and any combinations thereof.”⁹⁸

⁹⁵ See, e.g., EX1062 (Donovan-786 Decl.) ¶159.

⁹⁶ EX1008 ('558 Application) at claim 11.

⁹⁷ EX1008 ('558 Application) ¶[013].

⁹⁸ EX1008 ('558 Application) ¶[010]

The claimed concentration “from 1 to 20% (w/v)” is equivalent to 10 mg/mL to 200 mg/mL.⁹⁹

- c. Claim 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.”**

141. The non-provisional applications disclose this claim. For example, they recite:

“Other compositions disclose a composition comprising one or more benzodiazepine drugs or pharmaceutically-acceptable salts thereof in a concentration of about 10 mg/mL up to about 250 mg/mL.”¹⁰⁰

“In some embodiments, the benzodiazepine drug is selected from the group consisting of: alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepam, demoxazepam, diazepam, flumazenil, flurazepam, halazepam, midazolam, nordazepam, medazepam, nitrazepam, oxazepam, medazepam, lorazepam, prazepam, quazepam, triazolam, temazepam, loprazolam, any pharmaceutically-acceptable salts thereof, and any combinations thereof.”¹⁰¹

⁹⁹ See, e.g., EX1062 (Donovan-786 Decl.) ¶159.

¹⁰⁰ EX1039 (’439 Application) ¶[0160]; see also EX1005 (’397 Application) ¶[0160]; EX1001 (’786 Patent) at 34:61-64.

¹⁰¹ EX1039 (’439 Application) ¶[011] (emphasis added); see also EX1005 (’397 Application) ¶[0011] (emphasis added); EX1001 (’786 Patent) at 4:4-11 (emphasis added).

142. The 61/040,558 Provisional also discloses this claim. For example, the Provisional states:

“The pharmaceutical composition of claim 1, wherein the benzodiazepine drug is present in the pharmaceutical composition in a concentration from about 10mg/ml to about 250 mg/mL”¹⁰²

“Other compositions disclose a composition comprising one or more benzodiazepine drugs or pharmaceutically-acceptable salts thereof in a concentration of about 10 mg/mL up to about 250 mg/mL.”¹⁰³

d. Claim 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.”

143. The non-provisional applications disclose this claim. For example, they recite:

“In some embodiments, the benzodiazepine is present in a carrier system in a concentration from about 20 mg/mL to about 50 mg/mL”¹⁰⁴

¹⁰² EX1008 ('558 Application) at claim 12.

¹⁰³ EX1008 ('558 Application) ¶[140].

¹⁰⁴ EX1039 ('439 Application) ¶[014], ¶[038]; *see also* EX1005 ('397 Application) ¶[0014], ¶[0038]; EX1001 ('786 Patent) at 3:13-16.

144. The 61/040,558 Provisional also discloses this claim. For example, the Provisional states:

“The pharmaceutical composition of claim 11, wherein the benzodiazepine is present in the pharmaceutical composition in a concentration from about 20 mg/mL to about 50 mg/mL”¹⁰⁵

“In some embodiments, the benzodiazepine is present in a carrier system in a concentration from about 20 mg/mL to about 50 mg/mL”¹⁰⁶

“In some embodiments, the benzodiazepine drug is selected from the group consisting of: alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepam, demoxazepam, diazepam, flumazenil, flurazepam, halazepam, midazolam, nordazepam, medazepam, nitrazepam, oxazepam, medazepam, lorazepam, prazepam, quazepam, triazolam, temazepam, loprazolam, any pharmaceutically-acceptable salts thereof, and any combinations thereof.”¹⁰⁷

e. Claim 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).”

145. The non-provisional applications disclose this claim. For example, they recite:

¹⁰⁵ EX1008 ('558 Application) at claim 12.

¹⁰⁶ EX1008 ('558 Application) ¶[013].

¹⁰⁷ EX1008 ('558 Application) ¶[010].

“In some embodiments, the carrier system comprises one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 45% to about 85% (w/w)”¹⁰⁸

“The pharmaceutical composition of claim 1, wherein the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, is in an amount from about 45% to about 85% (w/w)”¹⁰⁹

146. The 61/040,558 Provisional also discloses this claim. For example, the

Provisional states:

“The pharmaceutical composition of claim 1, wherein the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 45% to about 85% (w/w)”¹¹⁰

“In some embodiments, the carrier system comprises one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 45% to about 85% (w/w)”¹¹¹

¹⁰⁸ EX1039 ('439 Application) ¶[015]; *see also* EX1005 ('397 Application) ¶[0015]; EX1001 ('786 Patent) at 3:17-20.

¹⁰⁹ EX1039 ('439 Application) at claim 13; *see also* EX1005 ('397 Application) at claim 13.

¹¹⁰ EX1008 ('558 Application) at claim 13.

¹¹¹ EX1008 ('558 Application) ¶[014].

- f. Claim 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).”**

147. The non-provisional applications disclose this claim. For example, they recite:

“In some embodiments, the carrier system 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)”¹¹²

“The pharmaceutical composition of claim 13, wherein the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, is in an amount from about 60% to about 75% (w/w)”¹¹³

148. The 61/040,558 Provisional also discloses this claim. For example, the Provisional states:

“The pharmaceutical composition of claim 13, wherein the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 60% to about 75% (w/w)”¹¹⁴

¹¹² EX1039 ('439 Application) ¶[015]; *see also* EX1005 ('397 Application) ¶[0015]; EX1001 ('786 Patent) at 3:20-23.

¹¹³ EX1039 ('439 Application) at claim 14; *see also* EX1005 ('397 Application) at claim 14.

¹¹⁴ EX1008 ('558 Application) at claim 14.

“In some embodiments, the carrier system 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)”¹¹⁵

g. Claim 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.”

149. The non-provisional applications disclose this claim. For example, they recite:

“In some embodiments, the carrier system comprises one or more alcohols or glycols, or any combinations thereof”¹¹⁶

“In some embodiments, the one or more alcohols are selected from the group consisting of: ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, any isomers thereof, and any combinations thereof”¹¹⁷

“Lower alkyl alcohols are those with six or fewer carbon atoms. Thus, any of ethanol, propyl alcohol, butyl alcohol, pentanol,

¹¹⁵ EX1008 ('558 Application) ¶[014].

¹¹⁶ EX1039 ('439 Application) ¶[016]; *see also* EX1005 ('397 Application) ¶[0016]; EX1001 ('786 Patent) at 3:29-32.

¹¹⁷ EX1039 ('439 Application) ¶[022]; *see also* EX1005 ('397 Application) ¶[0022]; EX1001 ('786 Patent) at 4:33-36.

benzyl alcohol, any isomers thereof, or any combinations thereof can be used.”¹¹⁸

150. The 61/040,558 Provisional also discloses this claim. For example, the Provisional states:

“The pharmaceutical composition of claim 15, wherein the one or more alcohols or glycols, or any combinations thereof, is in an amount from about 15% to about 55% (w/w)”¹¹⁹

“In some embodiments, one or more alcohols are selected from the group consisting of: ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, any isomers thereof, or any combinations thereof. In some embodiments, the one or more glycols are selected from the group consisting of: ethylene glycol, propylene glycol, butylene glycol, pentylene glycol, any isomers thereof, and any combinations thereof.”¹²⁰

“In some embodiments, the one or more alcohols are selected from the group consisting of: ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, any isomers thereof, and any combinations thereof”¹²¹

“Lower alkyl alcohols are those with six or fewer carbon atoms. Thus, any of ethanol, propyl alcohol, butyl alcohol, pentanol,

¹¹⁸ EX1039 (’439 Application) ¶[0134]; *see also* EX1005 (’397 Application) ¶[0134]; EX1001 (’786 Patent) at 30:55-58.

¹¹⁹ EX1008 (’558 Application) at claim 15.

¹²⁰ EX1008 (’558 Application) ¶[012].

¹²¹ EX1008 (’558 Application) ¶[020].

benzyl alcohol, any isomers thereof, or any combinations thereof can be used.”¹²²

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

151. The non-provisional applications disclose this claim. For example, they recite:

“In some embodiments, the carrier system comprises one or more alcohols or glycols, or any combinations thereof, in an amount from about 15% to about 55% (w/w)”¹²³

“In some embodiments, the one or more alcohols are selected from the group consisting of: ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, any isomers thereof, and any combinations thereof”¹²⁴

“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.”¹²⁵

¹²² EX1008 (’558 Application) ¶[120].

¹²³ EX1039 (’439 Application) ¶[016]; *see also* EX1005 (’397 Application) ¶[0016]; EX1001 (’786 Patent) at 3:29-32.

¹²⁴ EX1039 (’439 Application) ¶[022]; *see also* EX1005 (’397 Application) ¶[0022]; EX1001 (’786 Patent) at 4:33-36.

¹²⁵ EX1039 (’439 Application) ¶[0134]; *see also* EX1005 (’397 Application) ¶[0134]; EX1001 (’786 Patent) at 30:55-58.

152. The 61/040,558 Provisional also discloses this claim. For example, the Provisional states:

“The pharmaceutical composition of claim 15, wherein the one or more alcohols or glycols, or any combinations thereof, is in an amount from about 15% to about 55% (w/w)”¹²⁶

“In some embodiments, the carrier system comprises one or more alcohols or glycols, or any combinations thereof, in an amount from about 15% to about 55% (w/w)”¹²⁷

“In some embodiments, the one or more alcohols are selected from the group consisting of: ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, any isomers thereof, and any combinations thereof”¹²⁸

“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.”¹²⁹

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

153. The non-provisional applications disclose this claim. For example, they recite:

¹²⁶ EX1008 ('558 Application) at claim 15.

¹²⁷ EX1008 ('558 Application) ¶[015].

¹²⁸ EX1008 ('558 Application) ¶[020].

¹²⁹ EX1008 ('558 Application) ¶[120].

“In some embodiments, the carrier system comprises one or more alcohols or glycols, or any combinations thereof, in an amount from about 25% to about 40% (w/w)”¹³⁰

“In some embodiments, the one or more alcohols are selected from the group consisting of: ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, any isomers thereof, and any combinations thereof”¹³¹

“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.”¹³²

154. The 61/040,558 Provisional also discloses this claim. For example, the Provisional states:

“The pharmaceutical composition of claim 15, wherein the one or more alcohols or glycols, or any combinations thereof, is in an amount from about 25% to about 40% (w/w)”¹³³

¹³⁰ EX1039 ('439 Application) ¶[016]; *see also* EX1005 ('397 Application) ¶[0016]; EX1001 ('786 Patent) at 3:32-35.

¹³¹ EX1039 ('439 Application) ¶[022]; *see also* EX1005 ('397 Application) ¶[0022]; EX1001 ('786 Patent) at 4:33-36.

¹³² EX1039 ('439 Application) ¶[0134]; *see also* EX1005 ('397 Application) ¶[0134]; EX1001 ('786 Patent) at 30:55-58.

¹³³ EX1008 ('558 Application) at claim 16.

“In some embodiments, the carrier system comprises one or more alcohols or glycols, or any combinations thereof, in an amount from about 25% to about 40% (w/w)”¹³⁴

“In some embodiments, the one or more alcohols are selected from the group consisting of: ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, any isomers thereof, and any combinations thereof”¹³⁵

“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.”¹³⁶

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

155. The non-provisional applications disclose this claim. For example, they recite:

“In some embodiments, the pharmaceutical composition for nasal administration comprises”¹³⁷

¹³⁴ EX1008 ('558 Application) ¶[015].

¹³⁵ EX1008 ('558 Application) ¶[020].

¹³⁶ EX1008 ('558 Application) ¶[120].

¹³⁷ EX1039 ('439 Application) ¶[010]; *see also* EX1005 ('397 Application) ¶[0010]; EX1001 ('786 Patent) at 2:10-11.

“In some embodiments, the benzodiazepine drug is diazepam, or a pharmaceutically-acceptable salt thereof.”¹³⁸

“one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w)”¹³⁹

“In some embodiments, a synthetic tocopherol can include Vitamin E TPGS (Vitamin E polyethylene glycol succinate)”¹⁴⁰

“In some embodiments, the carrier system comprises one or more alcohols or glycols, or any combinations thereof”¹⁴¹

“In some embodiments, one or more alcohols are selected from the group consisting of: ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, any isomers thereof, or any combinations thereof”¹⁴²

“Lower alkyl alcohols are those with six or fewer carbon atoms. Thus, any of ethanol, propyl alcohol, butyl alcohol, pentanol,

¹³⁸ EX1039 ('439 Application) ¶[011]; *see also* EX1005 ('397 Application) ¶[0011]; EX1001 ('786 Patent) at 2:39-41.

¹³⁹ EX1039 ('439 Application) ¶[010]; *see also* EX1005 ('397 Application) ¶[0010]; EX1001 ('786 Patent) at 2:12-14.

¹⁴⁰ EX1039 ('439 Application) ¶[012]; *see also* EX1005 ('397 Application) ¶[0012]; EX1001 ('786 Patent) at 2:55-57.

¹⁴¹ EX1039 ('439 Application) ¶[016]; *see also* EX1005 ('397 Application) ¶[0016]; EX1001 ('786 Patent) at 3:29-32.

¹⁴² EX1039 ('439 Application) ¶[013]; *see also* EX1005 ('397 Application) ¶[0013]; EX1001 ('786 Patent) at 2:63-66, 6:66-7:2.

benzyl alcohol, any isomers thereof, or any combinations thereof can be used.”¹⁴³

“In some embodiments, the drug delivery system of the invention by advantageously comprise an absorption enhancer. The term ‘enhancer’, means any material which acts to increase absorption across the mucosa and/or increase bioavailability....in some embodiments, enhancing agents that are appropriate include chelating agents (EGTA, EDTA, alginates), surface active agents (especially non-ionic materials), acyl glycerols, fatty acids and salts, tyloxapol and biological detergents listed in the SIGMA Catalog, 1988, page 316-321 (which is incorporated herein by reference).”¹⁴⁴

156. The 61/040,558 Provisional also discloses this claim. For example, the Provisional states:

“The composition of one of claims 1-16, further comprising 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.”¹⁴⁵

“In some embodiments, the pharmaceutical composition for nasal administration comprises”¹⁴⁶

¹⁴³ EX1039 (’439 Application) ¶[0134]; *see also* EX1005 (’397 Application) ¶[0134]; EX1001 (’786 Patent) at 30:55-58.

¹⁴⁴ EX1039 (’439 Application) ¶¶[0172]-[0174] (emphasis added); *see also* EX1005 (’397 Application) ¶[0172], ¶[0174] (emphasis added); EX1001 (’786 Patent) at 37:16-47 (emphasis added).

¹⁴⁵ EX1008 (’558 Application) at claim 17.

¹⁴⁶ EX1008 (’558 Application) ¶[009].

“In some embodiments, the benzodiazepine drug is selected from the group consisting of: alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepam, demoxazepam, diazepam, flumazenil, flurazepam, halazepam, midazolam, nordazepam, medazepam, nitrazepam, oxazepam, medazepam, lorazepam, prazepam, quazepam, triazolam, temazepam, loprazolam, any pharmaceutically-acceptable salts thereof, and any combinations thereof.”¹⁴⁷

“In some embodiments, the carrier system comprises one or more alcohols or glycols, or any combinations thereof”¹⁴⁸

“In some embodiments, the one or more alcohols are selected from the group consisting of: ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, any isomers thereof, and any combinations thereof”¹⁴⁹

“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.”¹⁵⁰

“In some embodiments, the drug delivery system of the invention by advantageously comprise an absorption enhancer. The term ‘enhancer’, means any material which acts to increase absorption across the mucosa and/or increase bioavailability....in some embodiments, enhancing agents that are appropriate include chelating agents (EGTA, EDTA, alginates), surface active agents (especially non-ionic materials), acyl glycerols, fatty acids and salts, tyloxapol and biological detergents listed in the SIGMA

¹⁴⁷ EX1008 (’558 Application) ¶[010] (emphasis added).

¹⁴⁸ EX1008 (’558 Application) ¶[015].

¹⁴⁹ EX1008 (’558 Application) ¶[020].

¹⁵⁰ EX1008 (’558 Application) ¶[120].

Catalog, 1988, page 316-321 (which is incorporated herein by reference).”¹⁵¹

“A pharmaceutical composition comprising diazepam is prepared. It is formulated as a solution to be delivered via a nasal delivery device.”¹⁵²

k. Independent Claim 11

157. I have concluded that Claim 11 of the '786 Patent is supported in each of the parent applications, including the 61/040,558 Provisional.

i. Claim 11(preamble): “A pharmaceutical solution for nasal administration consisting of:”

158. The preamble of claim 11 is identical to the preamble of claim 1. My analysis for the preamble of claim 1 applies here as well.

ii. Claim 11(a): “a therapeutically effective amount of diazepam or a pharmaceutically acceptable salt thereof”

159. Claim element 11(a) is identical to claim element 1(a). My analysis for claim element 1(a) applies here as well.

iii. Claim 11(b): “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,

¹⁵¹ EX1008 ('558 Application) ¶[150], ¶[152] (emphasis added).

¹⁵² EX1008 ('558 Application) ¶¶[173-174].

any esters thereof, and any combinations thereof, in an amount from 30% to 95% (w/w);”

160. The non-provisional applications disclose this element. For example, they recite:

“one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w)”¹⁵³

“In some embodiments, 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, any isomers thereof, any esters thereof, any analogs or derivatives thereof, and any combinations thereof.”¹⁵⁴

161. The 61/040,558 Provisional also discloses this element. For example, the Provisional states:

“one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w)”¹⁵⁵

“In some embodiments, the one or more natural or synthetic tocopherols or tocotrienols are selected from the group consisting of: α -tocopherol, β -tocopherol, γ -tocopherol, δ -

¹⁵³ EX1039 ('439 Application) ¶[010]; *see also* EX1005 ('397 Application) ¶[0010]; EX1001 ('786 Patent) at 2:12-14.

¹⁵⁴ EX1039 ('439 Application) ¶[0012]; *see also* EX1005 ('397 Application) ¶[0012]; EX1001 ('786 Patent) at 2:49-55.

¹⁵⁵ EX1008 ('558 Application) ¶[009], claim 1.

tocopherol, α -tocotrienol, β -tocotrienol, γ -tocotrienol, δ -tocotrienol, tocophersolan, any isomers thereof, any esters thereof, any analogs or derivatives thereof, and any combinations thereof.”¹⁵⁶

iv. Claim 11(c): “one of more alcohols in an amount from 10% to 70% (w/w)), wherein the one or more alcohols comprises benzyl alcohol;”

162. Claim element 11(c) is identical to claim element 1(c). My analysis for claim element 1(c) applies here as well.

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

163. Claim element 11(d) is identical to claim element 1(d). My analysis for claim element 1(d) applies here as well.

i. Claim 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).”

164. The limitations added by claim 12 to independent claim 11 are identical to the limitations added by claim 2 to claim 1. My analysis for claims 2 and 11 apply here as well.

¹⁵⁶ EX1008 (’558 Application) ¶[011].

- m. Claim 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.”**

165. The limitations added by claim 13 to independent claim 11 are identical to the limitations added by claim 3 to claim 1. My analysis for claims 3 and 11 apply here as well.

- n. Claim 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.”**

166. The limitations added by claim 14 to independent claim 11 are identical to the limitations added by claim 4 to claim 1. My analysis for claims 4 and 11 apply here as well.

- o. Claim 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).”**

167. The non-provisional applications disclose this claim. For example, they recite:

“In some embodiments, the carrier system comprises one or more natural or synthetic tocopherols or tocotrienols, or any

combinations thereof, in an amount from about 45% to about 85% (w/w)”¹⁵⁷

“The pharmaceutical composition of claim 1, wherein the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, is in an amount from about 45% to about 85% (w/w)”¹⁵⁸

168. The 61/040,558 Provisional also discloses this claim. For example, the Provisional states:

“The pharmaceutical composition of claim 1, wherein the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 45% to about 85% (w/w)”¹⁵⁹

“In some embodiments, the carrier system comprises one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 45% to about 85% (w/w)”¹⁶⁰

¹⁵⁷ EX1039 ('439 Application) ¶[015]; *see also* EX1005 ('397 Application) ¶[0015]; EX1001 ('786 Patent) at 3:17-20.

¹⁵⁸ EX1039 ('439 Application) at claim 13; *see also* EX1005 ('397 Application) at claim 13.

¹⁵⁹ EX1008 ('558 Application) at claim 13.

¹⁶⁰ EX1008 ('558 Application) ¶[014].

- p. 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).”**

169. The non-provisional applications disclose this claim. For example, they recite:

“In some embodiments, the carrier system 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)”¹⁶¹

“The pharmaceutical composition of claim 13, wherein the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, is in an amount from about 60% to about 75% (w/w)”¹⁶²

“In some embodiments, 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, any isomers thereof, any esters thereof, any analogs or derivatives thereof, and any combinations thereof”¹⁶³

¹⁶¹ EX1039 ('439 Application) ¶[015]; *see also* EX1005 ('397 Application) ¶[0015]; EX1001 ('786 Patent) at 3:20-23.

¹⁶² EX1039 ('439 Application) at claim 14; *see also* EX1005 ('397 Application) at claim 14.

¹⁶³ EX1039 ('439 Application) ¶[012] (emphasis added); *see also* EX1005 ('397 Application) ¶[0012] (emphasis added); EX1001 ('786 Patent) at 2:49-55 (emphasis added).

170. The 61/040,558 Provisional also discloses this claim. For example, the Provisional states:

“The pharmaceutical composition of claim 13, wherein the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 60% to about 75% (w/w)”¹⁶⁴

“In some embodiments, the carrier system 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)”¹⁶⁵

“In some embodiments, 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, any isomers thereof, any esters thereof, any analogs or derivatives thereof, and any combinations thereof”¹⁶⁶

¹⁶⁴ EX1008 ('558 Application) at claim 14.

¹⁶⁵ EX1008 ('558 Application) ¶[014].

¹⁶⁶ EX1008 ('558 Application) ¶[011] (emphasis added).

- q. Claim 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.”**

171. The limitations added by claim 17 to independent claim 11 are identical to the limitations added by claim 7 to claim 1. My analysis for claims 7 and 11 apply here as well.

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

172. The limitations added by claim 18 to independent claim 11 are identical to the limitations added by claim 8 to claim 1. My analysis for claims 3 and 11 apply here as well.

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

173. The limitations added by claim 19 to independent claim 11 are identical to the limitations added by claim 9 to claim 1. My analysis for claims 9 and 11 apply here as well.

- t. **Claim 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.”**

174. The non-provisional applications disclose this claim. For example, they recite:

“Some embodiments comprise administering to one or more mucosal membranes of a patient a therapeutically effective amount of one or more benzodiazepine drugs, or pharmaceutically-acceptable salts thereof. Some embodiments of the composition disclose a composition comprising one or more benzodiazepine drugs or pharmaceutically-acceptable salts thereof in a concentration up to about 600 mg/mL.”¹⁶⁷

“Some embodiments of the invention provide a method of administering the benzodiazepine drug composition to a patient. The preferred embodiment comprises use of diazepam. Some embodiments of the method disclose a dosage level of diazepam of about 1.0 mg to about 20.0 mg until achievement of the desired result. . . . Some embodiments disclose a dosage level of about 5.0 mg to about 10.0 mg until the desired result is achieved.”¹⁶⁸

175. The 61/040,558 Provisional also discloses this claim. For example, the Provisional states:

¹⁶⁷ EX1039 (’439 Application) ¶[0160]; *see also* EX1005 (’397 Application) ¶[0160]; EX1001 (’786 Patent) at 34:54-61.

¹⁶⁸ EX1039 (’439 Application) ¶[0162] (emphasis added); *see also* EX1005 (’397 Application) ¶[0162] (emphasis added); EX1001 (’786 Patent) at 35:11-20 (emphasis added).

“The pharmaceutical composition of claim 11, wherein the benzodiazepine is present is in the pharmaceutical composition in a concentration from about 20 mg/mL to about 50 mg/mL”¹⁶⁹

“Some embodiments comprise administering to one or more mucosal membranes of a patient a therapeutically effective amount of one or more benzodiazepine drugs, or pharmaceutically-acceptable salts thereof. Some embodiments of the composition disclose a composition comprising one or more benzodiazepine drugs or pharmaceutically-acceptable salts thereof in a concentration up to about 600 mg/mL.”¹⁷⁰

“Some embodiments of the invention provide a method of administering the benzodiazepine drug composition to a patient. The preferred embodiment comprises use of diazepam. Some embodiments of the method disclose a dosage level of diazepam of about 1.0 mg to about 20.0 mg until achievement of the desired result. . . . Some embodiments disclose a dosage level of about 5.0 mg to about 10.0 mg until the desired result is achieved.”¹⁷¹

u. Claim 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.

176. The non-provisional applications disclose this claim. For example, they recite:

¹⁶⁹ EX1008 (’558 Application) at claim 12.

¹⁷⁰ EX1008 (’558 Application) ¶[0140].

¹⁷¹ EX1008 (’558 Application) ¶[0142] (emphasis added).

“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.”¹⁷²

177. The 61/040,558 Provisional also discloses this claim. For example, the Provisional states:

“The pharmaceutical composition of claim 1, wherein the benzodiazepine is present is in the pharmaceutical composition in a concentration from about 1 mg/mL to about 600 mg/mL”¹⁷³

“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.”¹⁷⁴

v. Claim 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).”

178. The non-provisional applications disclose this claim. For example, they recite:

¹⁷² EX1039 ('439 Application) ¶[0179]; *see also* EX1005 ('397 Application) ¶[0179]; EX1001 ('786 Patent) at 33:29-33.

¹⁷³ EX1008 ('558 Application) at claim 10.

¹⁷⁴ EX1008 ('558 Application) ¶[126].

“In some embodiments, enhancing agents that are appropriate include chelating agents (EGTA, EDTA, alginates), surface active agents (especially non-ionic materials), acyl glycerols, fatty acids and salts, tyloxapol and biological detergents listed in the SIGMA Catalog, 1988, page 316-321 (which is incorporated herein by reference). Also agents that modify the membrane fluidity and permeability are appropriate such as enamines (e.g. phenylalanine enamine of ethylacetoacetate), malonates (e.g. diethyleneoxymethylene malonate), salicylates, bile salts and analogues and fusidates. Suitable concentrations are up to 20% w/v.”¹⁷⁵

179. The 61/040,558 Provisional also discloses this element. For example, the Provisional states:

“In some embodiments, enhancing agents that are appropriate include chelating agents (EGTA, EDTA, alginates), surface active agents (especially non-ionic materials), acyl glycerols, fatty acids and salts, tyloxapol and biological detergents listed in the SIGMA Catalog, 1988, page 316-321 (which is incorporated herein by reference). Also agents that modify the membrane fluidity and permeability are appropriate such as enamines (e.g. phenylalanine enamine of ethylacetoacetate), malonates (e.g. diethyleneoxymethylene malonate), salicylates, bile salts and analogues and fusidates. Suitable concentrations are up to 20% w/v.”¹⁷⁶

“The composition of one of claims 1-16, furthering comprising at least one additional ingredient selected from the group consisting of: active pharmaceutical ingredients; enhancers;

¹⁷⁵ EX1039 (’439 Application) ¶[0139] (emphasis added); *see also* EX1005 (’397 Application) ¶[0139] (emphasis added); EX1001 (’786 Patent) at 37:42-52 (emphasis added).

¹⁷⁶ EX1008 (’558 Application) ¶[152] (emphasis added).

excipients; and agents used to adjust the pH buffer the composition, prevent degradation, and improve appearance, odor, or taste.”¹⁷⁷

w. Claim 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).”

180. The non-provisional applications disclose this claim. For example, they recite:

“In some embodiments, enhancing agents that are appropriate include chelating agents (EGTA, EDTA, alginates), surface active agents (especially non-ionic materials), acyl glycerols, fatty acids and salts, tyloxapol and biological detergents listed in the SIGMA Catalog, 1988, page 316-321 (which is incorporated herein by reference). Also agents that modify the membrane fluidity and permeability are appropriate such as enamines (e.g. phenylalanine enamine of ethylacetoacetate), malonates (e.g. diethyleneoxymethylene malonate), salicylates, bile salts and analogues and fusidates. Suitable concentrations are up to 20% w/v.”¹⁷⁸

181. The 61/040,558 Provisional also discloses this claim. For example, the Provisional states:

“The composition of one of claims 1-16, furthering comprising at least one additional ingredient selected from the group

¹⁷⁷ EX1008 (’558 Application) at claim 17 (emphasis added).

¹⁷⁸ EX1039 (’439 Application) ¶[0139] (emphasis added); *see also* EX1005 (’397 Application) ¶[0139] (emphasis added); EX1001 (’786 Patent) at 37:42-52 (emphasis added).

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.”¹⁷⁹

“In some embodiments, enhancing agents that are appropriate include chelating agents (EGTA, EDTA, alginates), surface active agents (especially non-ionic materials), acyl glycerols, fatty acids and salts, tyloxapol and biological detergents listed in the SIGMA Catalog, 1988, page 316-321 (which is incorporated herein by reference). Also agents that modify the membrane fluidity and permeability are appropriate such as enamines (e.g. phenylalanine enamine of ethylacetoacetate), malonates (e.g. diethyleneoxymethylene malonate), salicylates, bile salts and analogues and fusidates. Suitable concentrations are up to 20% w/v.”¹⁸⁰

- x. Claim 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).”**

182. The non-provisional applications disclose this claim. For example, they recite:

“In some embodiments, enhancing agents that are appropriate include chelating agents (EGTA, EDTA, alginates), surface active agents (especially non-ionic materials), acyl glycerols, fatty acids and salts, tyloxapol and biological detergents listed in the SIGMA Catalog, 1988, page 316-321 (which is incorporated herein by reference). Also agents that modify the membrane fluidity and permeability are appropriate such as enamines (e.g.

¹⁷⁹ EX1008 (’558 Application) at claim 17 (emphasis added).

¹⁸⁰ EX1008 (’558 Application) ¶[152] (emphasis added).

phenylalanine enamine of ethylacetoacetate), malonates (e.g. diethyleneoxymethylene malonate), salicylates, bile salts and analogues and fusidates. Suitable concentrations are up to 20% w/v.¹⁸¹

183. The 61/040,558 Provisional also discloses this claim. For example, the Provisional states:

“The composition of one of claims 1-16, furthering comprising 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.”¹⁸²

“In some embodiments, enhancing agents that are appropriate include chelating agents (EGTA, EDTA, alginates), surface active agents (especially non-ionic materials), acyl glycerols, fatty acids and salts, tyloxapol and biological detergents listed in the SIGMA Catalog, 1988, page 316-321 (which is incorporated herein by reference). Also agents that modify the membrane fluidity and permeability are appropriate such as enamines (e.g. phenylalanine enamine of ethylacetoacetate), malonates (e.g. diethyleneoxymethylene malonate), salicylates, bile salts and analogues and fusidates. Suitable concentrations are up to 20% w/v.”¹⁸³

¹⁸¹ EX1039 ('439 Application) ¶[0139] (emphasis added); *see also* EX1005 ('397 Application) ¶[0139] (emphasis added); EX1001 ('786 Patent) at 37:42-52 (emphasis added).

¹⁸² EX1008 ('558 Application) at claim 17 (emphasis added).

¹⁸³ EX1008 ('558 Application) ¶[152] (emphasis added).

- y. **Claim 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).”**

184. The non-provisional applications disclose this claim. For example, they recite:

“In some embodiments, enhancing agents that are appropriate include chelating agents (EGTA, EDTA, alginates), surface active agents (especially non-ionic materials), acyl glycerols, fatty acids and salts, tyloxapol and biological detergents listed in the SIGMA Catalog, 1988, page 316-321 (which is incorporated herein by reference). Also agents that modify the membrane fluidity and permeability are appropriate such as enamines (e.g. phenylalanine enamine of ethylacetoacetate), malonates (e.g. diethyleneoxymethylene malonate), salicylates, bile salts and analogues and fusidates. Suitable concentrations are up to 20% w/v.”¹⁸⁴

185. The 61/040,558 Provisional also discloses this claim. For example, the Provisional states:

“The composition of one of claims 1-16, furthering comprising 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

¹⁸⁴ EX1039 (’439 Application) ¶[0139] (emphasis added); *see also* EX1005 (’397 Application) ¶[0139] (emphasis added); EX1001 (’786 Patent) at 37:42-52 (emphasis added).

composition, prevent degradation, and improve appearance, odor, or taste.”¹⁸⁵

“In some embodiments, enhancing agents that are appropriate include chelating agents (EGTA, EDTA, alginates), surface active agents (especially non-ionic materials), acyl glycerols, fatty acids and salts, tyloxapol and biological detergents listed in the SIGMA Catalog, 1988, page 316-321 (which is incorporated herein by reference). Also agents that modify the membrane fluidity and permeability are appropriate such as enamines (e.g. phenylalanine enamine of ethylacetoacetate), malonates (e.g. diethyleneoxymethylene malonate), salicylates, bile salts and analogues and fusidates. Suitable concentrations are up to 20% w/v.”¹⁸⁶

z. Claim 26: “The pharmaceutical solution of claim 1, wherein the α -tocopherol is Vitamin E USP.”

186. The non-provisional applications disclose this claim. For example, they recite:

“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. . . . As used herein, Vitamin E refers to any of the natural or synthetic tocopherols, tocotrienols,

¹⁸⁵ EX1008 (’558 Application) at claim 17 (emphasis added).

¹⁸⁶ EX1008 (’558 Application) ¶[152] (emphasis added).

any isomers thereof, any esters thereof, any analogs or derivatives thereof, or any combinations thereof.”¹⁸⁷

187. The 61/040,558 Provisional also discloses this claim. For example, the Provisional states:

“The pharmaceutical composition 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, any isomers thereof, any esters thereof, any analogs or derivatives thereof, and any combinations thereof”¹⁸⁸

“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. . . . As used herein, Vitamin E refers to any of the natural or synthetic tocopherols, tocotrienols, any isomers thereof, any esters thereof, any analogs or derivatives thereof, or any combinations thereof.”¹⁸⁹

¹⁸⁷ EX1039 (’439 Application) ¶[0130] (emphasis added); *see also* EX1005 (’397 Application) ¶[0130] (emphasis added); EX1001 (’786 Patent) at 30:2-16 (emphasis added).

¹⁸⁸ EX1008 (’558 Application) at claim 7 (emphasis added).

¹⁸⁹ EX1008 (’558 Application) ¶[116] (emphasis added).

aa. Claim 27: “The pharmaceutical solution of claim 11, wherein the α -tocopherol is Vitamin E USP.”

188. The non-provisional applications disclose this claim. For example, they recite:

“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. . . . As used herein, Vitamin E refers to any of the natural or synthetic tocopherols, tocotrienols, any isomers thereof, any esters thereof, any analogs or derivatives thereof.”¹⁹⁰

189. The 61/040,558 Provisional also discloses this claim. For example, the Provisional states:

“The pharmaceutical composition 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, tocopherols, any isomers thereof, any esters thereof, any analogs or derivatives thereof, and any combinations thereof”¹⁹¹

“Vitamin E is a class of fat soluble methylated phenols. There are at least eight naturally-occurring compounds that comprise

¹⁹⁰ EX1039 ('439 Application) ¶[0130] (emphasis added); *see also* EX1005 ('397 Application) ¶[0130] (emphasis added); EX1001 ('786 Patent) at 30:2-16 (emphasis added).

¹⁹¹ EX1008 ('558 Application) at claim 7 (emphasis added).

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. . . . As used herein, Vitamin E refers to any of the natural or synthetic tocopherols, tocotrienols, any isomers thereof, any esters thereof, any analogs or derivatives thereof, or any combinations thereof.”¹⁹²

3. Response to Dr. Donovan’s Opinions

190. Dr. Donovan has opined that the Sigma Catalogue does not provide adequate written description support for the claims of the ’786 Patent.¹⁹³ I disagree with Dr. Donovan that there is insufficient written description support for *n*-dodecyl- β -D-maltoside. As described below, the skilled artisan would understand the catalogue to disclose *n*-dodecyl- β -D-maltoside as an enhancing agent as described in the specification.

191. Sigma is a large company that provides biochemical reagents and other supplies for scientific experimentation and other purposes. Sigma is a widely recognised name brand and a well-known supplier of these chemicals.¹⁹⁴ The Sigma Catalogue is a reliable source of such chemicals and their specifications, and a

¹⁹² EX1008 (’558 Application) ¶[116] (emphasis added).

¹⁹³ EX1062 (Donovan-786 Decl.) ¶¶50-53.

¹⁹⁴ See, e.g., EX2070 (Donovan Tr.) at 179:8-12.

skilled artisan would know not only of the brand, but also the catalogue.¹⁹⁵ A skilled artisan would have a copy of a Sigma Catalogue not only for ease of reference, but because the catalogue was a standard in the industry.¹⁹⁶

192. The '558 Provisional, as well as the Sigma Catalogue incorporated into the Provisional, directs a skilled artisan were to look to arrive at *n*-dodecyl- β -maltoside. At the outset, the '558 Provisional directs a skilled artisan to a type of chemical, both by name and by function, stating that “the drug delivery system of the invention may advantageously comprise an absorption enhancer.”¹⁹⁷ The '558 Provisional then defines the function of the absorption enhancer: “The term ‘enhancer’, means any material which acts to increase absorption across the mucosa and/or increases bioavailability.”¹⁹⁸ In order to determine whether this function was met, the '558 Provisional describes a process:

Whether a given compound is an “enhancer” can be determined by comparing two formulations comprising a non-associated, small polar molecule as the drug, with or without the enhancer, in an in vivo or good model test and determining whether the

¹⁹⁵ See, e.g., EX2070 (Donovan Tr.) at 151:14.

¹⁹⁶ See, e.g., EX2070 (Donovan Tr.) at 151:1-4; 179:8-12.

¹⁹⁷ EX1008 ('558 Provisional) ¶[150].

¹⁹⁸ EX1008 ('558 Provisional) ¶[150].

uptake of the drug is enhanced to a clinically significant degree.¹⁹⁹

193. After describing the function and properties of an absorption enhancer, the '558 Provisional continues two paragraphs later by directing a skilled artisan where to look to find an “enhancing agent” (i.e., the compound that serves as the absorption enhancer). The '558 Provisional states:

In some embodiments, enhancing agents that are appropriate include chelating agents (EGTA, EDTA, alginates), surface active agents (especially non-ionic materials), acyl glycerols, fatty acids and salts, tyloxapol and biological detergents listed in the SIGMA Catalog, 1988, page 316-321 (which is incorporated herein by reference).²⁰⁰

194. The '558 Provisional therefore directs a skilled artisan exactly where to look to find a list of chemical compounds that can be used as absorption enhancers, namely, those on pages 316-321 of a catalogue that a skilled artisan would likely have on their desk. On the first page of this excerpt, page 316, the Sigma Catalogue not only specifies *n*-dodecyl- β -D-maltoside, but shows that it was commercially available:

¹⁹⁹ EX1008 ('558 Provisional) ¶[150].

²⁰⁰ EX1008 ('558 Provisional) ¶[152].

BIOLOGICAL DETERGENTS

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

n-Decyl β -D-glucopyranoside
Digitonin
n-Dodecyl β -D-glucopyranoside
n-Dodecyl β -D-maltoside
n-Heptyl β -D-glucopyranoside
n-Octyl β -D-glucopyranoside
n-Octyl α -D-glucopyranoside
Nonidet P-40
n-Nonyl β -D-glucopyranoside
Triton X-100

195. A skilled artisan would understand that *n*-dodecyl- β -D-maltoside is one of the compounds disclosed in the Sigma Catalogue because of its prominent position within the relevant page numbers. *N*-dodecyl- β -D-maltoside is not simply listed amongst all the biological detergents, it is featured on the first page of the excerpt within a short list of potential compounds. A skilled artisan reading the Sigma Catalogue in the context of biological detergents would understand that *n*-dodecyl- β -D-maltoside is disclosed.²⁰¹

E. THE '786 PATENT CLAIMS ARE PATENTABLY DISTINCT FROM THE '876 PATENT CLAIMS

196. I have been asked to review the challenged claims of the '786 Patent, compare them to claims from U.S. Patent No. 9,763,876 ("the '876 Patent), and

²⁰¹ See, e.g., EX2070 (Donovan Tr.) at 178:20-179:7.

analyse whether the challenged claims are “patentably distinct” from the ’876 Patent. I have been informed by counsel that the standard for “patentably distinct” requires me to: first, identify the differences between the two sets of claims; second, analyse whether a skilled artisan would find the challenged claims of the ’786 Patent (Claims 1-27) to be obvious in view of the claims of the ’876 Patent.

197. As explained below, the claims of the ’786 Patent are patentably distinct. The ’786 Patent claims identify the specific compound, *n*-dodecyl- β -D-maltoside, whereas the ’876 Patent claims reference only broad categories such as “alkyl glycosides” and “dodecyl maltoside.” Selecting the specific *n*-dodecyl- β -D-maltoside species from the enormous, structurally diverse, genera of alkyl glycosides and dodecyl maltosides is not a routine variation but was instead a non-obvious choice.

1. Key Differences Between the ’786 Patent and the ’876 Patent Claims

198. The claims of the ’876 Patent differ significantly from those of the ’786 Patent. Most notably, the claims of the ’876 Patent recite either the vast category of compounds falling within the term “alkyl glycosides” or the narrower category of “dodecyl maltoside” (in a handful of dependent claims). As discussed above, alkyl glycosides encompass structurally distinct molecules varying in – amongst other

characteristics – chain length, branching, stereochemistry,²⁰² and linkage chemistry. Dodecyl maltoside (without further specification) likewise encompasses compounds that vary in branching and stereochemistry. In contrast, every '786 Patent claim requires *n*-dodecyl- β -D-maltoside, a single, precisely defined species.

199. From a chemical perspective, these differences are profound. Even changing the isomeric structure of *n*-dodecyl- β -D-maltoside's dodecyl moiety (i.e., the “*n*-dodecyl” portion of the compound)— creates 354 alternative branched isomers. When other permutations are considered (e.g., D- vs. L-maltose, α vs. β linkage, heteroatom substitutions), the number of compounds that (without further specification) qualify as “dodecyl maltoside” remains defined but expands dramatically. Broadening to the entire genus of alkyl glycosides, which includes multiple chain lengths and sugars, yielding a countless number of possible species.

2. The Claims of the '786 Patent Are Not Obvious in View of the Claims of the '876 Patent

200. Based on the differences between the claims of the '876 Patent and those of the '786 Patent identified above, a skilled artisan would not find the '786 Patent claims obvious over the '876 Patent.

²⁰² Here I refer to whether the optical rotation of the molecule is dextrorotatory (“D”) or laevorotatory (“L”) as well as whether the relative stereochemistry of anomeric carbons is α or β .

201. The claims of the '876 Patent provide no guidance to select *n*-dodecyl- β -D-maltoside from amongst hundreds of alternatives for dodecyl maltoside (or countless others when considering the broader class of “alkyl glycosides” recited in the independent claims), nor does its therapeutic context (benzodiazepine treatment) in any way suggest this specific compound. Moreover, minor structural changes to alkyl glycosides can dramatically alter functional properties—such as solubility, micelle formation, and absorption enhancement—because the performance of these molecules depends on their precise architecture. Without any indication that the linear, β -linked species would outperform branched or longer-chain variants, there is no reason to predict its selection. In fact, as further discussed below, Meezan teaches the opposite, recommending “highly branched” dodecyl maltoside and identifying tetradecyl maltoside as having “the greatest effect.”²⁰³

202. Based on these considerations, I conclude that the '786 Patent claims would not have been obvious to a skilled artisan in view of the '876 Patent claims and are patentably distinct.

²⁰³ EX1010 (Meezan) ¶¶[0149], [0157].

XI. CLAIM CONSTRUCTION

203. I have reviewed how a skilled artisan would have understood terms in the challenged claims. Dr. Donovan proposes the construction for one term, “Vitamin E.” I address this term and another below.

A. “VITAMIN E” (CLAIMS 10, 26, AND 27)

204. Dr. Donovan proposes that “Vitamin E” of claims 10, 26, and 27 means “any of the natural or synthetic tocopherols, tocotrienols, any isomers thereof, any esters thereof, any analogs or derivatives thereof, or any combinations thereof.”²⁰⁴ This does not seem correct, as “one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof” is already recited in claim 1 of the ’786 Patent. Nevertheless, as it does not seem germane to any issues, I have used Dr. Donovan’s definition.

B. “CONSISTING OF” (CLAIMS 1, 11, AND ALL CLAIMS)

205. Independent claim 1 and independent claim 11 each recite, “A pharmaceutical solution for nasal administration consisting of” several ingredients. Through their dependency on claims 1 and 11, claims 2-10 and 12-27 also recite this “consisting of” language. In the underlying district court litigation in Delaware, the

²⁰⁴ EX1062 (Donovan-786 Decl.) ¶¶56-57.

parties have disputed what this “consisting of” term means and have provided the following table:²⁰⁵

Term	Neurelis’s Position	Padagis’s Construction
A pharmaceutical solution for nasal administration consisting of	No construction necessary; the scope of “consisting of” is established by law.	“a pharmaceutical solution for nasal administration containing only those elements set forth in the claim and excluding anything else, particularly excluding water and oil” Otherwise indefinite.

206. In support of Padagis’s construction, Dr. Donovan provided opinions in the district court litigation, although not in her IPR declarations, that would seek to exclude even trace amounts of water from the scope of the claims. For example, she states:

It is my opinion that water content (even very small amounts of water) is not an “impurity ordinarily associated” with the claimed solution, and that water content is not “unrelated to” the alleged invention. Consequently, based on the case law cited by Neurelis and Dr. McConville, it is my opinion that the “consisting of” transition language of the Asserted Patents does not allow for the inclusion of small amounts of water.²⁰⁶

But the applicants intentionally drafted the claims to omit the qualifier that “the solution is at least substantially free of water.” In my opinion, this suggests to a POSA that the claimed solutions

²⁰⁵ EX2050 (Joint CC Brief) at 27.

²⁰⁶ EX2069 (Donovan-CC Decl.) ¶26.

did not intend for even very small amounts of water (e.g., less than about 0.1%) to be present in the claimed solutions.²⁰⁷

She suggests that even if a formulation contained “0.0000001% water,” that might not be within the scope of the claims, because she is unable to find “a threshold amount that distinguishes a ‘trace amount’ of residual solvent and what rises to the level of an ‘ingredient’ of the claimed solution.”²⁰⁸

207. In her deposition for the IPR declaration, she conceded that the claims do not include embodiments with even small amounts of water.²⁰⁹ As I discuss below, however, in applying the prior art against the challenged claims, Dr. Donovan ignored this claim-construction dispute. In her IPR declarations, Dr. Donovan fails to address whether the formulations of Gwozdz-PCT and Meezan have any water, trace or otherwise. Worse yet, she cites to embodiments that expressly disclose water as an ingredient.

²⁰⁷ EX2069 (Donovan-CC Decl.) ¶33.

²⁰⁸ EX2069 (Donovan-CC Decl.) ¶53.

²⁰⁹ EX2070 (Donovan Tr.) at 226:18-21.

XII. OVERVIEW OF THE ASSERTED PRIOR ART

A. GWOZDZ-PCT [EX1009]

208. EX1009 (“Gwozdz-PCT”) is WIPO Publication No. 2009/120933 (filed March 27, 2009) and purporting to trace priority to U.S. Provisional Patent App. No. 61/040,281 (filed March 28, 2008). Gwozdz-PCT names Garry Gwozdz, Andrew Loxley, and Mark Mitchnick as inventors and is entitled, “Pharmaceutical Solutions and Method for Solubilizing Therapeutic Agents.”

209. As I have discussed elsewhere, it is my opinion that the ’558 Provisional supplies a written description of the challenged claims. Consequently, I am informed by counsel—and therefore understand—that Gwozdz-PCT should not be considered prior art to the challenged claims. In my declaration, I will nevertheless address the disclosures of Gwozdz-PCT in the context of the Petition’s obviousness arguments and Dr. Donovan’s opinions about them. In no way should this discussion be construed as a view on my part that Gwozdz-PCT is prior art. That is not my view.

210. Gwozdz-PCT “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.”²¹⁰ Gwozdz-PCT states that it achieves a formulation that “is much less irritating to the skin and/or mucous membranes than pure alcohol solutions and generally provides higher loading of a therapeutic agent than emulsions, liposomes, encapsulations, or cyclodextrins.”²¹¹

211. Gwozdz-PCT explains that although therapeutic agents would otherwise be only “slightly soluble in water,” the “pharmaceutical solution of the present invention, however, provides for improved ability to dissolve hydrophilic and lipophilic therapeutic agents.”²¹² Gwozdz-PCT states that “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” such as through “a metered dose inhaler or nebulizer, or in a mist sprayer.”²¹³ Gwozdz-PCT states that its formulations are “providing increased bioavailability of the therapeutic agent.”²¹⁴ Thus, Gwozdz-PCT offers solutions that purport to

²¹⁰ EX1009 (Gwozdz-PCT) at 4:29-33.

²¹¹ EX1009 (Gwozdz-PCT) at 5:4-7.

²¹² EX1009 (Gwozdz-PCT) at 9:25-31.

²¹³ EX1009 (Gwozdz-PCT) at 9:19-10:2.

²¹⁴ EX1009 (Gwozdz-PCT) at 7:5-8; *see also* EX1009 (Gwozdz-PCT) at 5:30-31, 8:30-31.

increase solubility, increase bioavailability, and allow therapeutic agents to be delivered intranasally, with no shortcomings or need for improvement.

B. MEEZAN [EX1010]

212. EX1010 (“Meezan”) is U.S. Patent Application Publication No. 2006/004962, which names Elias Meezan, Dennis Pillion, and Edward Maggio as inventors. Meezan is directed 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.”²¹⁵ This broad disclosure of “alkyl glycoside or saccharide alkyl ester compositions” can represent an almost uncountable number of compounds. Meezan does not provide any disclosure of diazepam or other benzodiazepines. Rather, Meezan is focused on the delivery of therapeutic drugs of 1-30 kilo Daltons (kD) and even up to 100 kD.²¹⁶

The target therapeutic drugs in Meezan are:

[P]eptides or proteins, medically or diagnostically useful, of small to medium size, e.g. up to about 15 kD, 30 kD, 50 kD, 75 kD, etc., or a protein having between about 1-300 amino acids or more. The methods of the invention also anticipate the use of

²¹⁵ EX1010 (Meezan) ¶[0002].

²¹⁶ EX1010 (Meezan) ¶¶[0012], [0013], [0020], [0051], [00130].

smaller molecules, for example, an organic compound that has a molecular weight of less than 3 kD, or less than 1.5 kD.”²¹⁷

Meezan gives a series of such peptides or proteins, such as vasopressin, insulin, human growth hormone, and many others, but does not disclose benzodiazepines, generally, or diazepam specifically.²¹⁸

C. CARTT-784 [EX1065]

213. EX1065 (“Cartt-784”) is U.S. Patent Publication No. 2008/0279784 (filed May 7, 2008). Cartt-784 names Steve Cartt and David Madeiros of Questcor Pharmaceuticals as inventors and is entitled, “Nasal Administration of Benzodiazepines.”

214. Cartt-784 is directed to “Particulate formulations of benzodiazepines, such as diazepam, are used for nasal administration of diazepine drugs to patients.”²¹⁹ Nanoparticles of benzodiazepine are provided as a “suspension or dispersion” and can be aerosolized for delivery to a patient.²²⁰

²¹⁷ EX1010 (Meezan) ¶[0130].

²¹⁸ EX1010 (Meezan) ¶[0131]; EX2070 (Donovan Tr.) at 148:25-149:10.

²¹⁹ EX1065 (Cartt-784) at Abstract.

²²⁰ EX1065 (Cartt-784) ¶¶[0015]-[0023].

XIII. NON-OBVIOUSNESS OVER GWOZDZ-PCT AND MEEZAN

215. Dr. Donovan relies on the combination of Gwozdz-PCT and Meezan to assert obviousness. I understand that there is a dispute as to whether Gwozdz-PCT qualifies as prior art. Even assuming that Gwozdz-PCT were to qualify as prior art, I disagree with Dr. Donovan that the challenged claims would have been obvious.

216. First, even if a skilled artisan were to read Gwozdz-PCT and Meezan in combination with one another, the combination still would not disclose or suggest all claim limitations of the challenged claims. Second, there was no reason that would have prompted a skilled artisan to combine Gwozdz-PCT and Meezan to arrive at the claimed invention of the challenged claims, and a skilled artisan would not have a reasonable expectation of success. Dr. Donovan combines Gwozdz-PCT with Meezan through impermissible hindsight, using the disclosure of the Challenged Patent as a blueprint.

A. THE COMBINATION FAILS TO DISCLOSE EVERY ELEMENT OF THE CHALLENGED CLAIMS**1. Gwozdz-PCT and Meezan Do Not Disclose *N*-dodecyl- β -D-maltoside**

217. The independent claims of the '786 Patent recite "*n*-dodecyl- β -D-maltoside" in Element 1(d) and Element 11(d). Thus, this element is a requirement of every challenged claim (i.e., including all the dependent claims).

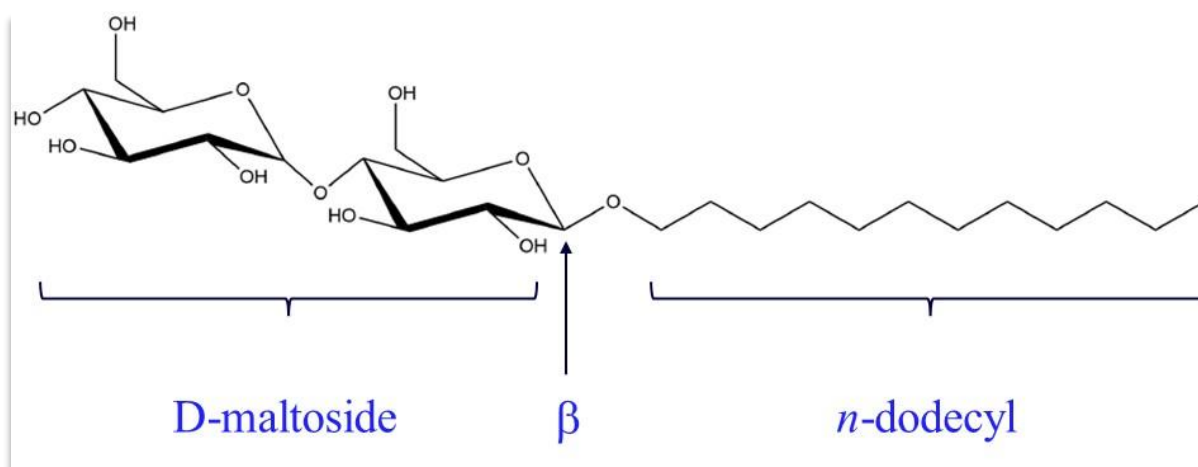
218. Gwozdz-PCT does not disclose *n*-dodecyl- β -D-maltoside, and Dr. Donovan does not contend otherwise. Rather, she relies on Meezan for the disclosure of dodecyl maltoside. She contends that “a POSA was motivated to combine the teachings of Meezan related to alkyl glycosides with the pharmaceutical solutions described in Gwozdz.”²²¹ She later states, “Meezan also specifically discloses alkyl glycosides, including dodecyl maltoside. *See id.*, ¶¶ [0056], [0058], [0061].”²²² Yet, nowhere in Gwozdz-PCT or Meezan is there a disclosure of the actual claim limitation, “*n*-dodecyl- β -D-maltoside.”

219. As I explained earlier in my declaration, *n*-dodecyl- β -D-maltoside (also known as lauryl-beta-D-maltoside) is a particular chemical compound having a specific chemical structure and resulting functional characteristics. As discussed above, the “*n*” refers to the fact that the dodecyl moiety is linear. *N*-dodecyl- β -D-maltoside is one out of more than 355 isomers of dodecyl- β -D-maltoside. At least 354 of the other dodecyl- β -D-maltoside isomers are branched.²²³ The structure of *n*-dodecyl- β -D-maltoside is depicted below:

²²¹ EX1062 (Donovan-786 Decl.) ¶101.

²²² EX1062 (Donovan-786 Decl.) ¶150.

²²³ As I explain below, there are 355 isomers of the dodecyl moiety. When one considers the presence of the other moieties and linkages (such as the type of



This chemical compound has a chemical formula ($C_{26}H_{46}O_{11}$). These atoms are divided between a specific disaccharide moiety (D-maltoside) and a specific alkyl moiety (*n*-dodecyl), and there is a specific glycosidic linkage between the two moieties (β). Neither Gwozdz-PCT nor Meezan disclose *n*-dodecyl- β -D-maltoside, either alone or in combination with one another. And Dr. Donovan does not explain (or even assert) how a skilled artisan would arrive at *n*-dodecyl- β -D-maltoside from the combination of Gwozdz-PCT with Meezan.

220. Importantly, and as shown in the skeletal formula above, the dodecyl chain of the *n*-dodecyl- β -D-maltoside molecule is linear, not branched. This is the compound every challenged claim requires. Other isomers of the compound having branched dodecyl chains do not fall within the literal scope of any challenged claim.

maltoside and the type of glycosidic linkage), there are many more than 355 isomers of “dodecyl maltoside.”

221. Dr. Donovan relies on Meezan as generically disclosing “dodecyl maltoside.” For example, Dr. Donovan states regarding the overview of Meezan:

Meezan explains that alkyl glycosides in concentrations ranging from about 0.01% to about 6% by weight (and in particular 0.125% and 0.25% by weight) resulted in enhanced absorption of the drug and increased bioavailability. *Id.* Additionally, Meezan again identifies dodecyl maltoside (i.e., “DDM”) as one of the preferred alkyl glycosides having an absorption-enhancing and bioavailability increasing effect on the drug compound.²²⁴

This assertion not only fails to disclose what type of dodecyl group is used (e.g., “*n*” versus branched), but it does not even disclose the type of maltoside (D-maltoside) or the stereochemistry of the glycosidic linkage between the dodecyl moiety and the maltoside (the claimed “beta” or β).

222. Then in discussing motivations to combine, Dr. Donovan again discusses the generic “dodecyl maltoside,” but not the species required by the challenged claims:

Thus, a POSA would be motivated to increase the solubility of diazepam using the Gwozdz solvent system. Given diazepam’s potency, and in recognition of its limited water solubility, a POSA would have been motivated to pursue strategies to maximize the solubility of diazepam, and would also look to enhance the permeation of diazepam, based on the teachings of Meezan.

²²⁴ EX1062 (Donovan-786 Decl.) ¶94.

For at least these reasons, a POSA would be motivated to add Meezan's alkyl glycosides (e.g., dodecyl maltoside) to Gwozdz's solvent system containing tocopherol, ethanol, and benzyl alcohol that was used to dissolve diazepam.²²⁵

223. To help further illustrate the generic nature of “dodecyl maltoside” of Meezan, consider each of the moieties, the glycosidic bonds between them, and the resulting permutations of chemical compounds of dodecyl maltoside.

- Starting with the “maltoside” moiety, there are two isomers of maltose: D-maltose and L-maltose.²²⁶
- Then consider the glycosidic linkage between the maltoside moiety and the alkyl moiety: there can be an alpha (α) glycosidic bond or a beta (β) glycosidic bond. (Plus, the linkage does not necessarily need to be at the terminal carbon atoms, but can instead be at the intermediate carbons, thus yielding more isomers.)
- Then consider the alkyl moiety itself (dodecyl): there is one linear (“*n*”) isomer and 354 branched isomers.

Thus, even if the focus is limited to naturally occurring D-maltose (and not considering L-maltose), there are still over 700 species of dodecyl-D-maltoside: 355 isomers of dodecyl- α -D-maltoside and 355 isomers of dodecyl- β -D-maltoside. The challenged claims are limited to only one of those over 700 isomers (*n*-dodecyl- β -

²²⁵ EX1062 (Donovan-786 Decl.) ¶¶114-115.

²²⁶ D-maltose is the naturally occurring isomer of maltose. L-maltose is its enantiomer, which can be synthesised by chemists.

D-maltoside), and that particular species is not disclosed in Gwozdz-PCT or in Meezan.

2. Gwozdz-PCT Includes Water in the Disclosed Formulations

224. Dr. Donovan relies on Gwozdz-PCT to disclose solutions of diazepam in Vitamin E, benzyl alcohol, and ethanol.²²⁷ Regarding ethanol, Gwozdz-PCT discloses that “[p]referred is the use of an ethanol that is biocompatible in the sense that it is not toxic and does not cause any physiological or pharmacological effects.”²²⁸ Gwozdz-PCT goes on to state that “[i]n this regard, the ethanol is desirably 180 to 200 proof ethanol, *i.e.*, in the range of 90-100% ethanol.”²²⁹ Accordingly, amongst the passages of Gwozdz-PCT on which Dr. Donovan rely are exemplary solutions of diazepam using 190-proof and 200-proof ethanol.

225. A skilled artisan would have understood that for ethanol that is measured at 180-200 proof (or 90% ethanol to nearly 100% ethanol²³⁰), almost all

²²⁷ EX1062 (Donovan-786 Decl.) ¶¶139-146.

²²⁸ EX1009 (Gwozdz-PCT) at 6:24-27.

²²⁹ EX1009 (Gwozdz-PCT) at 6:27-29.

²³⁰ Even 200-proof ethanol actually contains some small percentage of water, and Dr. Donovan concurs. EX2070 (Donovan Tr.) at 36:9-25.

the non-ethanol component of that composition would have been water.²³¹ It was well-known that due to the extreme miscibility of water and ethanol, there will always be some water present in ethanol, whether deriving from the initial fermentation in water or from hygroscopic absorption from the atmosphere.²³² The principal method of removing water from ethanol is distillation, using the fact that ethanol boils at a lower temperature than water, to fractionally distil off the ethanol. But water and ethanol produce an azeotrope such that distillation can only yield at most 95-96% pure ethanol with the remainder mostly water.²³³ To remove more water, more extreme methods (such as filtration using molecular sieves) must be used.

226. Thus, even “dehydrated” ethanol is not water-free. As noted above the USP’s definition of “dehydrated alcohol” refers to ethanol of $\geq 99.5\%$ purity (v/v).²³⁴ A person of ordinary skill would have understood that the balance of the composition is mostly water.²³⁵

²³¹ EX2070 (Donovan Tr.) at 36:9-25.

²³² EX2070 (Donovan Tr.) at 36:9-25.

²³³ EX2070 (Donovan Tr.) at 33:16-25; 36:9-25.

²³⁴ EX1038 (USP 26/ NF 21) at 3.

²³⁵ EX2070 (Donovan Tr.) at 36:9-25.

227. I also note that Dr. Donovan repeatedly relies on an embodiment of Gwozdz-PCT, including as her motivation to combine with Meezan, citing to Exhibit 1009 (Gwozdz-PCT) at 10:9-16, 10:11-16, and 10:12-16.²³⁶ She selects portions of that embodiment while ignoring the context. The full embodiment, copied below, expressly states that the pharmaceutical solutions with “penetration enhancers” (the only disclosure she cites in Gwozdz-PCT of a penetration enhancer)²³⁷ include water as an added ingredient:²³⁸

²³⁶ EX1062 (Donovan-786 Decl.) ¶¶80, 87, 104, 109, 149 (citing EX1009 (Gwozdz-PCT) at 10:9-16, 10:11-16, and 10:12-16).

²³⁷ I also note that this embodiment of Gwozdz-PCT uses the term “penetration enhancers” at column 10 line 14. However, as I discuss below, this “penetration enhancers” language was not included in the provisional from which Gwozdz-PCT claims priority. It was newly added with the filing of Gwozdz-PCT.

²³⁸ EX1009 (Gwozdz-PCT) at 10:1-16 (annotation added).

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via, for example, a metered dose inhaler or nebulizer, or in a mist sprayer.

The instant pharmaceutical solutions comprising a therapeutic agent, one or more tocopherols and/or
5 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
10 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
15 preservatives, penetration enhancers, humectants, suspending and/or viscosity modifying agents, tonicity and wetting or other biocompatible materials.

Regardless of whether a “saline solution or water” is used in the formulation of Gwozdz-PCT, water is present as an intended ingredient.

228. As I discuss above in the “Claim Construction” section, every challenged claim recites a pharmaceutical solution “consisting of” various components. Dr. Donovan previously offered opinions that the challenged claims should be interpreted to require the presence of no water, even in trace amounts.

It is my opinion that water content (even very small amounts of water) is not an “impurity ordinarily associated” with the claimed solution, and that water content is not “unrelated to” the alleged invention. Consequently, . . . it is my opinion that the “consisting

of” transition language of the Asserted Patents does not allow for the inclusion of small amounts of water.²³⁹

229. The embodiments cited by Dr. Donovan from Gwozdz-PCT, however, expressly include water—whether in the injectable saline formulation or as part of the ethanol. Under the claim construction proposed by Dr. Donovan in district court, she has failed to demonstrate that the “consisting of” requirement of the challenged claims is met by Gwozdz-PCT and Meezan. No disclosed composition in Gwozdz-PCT entirely excludes water.

230. So too with Meezan, which discloses “aqueous” or “saline” in numerous places.²⁴⁰ The focus of Meezan is combining macromolecular therapeutic agents “with various surfactants” in aqueous solution.²⁴¹ The purpose of this combination is to improve the bioavailability of those macromolecular therapeutic agents in aqueous solutions. Every Example in Meezan examines peptides or proteins which have been dissolved in water. Dr. Donovan fails to address, however, whether the combination of Gwozdz-PCT and Meezan exclude water from the formulation, whether in trace amounts or even as an excipient.

²³⁹ EX2069 (Donovan-CC Decl.) ¶26.

²⁴⁰ *See, e.g.*, EX1010 (Meezan) ¶[0074].

²⁴¹ EX1010 (Meezan) ¶[0003].

B. NO REASON TO COMBINE GWOZDZ-PCT AND MEEZAN TO ARRIVE AT THE CLAIMED INVENTION

231. In addition to the combination of Gwozdz-PCT and Meezan failing to disclose limitations of the challenged claims, Dr. Donovan does not establish any reason (other than hindsight) for a skilled artisan to have combined the two references. As I discuss below, there was no reason that would have prompted a skilled artisan to combine Gwozdz-PCT with Meezan to arrive at the claimed invention of the challenged claims, and a skilled artisan would not have a reasonable expectation of success. Dr. Donovan combines Gwozdz-PCT with Meezan through impermissible hindsight, using the disclosure of the Challenged Patent as a blueprint.

1. Dr. Donovan Relies on the Challenged Patent’s Statement of the Problem to be Solved

232. Dr. Donovan relies on the ’786 Patent itself when she characterises a “known problem in the art” in terms of “the inability to administer benzodiazepine drugs (e.g., diazepam) due to the limited solubility of the drug compounds.”²⁴² She characterises known shortcomings of “oral dosage,” “intravenous dosage,” and “rectal dosage,” and then asserts that there was a “known problem that existed

²⁴² EX1062 (Donovan-786 Decl.) ¶101.

related to the solubility of benzodiazepine drug compounds, and the dosage forms that could be developed based on this limited solubility.”²⁴³

233. Based on these problems identified (and solved) by the Challenged Patent, Dr. Donovan extrapolates that these problems were also known in the prior art:

In view of these shortcomings [i.e., those identified in the '786 Patent], a known problem existed related to the solubility of benzodiazepine drug compounds, and the dosage forms that could be developed based on this limited solubility. Consequently, a POSA was motivated to identify strategies to improve the solubility of benzodiazepine drugs.²⁴⁴

She then concludes that Gwozdz-PCT “provides this guidance” (i.e., how to improve solubility) and that “a POSA would have also looked to additional references for guidance regarding additive compositions to improve the efficacy of the pharmaceutical solutions of Gwozdz.”²⁴⁵

234. Dr. Donovan’s syllogism reduces to: (a) the challenged patent identifies and solves a problem; (b) therefore, that same problem must have also been known in the prior art; and (c) one would have been motivated to combine two prior art

²⁴³ EX1062 (Donovan-786 Decl.) ¶¶101-102; EX2070 (Donovan Tr.) at 51:9-20.

²⁴⁴ EX1062 (Donovan-786 Decl.) ¶102.

²⁴⁵ EX1062 (Donovan-786 Decl.) ¶¶103-104.

references (Gwozdz-PCT and Meezan) to solve that same problem. Ultimately, I believe that Dr. Donovan is defining the problem in terms of its solution, which reveals the improper hindsight in the selection of the prior art relevant to obviousness. But Gwozdz-PCT does not itself describe any issues with solubility or bioavailability, or other need for improvement once the therapeutic agent, including diazepam, is dissolved in the tocopherol and alcohol solvent system it discloses. Dr. Donovan's formulation of this problem was not derived from the prior art, but instead from the challenged claims.

235. Elsewhere in Dr. Donovan's report, she suggests that solubility and bioavailability of benzodiazepine were already solved in the art. For example, Dr. Donovan relies on an Emergency Medical Services guide from the State of Florida to support the notion that it was known in the prior art that diazepam could have been administered intranasally in a sufficient dose.²⁴⁶ She further states:

Numerous guidelines and references have recognized the need for prompt treatment, and have recommended various

²⁴⁶ EX1062 (Donovan-786 Decl.) ¶76 (discussing EX1019). In reality, the diazepam formulation in Exhibit 1019: required the intercession of medical personnel; provided a dilute (5 mg/ML) formulation, which is less than 10% the concentration of Gwozdz-PCT; required flooding the intranasal passageway to deliver the dosage, most of which would have dripped out; does not address tolerability (which may not have been an issue for a seizing/comatose patient); and does not provide any indication of regulatory approval.

transmucosal routes of benzodiazepine delivery when IV access has not yet been established. . . .

. . . 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.²⁴⁷

Dr. Donovan has a whole section of her report entitled “Prior Art Experience With Intranasal Delivery of Benzodiazepines For Treatment Of Seizures Prior to 2009,” in which she concludes that “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.”²⁴⁸ Thus, under Dr. Donovan’s analysis, the very “problem” she identified as the basis to combine Gwozdz-PCT and Meezan was either not a problem at all (because it had been solved), or it was a problem not known in the prior art. Either way, there would have been no reason for a skilled artisan to combine Gwozdz-PCT and Meezan, other than by reviewing the challenged claims through the lens of hindsight.

²⁴⁷ EX1062 (Donovan-786 Decl.) ¶¶60-61; EX2070 (Donovan Tr.) at 255:9-256:1 (noting that a 5/mg dose of diazepam was an effective dose).

²⁴⁸ EX1062 (Donovan-786 Decl.) ¶¶72-77.

2. Dr. Donovan Does Not Identify Any Shortcomings in Gwozdz-PCT or Reason to Modify Gwozdz-PCT

236. Even if one accepts Dr. Donovan's characterisation of the "known problem" of limited solubility of benzodiazepine, then Gwozdz-PCT states that it solves the problem. There would have been no need or reason to modify Gwozdz-PCT by introducing additional excipients from Meezan.

a. Gwozdz-PCT discloses that it provides sufficient solubility, without the need for additional excipients

237. Gwozdz-PCT states that it "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."²⁴⁹ Gwozdz-PCT states that it achieves a formulation that "is much less irritating to the skin and/or mucous membranes than pure alcohol solutions and generally provides higher loading of a therapeutic agent than emulsions, liposomes, encapsulations, or cyclodextrins."²⁵⁰

238. Gwozdz-PCT explains that although therapeutic agents would otherwise be only "slightly soluble in water," the "pharmaceutical solution of the

²⁴⁹ EX1009 (Gwozdz-PCT) at 4:29-33.

²⁵⁰ EX1009 (Gwozdz-PCT) at 5:4-5:7.

present invention, however, provides for improved ability to dissolve hydrophilic and lipophilic therapeutic agents.”²⁵¹ Gwozdz-PCT states that “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” such as through “a metered dose inhaler or nebulizer, or in a mist sprayer.”²⁵² Gwozdz-PCT does not identify any shortcomings of the formulation.

b. Gwozdz-PCT discloses that it provides sufficient bioavailability, without the need for additional excipients

239. Nevertheless, Dr. Donovan suggests that a skilled artisan would have “looked to additional references.” According to Dr. Donovan, “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., absorption enhancers) and bioavailability of drug compounds.”²⁵³ Dr. Donovan is wrong, because Gwozdz-PCT states that it already succeeded in “providing increased bioavailability of the therapeutic agent” by virtue

²⁵¹ EX1009 (Gwozdz-PCT) at 9:25-31.

²⁵² EX1009 (Gwozdz-PCT) at 9:19-10:2.

²⁵³ EX1062 (Donovan-786 Decl.) ¶104.

of enhanced solubility.²⁵⁴ Furthermore, Dr. Donovan asserts that, once diazepam was made sufficiently soluble (as in Gwozdz-PCT), improved bioavailability inherently followed:

It was well-known that benzodiazepines have sufficient lipophilic character to readily cross biologic membranes [EX1027 at 54], meaning that benzodiazepines would be considered a logical choice for intranasal administration.²⁵⁵

Gwozdz-PCT did not need any further help from Meezan or any other reference, and absent the hindsight provided by the '786 Patent itself, there would have been no reason to add an absorption enhancer or other excipient to the formulation of Gwozdz.

240. In summary, Gwozdz-PCT offers formulations that purport to increase solubility, increase bioavailability, and allow therapeutic agents to be delivered intranasally, with no identified shortcomings or need for improvement. According to Gwozdz-PCT, the “resulting pharmaceutical formulation is not an emulsion or vesicle, and can be used directly in the production of pharmaceutical

²⁵⁴ EX1009 (Gwozdz-PCT) at 7:5-8; *see also* EX1009 (Gwozdz-PCT) at 5:30-31, 8:30-31.

²⁵⁵ EX1062 (Donovan-786 Decl.) ¶65.

formulations.”²⁵⁶ Gwozdz-PCT did not identify any shortcomings in solubility or bioavailability, and there would be no reason for a skilled artisan to modify Gwozdz-PCT or combine with Meezan. The only reason to have modified the formulation of Gwozdz-PCT by adding excipients from Meezan is hindsight.

c. Gwozdz-PCT discloses that it provides sufficient dosage without excessive volume, without the need for additional excipients

241. Gwozdz-PCT discloses several formulations of diazepam in tocopherol/alcohol solutions, and due to the increased solubility provided by Gwozdz-PCT (without Meezan), sufficient diazepam could be delivered to patients without flooding the nasal passageway. In reviewing Gwozdz-PCT, a skilled artisan would not think anything further was needed from Meezan in this regard. Gwozdz-PCT discloses dissolving 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 combinations thereof.”²⁵⁷ In particular, Gwozdz-PCT discloses two specific formulations of diazepam in tocopherol/ethanol solutions: a 70:30 mixture of tocopherol and ethanol provides an 8% solution; and a 95:5 mixture provides a

²⁵⁶ EX1009 (Gwozdz-PCT) at 4:34-5:2.

²⁵⁷ EX1009 (Gwozdz-PCT) at 4:13-17.

9% solution.²⁵⁸ When Gwozdz-PCT states “8%” and “9%” solutions, it is not clear on the face of the document whether this refers to a solution that is 8-9% by weight (w/w) or a solution that is 8-9% by weight/volume (w/v). Nevertheless, as I explain below, regardless of whether the diazepam concentration measurements are interpreted as w/w or w/v, the two numbers are similar, each resulting in a relatively limited volume needed to supply a sufficient dose. This limited volume would be readily accommodated by the nasal passageway, and would demonstrate to a skilled artisan that no further improvement on Gwozdz-PCT would be needed.

242. The two concentration measurements can be compared by using the densities of the underlying components of these solutions:

- Dehydrated ethanol (“200 proof”) at 20°C = 0.7904-0.7935 g/mL²⁵⁹;
- D-α tocopherol at 20°C = 0.95 g/mL.²⁶⁰

243. Whether the 8-9% refers to w/w or to w/v, the numbers do not differ much under either read. Assuming for now that the “8%” in Gwozdz-PCT refers to “8% (w/w),” then for an exemplary composition of 8 mg diazepam (i.e., the active ingredient), the remainder of the composition would be 92 mg excipients (e.g.,

²⁵⁸ EX1009 (Gwozdz-PCT) at 7:20-28.

²⁵⁹ EX1016 (Rowe) at 4, 3 (Table II), 5 (Table III).

²⁶⁰ EX1016 (Rowe) at 7, 6 (Table I).

solvents). For a 70/30 solution of tocopherol/ethanol (w/w), that would equal 64.4 mg tocopherol and 27.6 mg ethanol. Given the densities above, this composition would convert to 67.8 μL (microliter) tocopherol and 34.9 μL ethanol, or a total of approximately 102.7 μL (approximately 0.1 mL).²⁶¹ Assuming for now that the “8%” in Gwozdz-PCT instead refers to “8% (w/v),” then that would correspond to 8 mg diazepam in 100 μL solvent (which would consist of 70 μL tocopherol and 30 μL of ethanol). The difference between those compositions is less than 3%, which I view as inconsequential in the context of the pharmaceutical solutions at issue here.

244. This difference is inconsequential since for an identical diazepam dose of, for example, 5 mg intranasally, one would require 62.5 μL of 8% solution (w/w), or 64.2 μL of 8% solution (w/v). A skilled artisan would know that the nasal mucosa can accommodate far more than this volume of fluid, including up to 150 μL (0.15 mL), without severe challenges of dripping or swallowing excess fluid.²⁶² Thus, the

²⁶¹ The actual end volume might be slightly less (i.e., very close to 100 μL total) due to interactions between the ethanol and tocopherol molecules. But the difference would be insubstantial.

²⁶² EX1027 (Wermeling I) at 354 (“The dose must have sufficient solubility to be administered in approximately 100 μL to 200 μL (1 spray per naris) of solution. The nasal cavity can retain 100 to 150 μL without causing immediate run-off out the front of the nose or down the nasopharynx.”). Dr. Donovan also agrees with this amount. EX1062 (Donovan-786 Decl.) ¶66 (“The nasal cavity can retain 100

difference between administering 62.5 μ L of 8% solution (w/w) or 64.2 μ L of 8% solution (w/v) is inconsequential; both would be accommodated easily by the nasal cavity. In other words, Gwozdz-PCT can achieve sufficient solubility of diazepam such that excess dosage volume is not required, and there is no need to modify Gwozdz-PCT with the addition of Meezan. Dr. Donovan admits as much:

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, Ex. 1009, 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.²⁶³

Thus, if Gwozdz-PCT itself obtained increased solubility—providing sufficient dosage of diazepam in a volume that can be accommodated by the nasal passageway—there would be no reason to modify the formation of Gwozdz-PCT to add anything from Meezan.

to 150 μ L without causing immediate run-off out the front of the nose or down the naso-pharynx.”).

²⁶³ EX1062 (Donovan-786 Decl.) ¶105.

245. Similar to the age-old adage of “if it ain’t broke, don’t fix it,” drug formulators would understand that any modifications to an already working formula (as in Gwozdz-PCT) would require additional expenses to study interactions and other effects. A skilled artisan reading Gwozdz-PCT would see no reason to modify the formulation of Gwozdz-PCT, let alone to add the dodecyl maltoside of Meezan (or the undisclosed *n*-dodecyl- β -D-maltoside).

d. The basis for Dr. Donovan’s motivation to combine was not present before 2009, conflicts with other claim limitations, and was not for intranasal applications

246. Dr. Donovan relies on a passage in Gwozdz-PCT disclosing that an embodiment may include a long list of “additional pharmaceutically acceptable additives,” including “penetration enhancers.”²⁶⁴ She continues: “*In view of this*, a POSA would have also looked to additional references for guidance regarding additive compositions to improve the efficacy of the pharmaceutical solutions of Gwozdz[-PCT]. Meezan provides such guidance”²⁶⁵ That is, it is based solely on the disclosure in Gwozdz-PCT that “penetration enhancers” could have been

²⁶⁴ EX1062 (Donovan-786 Decl.) ¶104 (quoting EX1009 (Gwozdz-PCT) at 10:12-16).

²⁶⁵ EX1062 (Donovan-786 Decl.) ¶104 (emphasis added).

added, Dr. Donovan finds a motivation to “look[] to additional references.” I disagree in multiple respects.

i. The “penetration enhancers” language in Gwozdz-PCT was added in 2009

247. Dr. Donovan states, “All of the teachings and disclosure I am providing herein are supported in the specification of the ’281 Provisional.”²⁶⁶ That statement is not correct. The supposedly key reference to “penetration enhancers” does not appear in the 2008 Gwozdz-Provisional (App. No. 61/040,281). Rather, its first appearance is in the 2009 Gwozdz-PCT, itself. This can easily be seen by comparing the identical paragraphs from the two documents. The disclosure from the 2008-Gwozdz-Provisional is below:²⁶⁷

10 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
15 preservatives, humectants, suspending and/or viscosity
modifying agents, tonicity and wetting or other
biocompatible materials.

²⁶⁶ EX1062 (Donovan-786 Decl.) ¶80.

²⁶⁷ EX1064 (’281 Provisional) at 10:10-17 (annotation added).

The disclosure from the 2009 Gwozdz-PCT is below:²⁶⁸

10 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
15 and/or viscosity modifying agents, tonicity and wetting or
other biocompatible materials.

There is no disclosure, whether express or inherent, of “penetration enhancers” in the Gwozdz-Provisional (EX1064). That material was added in the March 27, 2009, filing of Gwozdz-PCT (EX1009). I am informed by counsel, and therefore understand, that if a disclosure on which the Petition or Dr. Donovan relies in Gwozdz-PCT does not appear in the Gwozdz-Provisional, then that disclosure cannot be prior art to the challenged claims under even the 2009 priority date the Petition concedes. I see no other evidence Dr. Donovan cites to support her view that a skilled artisan would have had a motivation to combine Gwozdz-PCT with Meezan.

ii. The embodiment of the “other pharmaceutically acceptable additives [including] penetration

²⁶⁸ EX1009 (Gwozdz-PCT) at 10:10-17 (annotation added).

**enhancers” conflicts with other claim limitations
and is not for intranasal applications**

248. As I describe in the legal background section, I have been informed that hindsight reconstruction cannot be used to pick and choose amongst isolated disclosures in the prior art in order to reconstruct the challenged claims. This is what Dr. Donovan appears to be doing here, as she ignores the context in which the “other pharmaceutically acceptable additives [including] penetration enhancers” embodiment of Gwozdz-PCT is found.

(1) The “penetration enhancer” is for aqueous solutions

249. As I discussed above, the challenged claims of the '786 Patent are all “consisting of” claims, which I understand excludes elements that are not specifically recited, unless those elements are either unrelated to the invention or are an impurity normally associated with a recited component. The embodiment in which the “other pharmaceutically acceptable additives [including] penetration enhancers” language appears specifically includes added saline or water, and does so for a reason related to the invention of Gwozdz-PCT (it is an injection).

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 ... penetration enhancers ²⁶⁹

Therefore, the embodiment in which this “other pharmaceutically acceptable additives [including] penetration enhancers” disclosure appears would, if anything, have led a skilled artisan to develop injectable aqueous/saline compositions—not the compositions of the challenged claims.

(2) The “other pharmaceutically acceptable additives [including] penetration enhancer” is not for nasal applications

250. As a further example of the hindsight used by Dr. Donovan to try to piece together the challenged claims, consider the arrangement of the embodiments of Gwozdz-PCT. Gwozdz-PCT first provides an introduction that includes a laundry list of applications, concluding that the “most suitable route in any given case will depend on the nature and severity of the condition treated and on the nature of the particular therapeutic agent which is being used.”²⁷⁰ Gwozdz-PCT then provides description of specific embodiments. First, Gwozdz-PCT discusses nasal

²⁶⁹ EX1009 (Gwozdz-PCT) at 10:3-14 (emphasis added).

²⁷⁰ EX1009 (Gwozdz-PCT) at 8:32-9:19.

applications;²⁷¹ then injections;²⁷² then oral administration;²⁷³ then parenteral administration;²⁷⁴ then topical application;²⁷⁵ then transdermal administration.²⁷⁶

The one reference to “penetration enhancer” does not appear in the section for “nasal applications,” which Dr. Donovan concedes.²⁷⁷ Rather, the one reference to “penetration enhancers” appears only in the embodiment on injection application.²⁷⁸ Thus, Dr. Donovan is basing her motivation to combine Gwozdz-PCT and Meezan by extracting a “penetration enhancer” from an injection administration and then, absent any reasoning or explanation, applying it to a nasal administration.

²⁷¹ EX1009 (Gwozdz-PCT) at 9:20-10:2.

²⁷² EX1009 (Gwozdz-PCT) at 10:3-16.

²⁷³ EX1009 (Gwozdz-PCT) at 10:17-11:16

²⁷⁴ EX1009 (Gwozdz-PCT) at 11:17-26.

²⁷⁵ EX1009 (Gwozdz-PCT) at 11:27-12:27.

²⁷⁶ EX1009 (Gwozdz-PCT) at 12:28-13:3.

²⁷⁷ EX2070 (Donovan Tr.) at 87:15-21.

²⁷⁸ EX1009 (Gwozdz-PCT) at 10:3-16.

(3) No other motivation to add ingredients to Gwozdz-PCT

251. As discussed above, apart from this “penetration enhancer” disclosure, I see no evidence in Gwozdz-PCT that a skilled artisan would have thought there was any reason to add another ingredient to a solution of diazepam tocopherol/alcohol that Gwozdz-PCT discloses; let alone any reason to focus on alkyl glycosides; let alone any reason to focus on Meezan. That is, nowhere does Gwozdz-PCT disclose any inadequacy with the solubility or bioavailability of diazepam in a tocopherol/alcohol solution.

252. Quite the contrary. Gwozdz-PCT 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.”²⁷⁹ According to Dr. Donovan, it was commonly understood that diazepam, by its very nature, would “readily cross biological membranes;” it did not need help in this regard.²⁸⁰

iii. The monograph cited by Dr. Donovan demonstrates why a skilled artisan would not be

²⁷⁹ EX1009 (Gwozdz-PCT) at 7:3-8 (emphasis added).

²⁸⁰ EX1062 (Donovan-786 Decl.) ¶65.

motivated to add alkyl glycosides to Gwozdz-PCT

253. Relying on Rowe (EX1016), Dr. Donovan states that a skilled artisan would have been “motivated to include benzyl alcohol in the intranasal spray of Gwozdz despite any potential irritation,” because “benzyl alcohol was known to function as an antimicrobial preservative, which would provide another benefit to its inclusion in the solvent system.”²⁸¹ Yet, the monograph that Dr. Donovan relies on states that “antimicrobial activity [of benzyl alcohol] is reduced in the presence of nonionic surfactants.”²⁸² The same monograph states that “Ethanol is inactivated in the presence of nonionic surfactants....”²⁸³ As *n*-dodecyl- β -maltoside is a type of non-ionic surfactant, this is another reason that a skilled artisan would not have been motivated to add *n*-dodecyl- β -maltoside to the alcohol-containing formulations that Gwozdz-PCT discloses.

254. The same monograph on which Dr. Donovan relies also explains that ethanol is a “skin penetrant.”²⁸⁴ Dr. Donovan agreed at her deposition that this is

²⁸¹ EX1062 (Donovan-786 Decl.) ¶116 (cleaned up).

²⁸² EX1016 (Rowe) at 10 (within Section 12, “Incompatibilities”).

²⁸³ EX1016 (Rowe) at 4 (within Section 10, “Typical Properties”).

²⁸⁴ EX1016 (Rowe) at 3 (Section 6, “Functional Category” of ethanol).

synonymous with a penetration enhancer.²⁸⁵ Thus, as Gwozdz-PCT already has ethanol, a skilled artisan would not have been motivated to add a second penetration enhancer.

3. Even If a Skilled Artisan Were to Modify Gwozdz-PCT, There is No Reason to Modify It by Combining with Meezan

255. I do not understand Dr. Donovan to argue that Meezan supplies a motivation to combine its teachings with those of Gwozdz-PCT, and indeed Meezan does not.

256. Meezan does not mention “diazepam” or “benzodiazepine” in any form, and it does not disclose any applications with benzodiazepines. Nor does Meezan mention, or disclose applications with, tocopherols. A skilled artisan would have recognised that Meezan and Gwozdz-PCT are directed to different applications and would not have combined the references in the way Dr. Donovan does. To try to stitch together the two references, Dr. Donovan selects isolated passages from Meezan out of context. I have been informed that one important way to avoid applying hindsight in an obviousness analysis is to consider the reference (Meezan) as a whole for everything it teaches, rather than picking and choosing amongst isolated passages.

²⁸⁵ EX2070 (Donovan Tr.) at 169:21-170:4.

a. Meezan is directed to large macromolecules, not smaller molecules like benzodiazepines

257. To the extent a skilled artisan would have even set forth to modify the formulation of Gwozdz-PCT (which as I discuss above, there is no reason to), a skilled artisan would not have looked to the disclosure of Meezan for that modification.

258. The words “benzodiazepine” and “diazepam” are never mentioned in Meezan.²⁸⁶ I find it notable that Meezan does *not* refer to benzodiazepines, given the vast array of drugs, proteins, peptides, nucleic acids, and over 30 broad categories of drugs it mentions.²⁸⁷ While one of those broad categories is “anti-seizure agents,” the exemplary compounds of this type (topiramate and zonisamide) are not benzodiazepines.²⁸⁸ Accordingly, I understand that the Patent Office already has found that “Meezan does not teach using a benzodiazepine active ingredient.”²⁸⁹ This makes sense to me since nowhere does Meezan mention – let alone apply its teachings to – benzodiazepines generally or diazepam specifically.

²⁸⁶ EX2070 (Donovan Tr.) at 148:25-149:10.

²⁸⁷ EX1010 (Meezan) at ¶¶[0050]-[0052].

²⁸⁸ EX1010 (Meezan) at ¶[0052].

²⁸⁹ *See, e.g.*, EX1007 (’439 FH) at 3315 (Office Action dated March 30, 2017).

259. The absence of any examples of diazepam or other benzodiazepines is because Meezan concerns itself with stabilising solutions of peptides, proteins, nucleic acids, and other macromolecules;²⁹⁰ and with increasing the bioavailability of such macromolecules.²⁹¹ For example, Meezan states the following regarding the molecules:

Therapeutic agents or drugs of the present invention can be peptides or proteins, medically or diagnostically useful, of small to medium size, e.g. up to about 15 kD, 30 kD, 50 kD, 75 kD, etc., or a protein having between about 1-300 amino acids or more. The methods of the invention also anticipate the use of small molecules, for example, an organic compound that has a molecular weight of less than 3 kD, or less than 1.5 kD.²⁹²

However, each of the examples (e.g., Examples 1-7) of Meezan examines the effects of alkyl glycosides on aqueous solutions of the large molecules, such as vasopressin, insulin, and human growth hormone.²⁹³ In contrast, no data or examples (even prophetic examples) are provided of alkyl glycosides used with solutions of

²⁹⁰ EX1010 (Meezan) at, e.g., ¶¶[0064], [0070], [0092], and Example 2, ¶¶[0149]-[0152].

²⁹¹ EX1010 (Meezan) at, e.g., Examples 1-7, ¶¶[0146]-[0172].

²⁹² EX1010 (Meezan) ¶[0130].

²⁹³ EX1010 (Meezan) ¶[0131].

benzodiazepines or any other small molecules.²⁹⁴ This absence matters because bioavailability of macromolecules (such as proteins) present different challenges than bioavailability of small molecules (such as benzodiazepines).

260. While Meezan says it “anticipate[s]” using the disclosed methods with “small” molecules, that would have informed a skilled artisan that such an application was simply a hypothesis – not a known application or actual teaching.²⁹⁵ This observation correlates with the fact that every Example presents data for peptides or proteins, and not for small molecules. This observation also correlates with the disclosed sizes for what Meezan considers “small molecules”:

The methods of the invention also anticipate the use of small molecules, for example, an organic compound that has a molecular weight of less than 3 kD, or less than 1.5 kD.²⁹⁶

Diazepam is significantly smaller, with a molecular weight of around 285 Daltons. Meezan also refers to compounds that are “low molecular weight,” but Meezan defines the range very broadly to include molecules of 1,000-30,000 Daltons (“1-30 kiloDaltons”),²⁹⁷ which again would not include diazepam (m.w. 284.74 g/mol) but

²⁹⁴ EX2070 (Donovan Tr.) at 141:9-143:18.

²⁹⁵ EX1010 (Meezan) ¶[0130].

²⁹⁶ EX1010 (Meezan) ¶[0130].

²⁹⁷ EX1010 (Meezan) ¶¶[0012]-[0013].

which would include many peptides and proteins. The broader context of Meezan clarifies that the “low molecular weight” is in reference to much larger proteins:

- “low molecular weight peptides such as Exenatide, GLP-1 and the like”;²⁹⁸
- “low molecular weight heparin and inhibitory RNA”²⁹⁹

These peptides, proteins, and other biologics have weights that are orders of magnitude larger than diazepam.

261. Dr. Donovan attempts to bridge the divide between what Meezan actually teaches (macromolecules) and what Gwozdz-PCT teaches (diazepam) as follows:

Additionally, it is well-known that larger molecules inherently have a more difficult time crossing the cell membrane than do 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.³⁰⁰

²⁹⁸ EX1010 (Meezan) ¶[0004].

²⁹⁹ EX1010 (Meezan) ¶[0004]; *see also* EX1010 (Meezan) ¶¶[0008], [0051], [0076], [0089], [0099], [0132], [0136] (heparin, nicotine, interferon, PYY, GLP-1, Exendin, HGH, parathyroid hormone).

³⁰⁰ EX1062 (Donovan-786 Decl.) ¶111.

But that just demonstrates the hindsight used for the obviousness combination. Under Dr. Donovan’s reasoning, a small molecule (e.g., diazepam) does not have as much difficulty passing through the cell membrane as a large molecule. Thus, while a “permeation enhancer” may have been needed for a large molecule, a skilled artisan would have considered the permeation enhancer superfluous—and thus has no reason to use it—for a small molecule such as diazepam. There would have been no reason to modify the working formulation of Gwozdz-PCT with any of the multitude of untested permeation enhancers of Meezan.

b. Meezan does not teach compatibility with tocopherol or tocopherol/alcohol carriers

262. In addition to failing to disclose application of the alkyl glycosides for diazepam or other benzodiazepines, Meezan also fails to teach combining its alkyl glycosides with solutions of tocopherols or of tocopherol/alcohol solutions. Dr. Donovan relies on paragraph [0074] of Meezan to state that “Meezan also discloses using alkyl glycosides in non-aqueous systems.”³⁰¹ She then summarizes the paragraph as follows:³⁰²

Additionally, the therapeutic compositions of the invention can consist of a pharmaceutically acceptable carrier. A

³⁰¹ EX1062 (Donovan-786 Decl.) ¶113.

³⁰² EX1062 (Donovan-786 Decl.) ¶113.

‘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,...³⁰³

This is Dr. Donovan’s only support for using the disclosure of Meezan with a non-aqueous system (e.g., as in the challenged claims). I do not agree that this passage discloses or suggests using the alkyl glycosides of Meezan with the tocopherol/alcohol solutions of Gwozdz-PCT.

263. First, even Dr. Donovan does not contend that Meezan discloses using its disclosed alkyl glycosides with a tocopherol-containing solution like that of Gwozdz-PCT. Indeed, nowhere does “tocopherol,” “tocotrienol,” “Vitamin E,” or any analogue of those terms appear in Meezan.³⁰⁴

264. Second, and in contrast, every disclosed Example in Meezan adds an alkyl glycoside to an aqueous solution of peptides or proteins. None of the Examples exemplifies applying the alkyl glycosides of Meezan to any form of nonaqueous solution (let alone a non-aqueous solution of diazepam). The presence of water in

³⁰³ EX1062 (Donovan-786 Decl.) ¶113 (summarizing EX1010 (Meezan) ¶[0074]).

³⁰⁴ EX2070 (Donovan Tr.) at 150:1-7.

the solutions of Meezan provides another reason a skilled artisan would not add Meezan to Gwozdz-PCT to arrive at the claimed invention. The claimed invention requires tocopherols, and it was known that tocopherols are susceptible to degradation in water, as I describe below.³⁰⁵

265. Third, to the extent Dr. Donovan contends that Meezan suggests (though does not disclose) Vitamin E through its reference to an “oil” (as in paragraph [0074] of Meezan), I understand such a contention to be inconsistent with the position that the Petitioner (and Dr. Donovan, herself) is taking in a court proceeding that is occurring in parallel with this Proceeding. In the court case, the Petitioner argues – with support from Dr. Donovan – that “the Asserted Claims cannot include other potential ingredients, including water *and oil*.”³⁰⁶ Both also argue that if oil is permitted within the scope of the claims, the claims are indefinite.³⁰⁷ Dr. Donovan has not explained why she believes a different position

³⁰⁵ See EX2070 (Donovan Tr.) at 283:1-284:13.

³⁰⁶ EX2050 (Joint CC Brief) at 9. See also EX2069 (Donovan CC Decl.) at 17-18 (“water content and oil content are not simply ‘impurities’ that can be included within the scope of the claimed solutions . . .”).

³⁰⁷ EX2050 (Joint CC Brief) at 9. See also EX2069 (Donovan CC Decl.) at 18 (“If the Claims of the Asserted Patents are Construed to Allow for the Inclusion of Unrecited Components, Including Water *and Oil*, the Claims are Indefinite”) (emphasis added).

on what is or is not permitted within the claims is justified here. And if Vitamin E is not an “oil,” then Dr. Donovan cannot rely on disclosure of “oil” or “oleaginous” (oily) agents in Meezan to mean Vitamin E. Since this is the only passage from Meezan on which either relies to argue disclosure of using Meezan’s alkyl glycosides with tocopherol-containing solutions of Gwozdz-PCT, Meezan cannot (and does not) disclose making that combination.

c. Multifactorial effect on therapeutic agent and other excipients

266. As explained above, Gwozdz-PCT discloses a working formulation to deliver diazepam and that contains tocopherol/ethanol. In contrast, Meezan does not disclose diazepam and does not disclose tocopherol/ethanol. To the extent a skilled artisan would have modified Gwozdz-PCT at all to add a penetration enhancer, a skilled artisan would have sought out an appropriate excipient that was demonstrated as compatible for the particular formulation at issue—not the alkyl glycosides of Meezan.

267. A skilled artisan would have understood that the inclusion of any additional excipient into a formulation can have a multifactorial detrimental effect, because any such excipient can interact both with the drug (e.g., diazepam) and any other excipient present (e.g., Vitamin E, ethanol, or benzyl alcohol). For example, the monograph cited by Dr. Donovan explains that the presence of non-ionic

surfactants (such as *n*-dodecyl- β -maltoside) inactivates ethanol as an antimicrobial³⁰⁸ and reduces the effectiveness of benzyl alcohol.³⁰⁹

268. In addition, a skilled artisan would have understood the excipient could also interact with any other excipients already included in the formulation, in this case the alcohol and/or the tocopherol, thereby negatively affecting its ability to solubilise the diazepam and also influencing the long-term physical stability of the formulation. This is especially the case with an excipient like tocopherol, which was known to be unstable generally and sensitive to degradation from exposure to light, heat, oxygen, and water, leading to discolouration over time; something never wanted in formulation development.³¹⁰ A skilled artisan would have known that the simpler the formulation the better, as there is less to go wrong and a hence higher chance of success — more so when considering adding untested excipients (such as dodecyl maltoside) to an already working formulation.

³⁰⁸ EX1016 (Rowe) at 14 (within Section 10, “Typical Properties”).

³⁰⁹ EX1016 (Rowe) at 10 (within Section 12, “Incompatibilities”).

³¹⁰ EX2070 (Donovan Tr.) at 283:1-284:13.

4. The Combination of Gwozdz-PCT and Meezan Does Not Suggest *N*-dodecyl- β -D-maltoside

269. Even if a skilled artisan would have considered Meezan, there would have been no reason to modify Gwozdz-PCT to add alkyl glycosides, let alone dodecyl maltoside, let alone *n*-dodecyl- β -D-maltoside (which is not even disclosed in Meezan). To the contrary, Meezan teaches to use “highly branched” alkyl glycosides rather than linear alkyl glycosides like *n*-dodecyl- β -D-maltoside.

a. Meezan suggests branched alkyl glycosides, not linear “*n*-dodecyl-beta-D-maltoside.”

270. In the detailed write-up for Claim Element 1(d) and Claim Element 11(d), Dr. Donovan fails to point to any disclosure in Gwozdz-PCT or Meezan for the claimed “*n*-dodecyl-beta-D-maltoside.”³¹¹ Rather, she extrapolates at the end of her write-up that “a POSA would routinely select *n*-dodecyl-beta-D-maltoside.”³¹² She provides no citations to Gwozdz-PCT or Meezan, no citations to other evidence, and no reasoning to support this conclusory assertion that a skilled artisan “routinely” would select the claimed isomer out of the over 700 other isomers for the “dodecyl maltoside” disclosed in Meezan (or indeed why the artisan would select

³¹¹ EX1062 (Donovan-786 Decl.) ¶¶147-153, ¶198.

³¹² EX1062 (Donovan-786 Decl.) ¶151.

any form of dodecyl maltoside amongst the legion of alkyl glycosides Meezan discloses). Dr. Donovan's conclusion is pure, unsupported hindsight.

271. I have independently reviewed Gwozdz-PCT and Meezan, and I too find no disclosure in either reference of *n*-dodecyl- β -D-maltoside. The references to any form of dodecyl maltoside appear as follows:

- “dodecylmaltoside” or “dodecyl maltoside”;³¹³
- “DDM”³¹⁴
- “dodecyl- α -D-maltoside”³¹⁵
- “dodecyl- β -D-maltoside”³¹⁶; and
- “dodecyl- μ -D-maltoside”³¹⁷

None of these references specifies *n*-dodecyl- β -D-maltoside, and there is nothing in either Gwozdz-PCT or Meezan to suggest that the linear (non-branched) isomer should be used. (To the contrary, as discussed below.) Further, the dodecyl

³¹³ EX1010 (Meezan) ¶¶[0092], [0158], Table I.

³¹⁴ EX1010 (Meezan) ¶¶[0092], [00149].

³¹⁵ EX1010 (Meezan) ¶[0056].

³¹⁶ EX1010 (Meezan) ¶¶[0056], [0156], [0157].

³¹⁷ EX1010 (Meezan) ¶[0155].

maltoside itself is not even called out, but is instead buried in a longer list of other types of alkyl groups, such as the following:

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 ³¹⁸

272. As I describe above, the only location where Meezan describes the isomeric structure of dodecyl maltoside is in Paragraph [0149]. There, Meezan states:

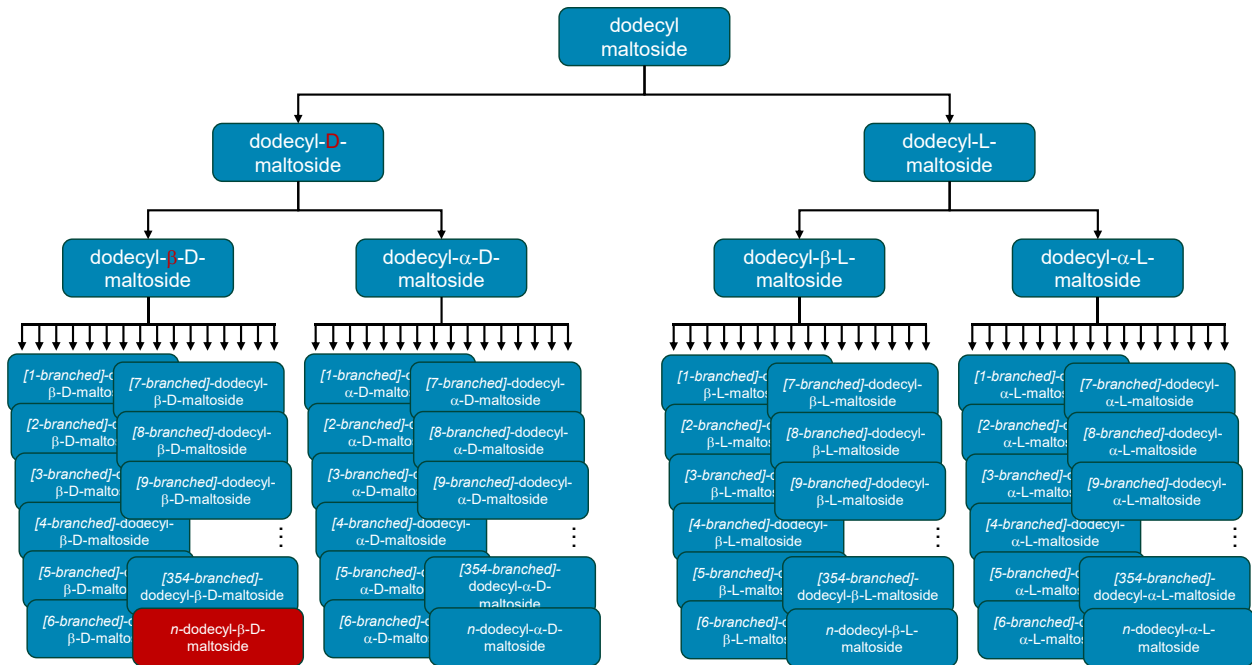
Stability of the alkyl glycoside depends, in part, on the number of carbon atoms, or branching of the alkyl chain, with tetradecylmaltoside (TDM) having the greatest effect; but other **highly branched alkyl chains including DDM** [dodecyl maltoside] also have stabilizing effects.³¹⁹

In this passage Meezan leads a skilled artisan to conclude that the dodecyl maltoside to use is one with “branching” or even “highly branched” isomers. This description necessarily refers to the isomerization of the “dodecyl” moiety, rather than the “maltoside” moiety, because maltose is a disaccharide (i.e., only two units) and thus cannot be branched (let alone “highly” branched). Amongst the 355 isomers of

³¹⁸ EX1010 (Meezan) ¶¶[0056]; *see also* ¶¶[0056]-[0058].

³¹⁹ EX1010 (Meezan) ¶[0149] (emphasis added); *see* EX1062 (Donovan-786 Decl.) ¶93.

dodecyl- β -D-maltoside (and even more if alpha glycosidic linkages and L-maltoside are included), Meezan is teaching to use the branched isomers, not the claimed “*n*-dodecyl-beta-D-maltoside” (which is linear and not branching).



273. If anything, Meezan tells a skilled artisan to select a “highly branched” maltoside and *not* the linear isomer (*n*-dodecyl- β -D-maltoside). Meezan teaches away from the challenged claims.

b. Meezan suggests using alkyl glycosides with longer chains than dodecyl maltoside

274. As I have previously discussed, I do not believe a skilled artisan would have found motivation in Gwozdz-PCT or for other reasons that would have led that person to Meezan. Nor do I believe Meezan supplies any motivation to combine its

teachings with the diazepam/tocopherol/alcohol solution of Gwozdz-PCT. I also do not believe Meezan discloses, or even suggests, *n*-dodecyl- β -D-maltoside. Instead, it discloses “highly branched” dodecyl maltoside.³²⁰

275. That all having been said, *if* a skilled artisan who already knew of Gwozdz-PCT happened upon Meezan and considered its disclosures, I believe that person would have found that Meezan suggests using alkyl glycosides with longer chains than 12 carbons (dodecyl) as more efficacious options – in particular branched tetradecyl-maltoside (TDM, 14 carbons). The Figures, Examples, specification, and claims all point to TDM as the most preferred option. Other alkyl glycosides also performed better than dodecyl maltoside and would have been preferable to a skilled artisan.

i. Importance of “highly branched” and longer chains

276. Meezan repeatedly discloses the importance of how “an ideal enhancing surfactant will stabilize the therapeutic agent.”³²¹ To achieve this goal,

³²⁰ EX1010 (Meezan) ¶[0149].

³²¹ EX1010 (Meezan) ¶[0003]; *see also* EX1010 (Meezan) ¶¶[0064], [0070], [0092], and Example 2, ¶¶[0149]-[0152] (disclosing the goal of stabilizing the therapeutic agent).

Meezan recommends using “highly branched” glycosides.³²² As a matter of basic organic chemistry, and I discuss above in the technical background on “alkanes,” the longer the carbon chain, the more branching that can occur.³²³ So too, Meezan discloses that tetradecyl maltoside (“TDM,” a maltoside bonded to a 14-carbon alkyl chain) actually has “the greatest effect,” not dodecyl maltoside (a maltoside bonded to a 12-carbon alkyl chain).³²⁴ This is because, according to Meezan, the longer the alkyl chain, the more effective the absorption enhancer.³²⁵ Elsewhere, Meezan refers to the “alkyl chain length, as well as the carbohydrate moiety,” as having a “critical” role on the absorption of certain therapeutic agents.³²⁶ Contrary to Dr. Donovan’s contention, Meezan discloses that the identity of the alkyl glycoside is important, and Meezan teaches to use a longer and more branched chain: TDM is better than DDM, and “highly branched” alkyl groups have the greatest effect. Yet the claimed species is linear (not branched).

³²² EX1010 (Meezan) ¶[0149].

³²³ *See supra*, Section IX.A.2; EX2070 (Donovan Tr.) at 21:2-14.

³²⁴ EX1010 (Meezan) ¶[0149].

³²⁵ EX1010 (Meezan) ¶[0157].

³²⁶ EX1010 (Meezan) ¶[0160].

277. Consequently, I see no evidence that Meezan discloses the *n*-dodecyl- β -D-maltoside element that every challenged claim requires, nor that selecting dodecyl maltoside (let alone *n*-dodecyl- β -D-maltoside) would have been a routine and obvious choice.

ii. Examples 1-7 of Meezan would have led a skilled artisan to TDM, not dodecyl maltoside (and certainly not *n*-dodecyl- β -D-maltoside)

278. A skilled artisan reviewing Meezan would have observed that the application includes some data analysing certain qualities of several alkyl glycosides. These data are presented in seven numbered Examples.³²⁷ The skilled artisan would have made several observations from the content of these disclosures.

279. First, for every example that incorporates an alkyl glycoside with an active drug substance, the drug substance is a peptide or a protein (as opposed to diazepam) apparently dissolved in aqueous medium (as would be expected for peptides and proteins). This choice would have made sense to a skilled artisan in 2008 or 2009, as it was well known then (and now) that large molecules like peptides, proteins, and nucleic acids are poorly absorbed when administered by extravascular routes. As Dr. Donovan states, “it is well-known that larger molecules

³²⁷ EX1010 (Meezan) at ¶¶[0146]-[0172].

inherently have a more difficult time crossing the cell membrane than do smaller molecules.”³²⁸ This evidence would not have led the skilled artisan to apply Meezan to a small molecule application, such as the diazepam solutions of Gwozdz-PCT, as there would be no need to do so.

280. Second, every Example in Meezan examines characteristics of TDM. Example 1 provides evidence that TDM is nontoxic when administered intranasally over time.³²⁹ Example 2 provides evidence that TDM increases bioavailability of a peptide administered intranasally while decreasing variability of its absorption.³³⁰ Examples 3-7 provide evidence that TDM increases bioavailability of other peptides administered intranasally and ocularly.³³¹ Throughout these various routes of delivery, TDM works better than dodecyl maltoside, as discussed below.

281. Third, TDM compared favourably to other alkyl glycosides that were tested. When 0.125% TDM and 0.125% DDM eye drops were tested for their ability to increase insulin absorption when administered ocularly in rats, TDM showed

³²⁸ EX1062 (Donovan-786 Decl.) ¶111.

³²⁹ EX1010 (Meezan) at ¶¶[0146]-[0148].

³³⁰ EX1010 (Meezan) at ¶¶[0149]-[0152].

³³¹ EX1010 (Meezan) at ¶¶[0153]-[0172].

substantial efficacy (lowering measured blood glucose levels from 322 mg/dL to 208 mg/dL), while dodecyl maltoside was ineffective at that dose (with the blood glucose levels not materially changing from 338 mg/dL to 342 mg/dL at 120 h).³³²

TABLE I

Effect of Eye Drops Containing Insulin Plus Various Concentrations of Dodecyl Maltoside on Blood Glucose Values (in mg/dl) in Rat

Time (min)	Dodecyl Maltoside Concentration			
	0.125%	0.25%	0.375%	0.50%
-20	305 ± 60	271 ± 38	305 ± 51	375 ± 9
-10	333 ± 58	295 ± 32	308 ± 27	366 ± 12
0	338 ± 67	323 ± 62	309 ± 32	379 ± 4
30	349 ± 64	250 ± 48	212 ± 18	297 ± 18
60	318 ± 38	168 ± 22	134 ± 4	188 ± 25
90	325 ± 57	188 ± 55	125 ± 12	144 ± 13
120	342 ± 78	206 ± 63	119 ± 19	123 ± 5

TABLE II

Effect of Insulin Eye Drops, Containing 0.125% Tetradecyl Maltoside and Nose Drops Containing 0.5% Tetradecyl Maltoside on Blood Glucose Values in Rats

Blood Glucose (mg/dl)	
Time (min)	
-20	319
-10	311
Eye drops added	
0	322
15	335
30	276
45	221
60	212
75	167
90	174
105	167
120	208
Nose Drops Added	
135	129
150	74
165	76
180	68

Dodecyl-sucrose and tridecyl-maltoside were also more effective than dodecyl maltoside.³³³

282. Similarly, as seen in Example 5, when 0.5% TDM solutions were tested against 0.5% solutions of decyl maltoside, dodecyl sucrose, and tridecyl maltoside

³³² EX1010 (Meezan) at ¶¶[0153]-[0164] (Tables I and II) (annotations added).

³³³ EX1010 (Meezan) at ¶¶[0158]-[0159].

for their relative ability to reduce blood glucose (by increasing the absorption of insulin), TDM appeared to be the best performer.³³⁴

TABLE II	
Effect of Insulin Eye Drops, Containing 0.125% Tetradecyl Maltoside and Nose Drops Containing 0.5% Tetradecyl Maltoside on Blood Glucose Values in Rats	
Blood Glucose (mg/dl)	
Time (min)	
-20	319
-10	311
Eye drops added	
0	322
15	335
30	276
45	221
60	212
75	167
90	174
105	167
120	208
Nose Drops Added	
135	129
150	74
165	76
180	68

TABLE III			
Effect of Eye Drops Containing Insulin or Glucagon and 0.5% Decyl Maltoside, 0.5% Dodecyl Sucrose, or 0.5% Tridecyl Maltoside on Blood Glucose Values in Rats			
Surfactant Agent			
Time (min)	Dodecyl Sucrose	Decyl Maltoside	Tridecyl Maltoside
Blood Glucose Concentration (mg/dl)			
-20	266	249	255
-10	305	287	307
Insulin Eye Drops Added			
0	351	337	323
10	347	304	309
20	252	292	217
30	161	221	131
40	120	164	100
50	105	138	87
60	114	114	107
70	113	104	115
80	104	110	79
90	86	120	85
100	113	92	76
110	107	81	74
120	112	87	75

I note that the TDM values at 0.5% are not comparable to the values for the other alkyl glycosides because TDM was administered intranasally (following ocular administration of a 0.125% solution) whereas the other alkyl glycosides were administered ocularly at 0.5%. Thus, not even Meezan delivered the dodecyl maltoside intranasally. In any event, it was clear that TDM performed the best in this study.

³³⁴ EX1010 (Meezan) at Tables II, III (annotations added).

283. Fourth, dodecyl maltoside was the worst-performing alkyl glycoside when compared with decyl maltoside, dodecyl sucrose, and tridecyl maltoside. Intraocular administration of 0.5% solutions of each, formulated with insulin, to rats showed that dodecyl maltoside was the least effective and tridecyl maltoside was the most effective.³³⁵

TABLE I					TABLE III			
Effect of Eye Drops Containing Insulin Plus Various Concentrations of Dodecyl Maltoside on Blood Glucose Values (in mg/dl) in Rat					Effect of Eye Drops Containing Insulin or Glucagon and 0.5% Decyl Maltoside, 0.5% Dodecyl Sucrose, or 0.5% Tridecyl Maltoside on Blood Glucose Values in Rats			
Dodecyl Maltoside Concentration					Surfactant Agent			
Time (min)	0.125%	0.25%	0.375%	0.50%	Time (min)	Dodecyl Sucrose	Decyl Maltoside	Tridecyl Maltoside
Blood Glucose Concentrations (mg/dl)					Blood Glucose Concentration (mg/dl)			
-20	305 ± 60	271 ± 38	305 ± 51	375 ± 9	-20	266	249	255
-10	333 ± 58	295 ± 32	308 ± 27	366 ± 12	-10	305	287	307
0	338 ± 67	323 ± 62	309 ± 32	379 ± 4	Insulin Eye Drops Added			
30	349 ± 64	250 ± 48	212 ± 18	297 ± 18	0	351	337	323
60	318 ± 38	168 ± 22	134 ± 4	188 ± 25	10	347	304	309
90	325 ± 57	188 ± 55	125 ± 12	144 ± 13	20	252	292	217
120	342 ± 78	206 ± 63	119 ± 19	123 ± 5	30	161	221	131
					40	120	164	100
					50	105	138	87
					60	114	114	107
					70	113	104	115
					80	104	110	79
					90	86	120	85
					100	113	92	76
					110	107	81	74
					120	112	87	75

284. In summary, Meezan provides examples of ocular and nasal administration. Throughout the Examples, Meezan extols the benefits of TDM (and dodecyl sucrose), including how they were nontoxic and that TDM was highly effective at increasing absorption of insulin. Meezan explains that amongst the

³³⁵ EX1010 (Meezan) at Tables I, III (annotations added).

options, dodecyl maltoside was the least effective alkyl glycoside tested at increasing absorption of insulin; and that at comparable doses, TDM increased absorption of insulin whereas dodecyl maltoside was totally ineffective. Thus, to the extent a skilled artisan would have even looked to Meezan for an absorption enhancer to use with Gwozdz-PCT, the skilled artisan would have been led to use TDM and not dodecyl maltoside, and certainly not *n*-dodecyl- β -D-maltoside.

285. In addition to the Examples, the remainder of the specification of Meezan also teaches away from *n*-dodecyl- β -D-maltoside. The dodecyl maltoside Meezan examines possessed a “highly branched” alkyl group rather than the claimed linear one.³³⁶ Insofar as the person of ordinary skill were to draw the conclusion from Table I that at least at high relative concentrations “dodecyl maltoside” could improve absorption of insulin (albeit worse than every other alkyl glycoside tested), the “dodecyl maltoside” showing that effect was “highly branched,” and not the claimed *n*-dodecyl- β -D-maltoside.

iii. Other reasons a skilled artisan would not be motivated to use *n*-dodecyl- β -D-maltoside

286. At the outset, Meezan provides a “Summary of the Invention” in which it states that “the present invention” includes “enhancing agents” that include “an

³³⁶ EX1010 (Meezan) at ¶[0149].

alkyl glycoside and/or saccharide alkyl ester.”³³⁷ Each of these categories of compounds (“alkyl glycosides” and “saccharide alkyl esters”) are so generic as to encompass uncountable numbers of potential molecules. A skilled artisan would not understand Meezan to disclose that *n*-dodecyl- β -D-maltoside is a “preferred” alkyl glycoside (or even that Meezan discloses this molecule at all, as I discussed previously). Rather, when Meezan discusses the concept of “preferred” molecules, with one exception (i.e., TDM) the scope of what is “preferred” is so broad as to provide little guidance to a skilled artisan. Thus, I also disagree with Dr. Donovan when she states that “Meezan again identifies dodecyl maltoside (i.e., ‘DDM’) as one of the preferred alkyl glycosides having an absorption-enhancing and bioavailability-increasing effect on the drug compound.”³³⁸

287. I reiterate that notwithstanding the breadth—and lack of specificity—of this disclosure, I do not believe Meezan describes *n*-dodecyl- β -D-maltoside, as required by every challenged claim. As I discuss above, when Meezan identifies the more generic “dodecyl maltoside,” that is in the context of suggesting that a skilled

³³⁷ EX1010 (Meezan) at ¶[0004].

³³⁸ EX1062 (Donovan-786 Decl.) ¶94.

artisan use molecules with “highly branched” alkyl chains, which contrasts with the linear alkyl chain of *n*-dodecyl- β -D-maltoside.

288. The vastness of this domain of “alkyl glycoside and/or saccharide alkyl ester” results from the modular nature of these types of compounds, the many options for those moieties, and the various permutations resulting from varying one or more of those moieties. The variables that Meezan discloses and that characterise these categories of compounds include:

- The saccharide or glycoside (e.g., single-unit sugars such as glucose, fructose, and galactose, or two-unit sugars such as maltose, etc.);
- The stereochemistry of the saccharide or glycoside (e.g., D or L);
- The anomeric structure of the saccharide or glycoside (e.g., α or β);
- Substitution of heteroatoms (e.g., sulphur) in the saccharide or glycoside;
- The alkyl chain (its size and its isomeric structure);
- The linking chemistry between the moieties.

These variables are addressed more fully as follows.

289. **Alkyl Groups**. Meezan discloses alkyl groups from 8 to 24 carbon atoms in molecular weight.³³⁹ Meezan further states that “the hydrophobic alkyl can

³³⁹ EX1010 (Meezan) at ¶[0056] (“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-,

thus be chosen of any desired size, depending on the hydrophobicity desired and the hydrophilicity of the saccharide moiety.”³⁴⁰

290. Concerning the isomerization of the alkyl moieties in the disclosed compounds, with the exception of dodecyl- and tetradecyl-maltoside (which Meezan describes as “highly branched”), the amount and variety of branching of these moieties is not described.³⁴¹ A skilled artisan would have understood that alkyl moieties can possess many different isomeric configurations, where the number of isomers increases geometrically as molecular weight increases. I discuss this more in the technology background section of “alkanes,” above. For example, as I discussed above, while an octyl (8-mer) group can exist as 18 different isomers, a dodecyl (12-mer) group can exist as 355 different isomers, and a 20-mer can exist as 366,319 different isomers. Meezan describes alkyl moieties of 9-24 carbon atoms as “preferred” and 9-16 carbon atoms as “more preferred.”³⁴² A skilled artisan would gravitate towards the heavier alkyl chains (and not dodecyl), because of Meezan’s

and octadecyl”); EX1010 (Meezan) at ¶[0058] (“one preferred range of alkyl chains is from about 9 to about 24 carbon atoms.”).

³⁴⁰ EX1010 (Meezan) at ¶[0058].

³⁴¹ EX1010 (Meezan) at ¶[0149].

³⁴² EX1010 (Meezan) at ¶[0058].

emphasis on alkyl chain length and the importance of branching, and because the longer the carbon chain the more branching can occur.

291. **Glycoside**. Meezan discloses many options as potential glycosides (the sugar moiety), including glucoside, sucroside, maltoside, lactoside, maltotrioside, maltotetroside, trehaloside, palatinose derivatives, and isomaltamine derivatives.³⁴³ Meezan does not narrow the field to “maltose” (maltoside), because Meezan states that “*some* preferred glycosides include maltose, sucrose, and glucose.”³⁴⁴

292. **Heteroatoms**. Meezan expresses a preference for heteroatom substitution (i.e., replacing a carbon atom with a non-carbon and non-hydrogen atom to alter the molecule’s properties). Meezan discloses that “to decrease susceptibility of alkyl saccharides or saccharide alkyl esters to hydrolytic cleavage of the drug, various oxygen atoms within the drugs can be substituted for by sulfur.”³⁴⁵ The purpose of substituting heteroatoms (e.g., sulphur) for oxygen at strategic locations in the molecule would be to render the resulting molecule more chemically and biochemically stable. Several specific thioglycosides are disclosed as options for

³⁴³ EX1010 (Meezan) at ¶¶[0056], [0059], [0159].

³⁴⁴ EX1010 (Meezan) at ¶[0058] (emphasis added).

³⁴⁵ EX1010 (Meezan) at ¶[0075].

absorption enhancers.³⁴⁶ In contrast, dodecyl maltoside does not have any heteroatoms.

293. **Linking Chemistry.** Meezan discloses that “[t]he linkage between the hydrophobic alkyl group and the hydrophilic saccharide can include, among other possibilities, a glycosidic, thioglycosidic, amide, ureide, or ester linkage.”³⁴⁷ Accordingly, Meezan discloses both alkyl glycosides (having ether linkages to the glycoside) and saccharide alkyl esters (connected by ester linkages), as well as specific thioglycosides (noted above), amides (*e.g.*, “long chain aliphatic carbonic acid amides of sucrose β -amino-alkyl ethers”; “derivatives of palatinose and isomaltamine linked by amide linkage to an alkyl chain”), and ureides (*e.g.*, “derivatives of isomaltamine linked by urea to an alkyl chain”; and “long chain aliphatic carbonic acid ureides of sucrose β -amino-alkyl ethers”).³⁴⁸ Meezan expresses no preference for α - vs. β -anomers: “oligosaccharides can have either α

³⁴⁶ EX1010 (Meezan) at ¶[0056] (disclosing “alkyl thiomaltosides, such as heptyl, octyl, dodecyl-, tridecyl-, and tetradecyl- β -D-thiomaltoside”; “alkyl thioglucosides, such as heptyl- or octyl 1-thio α - or β -D-glucopyranoside”; and “alkyl thiosucroses”).

³⁴⁷ EX1010 (Meezan) at ¶[0061] (citations omitted).

³⁴⁸ EX1010 (Meezan) at ¶¶[0002], [0056].

(alpha) or β (beta) anomeric configuration”³⁴⁹; “[a]llyl glycosides of the present invention can include . . . α - or β -D-maltoside, -glucoside or -sucroside.”³⁵⁰

294. **Anomeric Configuration.** Meezan discloses that the compounds of the invention “can have either α (alpha) or β (beta) anomeric configuration”³⁵¹ and that “[a]llyl glycosides of the present invention can include, but are not limited to . . . α - or β - . . . [glycosides].”³⁵²

295. From just the options listed above (which are not exhaustive of every option Meezan discloses), a skilled artisan would understand Meezan to disclose alkyl glycosides and saccharide alkyl esters beyond enumeration. When dodecyl maltoside is merely one of thousands of undifferentiated options falling within the scope of what Meezan says is “preferred,” that is equivalent to no preference at all. The only reasonably particular preference that Meezan discloses is for tetradecylmaltoside (not dodecyl maltoside): “An even more preferred range is from

³⁴⁹ EX1010 (Meezan) at ¶[0075].

³⁵⁰ EX1010 (Meezan) at ¶[0056].

³⁵¹ EX1010 (Meezan) at ¶[0075].

³⁵² EX1010 (Meezan) at ¶[0056].

about 9 to about 16 *or about 14 carbon atoms*.”³⁵³ And even for this option, Meezan elsewhere discloses tetradecylmaltoside as “highly branched,” rather than having a linear alkyl chain.³⁵⁴

296. Dr. Donovan’s assertion that a skilled artisan would naturally choose *one particular* compound (*n*-dodecyl- β -D-maltoside, which is not even disclosed and for which Meezan teaches against) is unsupported and pure hindsight. Thus, what Dr. Donovan states about the ’558 Provisional more appropriately applies to Meezan:

The ’558 Provisional discloses a vast number of potential candidates in paragraph [152], without any direction as to which compound classes are preferred, or any guidance for choosing one candidate over another.³⁵⁵

Whereas the ’558 Provisional does disclose *n*-dodecyl- β -D-maltoside, Meezan does not. To the contrary, out of the countless number of options for alkyl saccharides, Meezan teaches a skilled artisan to use a “highly branched” alkyl group, which directs the skilled artisan away from *n*-dodecyl- β -D-maltoside.

³⁵³ EX1010 (Meezan) at ¶[0058] (emphasis added).

³⁵⁴ EX1010 (Meezan) at ¶[0149].

³⁵⁵ EX1062 (Donovan-786 Decl.) ¶49.

iv. Meezan expresses no preference toward *n*-dodecyl- β -D-maltoside

297. Dr. Donovan relies on a passage discussing Example 2 as the basis for arguing that dodecyl maltoside is “preferred,”³⁵⁶ but that passage is not relevant for several reasons. First, Example 2 does not investigate dodecyl maltoside; rather, it *only* provides data resulting from experiments with tetradecylmaltoside (TDM). Second, the data discussed in Example 2 concerning increased bioavailability is only for TDM: “Even more interesting, alkyl glycosides of the invention in the range of about 0.01% to about 6% have increased bioavailability (see **FIG. 1**).”³⁵⁷ Figure 1 presents data solely for TDM. Third, although Example 2 mentions dodecyl maltoside, what it says is that “***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***.”³⁵⁸ That is, the effect of dodecyl maltoside that is addressed is its ability to stabilise drugs – not increase their solubility and bioavailability. There is no evidence that diazepam is in any way

³⁵⁶ EX1062 (Donovan-786 Decl.) ¶93.

³⁵⁷ EX1010 (Meezan) at ¶[0149].

³⁵⁸ EX1010 (Meezan) at ¶[0149] (emphasis added).

unstable in the solutions of Gwozdz-PCT, or that it would need a stabiliser. Fourth, the molecule on whose function TDM is assessed is not a small molecule (like diazepam), but rather a peptide (salmon calcitonin) having a molecular weight more than ten times that of diazepam, formulated in an aqueous medium – unlike the generally nonaqueous medium of Gwozdz-PCT.

298. When Meezan does get around to examining dodecyl maltoside in Example 3, it again does so in the context of an aqueous solution (not non-aqueous), on a protein (not a small molecule), and delivered ocularly (not intranasally).³⁵⁹ And as discussed above, it was the poorest performer of the lot that was tested.

299. Dr. Donovan's views about the skilled artisan to select one alkyl glycoside over another are inconsistent. On the one hand, in the passages on motivation to combine just discussed she takes the position that a skilled artisan would naturally select *n*-dodecyl- β -D-maltoside from amongst the countless other options (none of which disclose linear chains).³⁶⁰ Having made this selection, the skilled artisan would then – in Dr. Donovan's telling – have “a reasonable expectation ... that the Gwozdz[-PCT] formulations could be successfully

³⁵⁹ EX1010 (Meezan) at ¶¶[0153]-[0162].

³⁶⁰ See EX1062 (Donovan-786 Decl.) ¶91 (citing Meezan at ¶¶[0056]-[0058]).

developed to improve the solubility of benzodiazepine drugs (including diazepam), and that the alkyl glycoside compounds of Meezan (including dodecyl-beta-D-maltoside) could be successfully incorporated into the Gwozdz[-PCT] pharmaceutical solution.”³⁶¹

300. Simultaneously, Dr. Donovan offers the opinion that when that same skilled artisan looks at the specification of the ’558 Provisional and the Sigma Catalogue and sees 100-200 biological detergents (including an express mention of *n*-dodecyl-β-D-maltoside), that same skilled artisan would say that the Provisional “does not identify with any specificity” to select *n*-dodecyl-β-D-maltoside.³⁶² And she further states that “Additionally, it would require the POSA to conduct undue experimentation to determine whether any of the alkyl glycosides are useful *or preferred* over any of the other biological detergent candidates.”³⁶³

XIV. NON-OBVIOUSNESS OVER GWOZDZ-PCT, MEEZAN, AND CARTT-784

301. Dr. Donovan proposes combining Gwozdz-PCT and Meezan with Cartt-784 and proffers that claims 20-21 of the ’786 Patent would have been obvious

³⁶¹ EX1062 (Donovan-786 Decl.) ¶105.

³⁶² EX1062 (Donovan-786 Decl.) ¶50.

³⁶³ EX1062 (Donovan-786 Decl.) ¶51 (emphasis added).

over this combination of three references.³⁶⁴ She relies on Cartt-784 for the dosing requirements of “from about 5 to about 20 mg” (claim 20) and “from about 1 mg to about 20 mg” (claim 21).³⁶⁵

302. My previous analysis regarding the combination of Gwozdz-PCT and Meezan is incorporated by reference herein. If it would not have been obvious to combine Gwozdz-PCT and Meezan, it would also not have been obvious to further combine these references with Cartt-784.

303. Dr. Donovan’s sole motivation for this three-reference combination is that they are “all directed to nasal formulations.”³⁶⁶ This is an overly simplistic view, with Dr. Donovan again applying hindsight.

304. As I describe above, Meezan does not even mention diazepam or any other form of benzodiazepine, so it certainly is not “directed” to this application. Meezan is instead directed to proteins and other macromolecules, in contrast to the relatively small (285 Dalton) size of diazepam.

³⁶⁴ EX1062 (Donovan-786 Decl.) ¶124.

³⁶⁵ EX1062 (Donovan-786 Decl.) ¶249.

³⁶⁶ EX1062 (Donovan-786 Decl.) ¶120.

305. It is also important to note that the delivery technologies for the therapeutic agent are fundamentally different between Gwozdz-PCT and Cartt-784. Gwozdz-PCT is directed to solutions of benzodiazepine, whereas Cartt-784 is directed to suspensions.³⁶⁷ Cartt-784 assembles nanoparticles of benzodiazepine, which are then suspended in a liquid phase. I further discuss solutions and suspensions above in the Technology Background section of this declaration. A skilled artisan would have understood that suspensions and solutions have different characteristics including drug loading and dosing, pK profiles and bioavailability and other characteristics. For example, in general terms, when a drug is in solution, it is immediately available for absorption whereas when in suspension it needs to be dissolved (i.e., in solution) before it can be absorbed and so there is a delay in permeation and absorption. The rate of dissolution is influenced by properties of the drug particle (e.g., particle size and crystal form) along with the properties of the medium in which the particle is contained (e.g., viscosity and temperature). For example, nanoparticles, with a much smaller particle size than microparticles and thus a much larger relative particle surface area compared to microparticles, have a faster rate of dissolution and absorption and increased bioavailability.

³⁶⁷ EX1065 (Cartt-784) ¶¶[0015]-[0023].

306. More fundamentally, solutions and suspensions are different delivery mechanisms. Absent hindsight, there would have been no reason—and Dr. Donovan certainly has not identified any such reason—to start with a working formulation (as in Gwozdz-PCT) and then look to a suspension formulation for dosing. As I describe above, Gwozdz-PCT states that it was able to deliver a sufficient amount of diazepam, with sufficient bioavailability, in a dose that was readily accommodated by the nasal passageway. If any modification to the dosing of Gwozdz-PCT were needed (and again, Dr. Donovan has not identified any), a skilled artisan would have looked to another solution for guidance. In short, Dr. Donovan has not identified any non-hindsight reason to combine Gwozdz-PCT and Meezan with Cartt-784.

XV. CONCLUSION

307. I, Marc Brown, do hereby declare and state, that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code. I declare under penalty of perjury that the foregoing is true and correct.

Executed this January 5, 2026.

A handwritten signature in black ink, appearing to read "M. B. Brown", is written on a light green rectangular background.

Dr. Marc Brown