

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AQUESTIVE THERAPEUTICS, INC.,
Petitioner

v.

HALE BIOPHARMA VENTURES, LLC
Patent Owner

U.S. Patent No. 9,763,876

Case IPR2019-00451

**EXPERT DECLARATION OF PROFESSOR SVEINBJÖRN GIZURARSON
IN SUPPORT OF PATENT OWNER'S RESPONSE TO PETITION FOR
INTER PARTES REVIEW OF U.S. PATENT NO. 9,763,876**

**Exhibit
1072**

03/17/2026

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1. My name is Sveinbjörn Gizurarson. I am a Professor in the Faculty of Pharmaceutical Sciences, School of Health Science, University of Iceland, where I have worked on and developed pharmaceutical formulations for intranasal administration, including benzodiazepine formulations. Counsel for Patent Owner Neurelis, Inc. (“Neurelis”) retained me as a technical expert to provide my opinion regarding U.S. Patent No. 9,763,876 (the ’876 Patent) [Ex. 1001], specifically Aquestive Pharmaceuticals’ (“Aquestive”) challenge of claims 1-36 of the ’876 Patent based on the combination of Gwozdz [EX1014] and Meezan [EX1011] as it applies to claims 1-16 and 24-36, and the combination of Gwozdz, Meezan and Cartt’784 [EX1015], as it applies to claims 17-23.¹ My opinions in this expert declaration support Neurelis’ Response that all challenged claims of the ’876 Patent are valid.

¹ I understand from Neurelis’ counsel that while Dr. Nicholas Peppas’ declaration [EX1041] sets forth an additional ground for invalidity (Ground 1: Sonne [EX1013] and Meezan), that ground was rejected by the Patent Trials Appeal Board in a separate *inter partes* review petition filed by Aquestive. As such, my opinions relate to Dr. Nicholas Peppas’ positions only with regards to Ground 2 (Gwozdz and Meezan) as well as Ground 3 (Gwozdz, Meezan and Cartt’784).

I. Qualifications And Background

A. Education and Experience

2. I received my Masters degree and Ph.D in Pharmacy from the University of Copenhagen in 1986 and 1990, respectively, in the laboratory of Dr. Erik Bechgaard. The title of my Ph.D thesis was “Intranasal application of insulin. Pharmaceutical and physiological factors affecting successful absorption of insulin.” I completed my graduate work while employed as a Project Manager at Novo Nordisk, one of the world’s leading pharmaceutical companies. Novo Nordisk at the time was very interested in insulin delivery via intranasal administration, but my work as a Project Manager spanned a wide range of subject matter, and focused on intranasal delivery of benzodiazepines for the treatment of epileptic seizures, as well as the effects of various excipients on nasal membrane physiology.

3. After graduate school, I became a post-doctoral fellow from 1990-1991 at the National Institute of Health in Tokyo, Japan. When working at Novo Nordisk, I became interested in some of the immunological side-effects that occurred following nasal administration, which introduced me to the field of mucosal vaccines and mucosal immunizations. It was there that I learned to know the newly developed intranasal product, Rhinocort® (budesonide nasal spray) for relief of hay fever or other

upper respiratory allergies, by the Japanese company Teijin.² I became familiar with both the formulation and delivery aspects of intranasal administration while training in Tokyo. I have in my personal collection at the University the first bulb-type applicator and multi-dose device that was used to deliver the Rhinocort[®] budesonide powder intranasally during my post-doctoral program.

4. After my post-doctoral work in Japan, I was offered a position as an Assistant Professor, Faculty of Pharmaceutical Sciences at the University of Iceland in 1991. I was promoted to Associate Professor in 1993, and appointed as a Tenured Full Professor in 1996. I currently teach, supervise university and graduate students and perform research in the pharmaceutical delivery field, including intranasal formulations of benzodiazepines. I have served as an opponent³ in six Ph.D dissertation defense proceedings in Iceland, Denmark and Sweden.

² Petitioner's expert Dr. Nicholas Peppas in his brief review of the "General State of the Prior Art" states that Rhinocort[®] was used in the "treatment of the flu (i.e., influenza)" *See* Peppas Declaration, EX1041), ¶100. That is incorrect. To my knowledge, Rhinocort[®] was never approved for the treatment of the flu.

³ An outside expert participant in some university graduate school programs.

5. My work at the University of Iceland has led to the submission and acceptance in August 2018 by U.S. Food & Drug Administration of a New Drug Application (NDA) for intranasal midazolam (NAYZILAM[®]), a benzodiazepine nasal formulation indicated as a rescue drug for cluster seizures and acute repetitive seizures (intermittent, stereotypic episodes of frequent seizure activity) in patients 12 years of age and older. The drug is marketed by UCB in the United States. *See* <https://www.biospace.com/article/releases/ucb-announces-nayzilam-midazolam-nasal-spray-now-approved-by-fda-to-treat-intermittent-stereotypic-episodes-of-frequent-seizure-activity-in-people-living-with-epilepsy-in-the-u-s-/> (accessed October 31, 2019) [EX2018].

6. I also started multiple pharmaceutical companies while an academic at the University of Iceland. I founded and was the Chief Executive Officer of Lyfjapróun Biopharmaceuticals in Iceland from 1991-2005. My company was acquired by Actavis in 2007. I also founded LipoMedica ehf in 1998, which merged with Icelandic company Bio-Gels Pharmaceuticals in 2005, which specialized in mucosal drug delivery systems. In 2001, I founded Hananja ehf, an Icelandic entity accredited by the European Union and a specialty biopharmaceutical company focused on discovery and development of innovative treatments for life-threatening diseases, specifically nasal spray drug products.

7. In 2004, I was a founder of Mentis Cura ehf, an Icelandic company focused on digital diagnostics based on machine learning for the diagnosis of disorders of the central nervous system, such as dementia and ADHD. Mentis Cura has two CE marked⁴ products on the European market: Sigla and Katla. I was also a founder of Nepstone ehf in 2005, a preclinical-stage pharmaceutical company developing peptides to treat dermatological conditions that arise due to an autoimmune disease (*e.g.*, psoriasis and eczema). In 2015, I founded Capretto ehf, an Icelandic based medical device company utilizing antimicrobial lipids. We are working towards introducing a medical device incorporating monolipid antimicrobials (natural product) for infection therapy to the market shortly. I also founded Calor ehf in 2016, an Icelandic pharmaceutical company focused on excipients that enhance stability of therapeutic agents in solution. My latest venture is Eclampsin ehf, an Icelandic company I founded this year in 2019, which focuses on the development of a naturally occurring protein (placental protein 13), only found in the placenta, to prophylactically treat preeclampsia. I am also working on establishing a not-for-profit pharmaceutical manufacturing organization in Malawi, Africa, focusing on the manufacturing of life-saving medicine for infants and small children under 5 years of

⁴ European health, safety and environmental certification.

age (a neglected population) in a form they need it, to treat neglected diseases in third world countries, including severe and cerebral malaria and schistosomiasis, two of the major disease burdens in the world.

8. I have published over 260 peer-reviewed articles, books, book chapters and review articles in the pharmaceutical field, many related to intranasal administration of therapeutic agents, including benzodiazepines. Articles especially relevant to the '876 Patent include a 1993 review article on the relevance of nasal physiology to drug absorption studies (published as an invited contribution to the journal *Advanced Drug Delivery Reviews*), amongst others. I also hold numerous patents covering the same subject matter of intranasal administration and pharmaceutical preparations.

9. I was on the Editorial Board for the Scandinavian Journal of Laboratory Animal Sciences, and am a reviewer for several peer-reviewed journals, including the International Journal of Pharmaceutical Sciences, European Journal of Pharmaceutics and Biopharmaceutics, Molecular Pharmaceutics, Expert Opinion on Drug Delivery, among others. I am or was a member of the American Association of Pharmaceutical Scientists, American College of Clinical Pharmacology, International Licensing Executive Society, Christian Pharmacists Fellowship International and the Icelandic Pharmaceutical Society.

10. I have received numerous awards for my work, including an Innovation Award in 2007 from the University of Iceland, and from the Trade Council of Iceland in 2004, as well as a Young Investigator Research Achievement Award in 1996 from the National Research Council. I have served on the Accreditation Board at the University of Iceland in 2010, 2015 and 2019 in order to prepare the Faculty of Pharmaceutical Sciences for accreditation audits during these time periods. On behalf of the Danish Ministry of Education, I have also accredited the Faculty of Pharmaceutical Sciences, Syd-Dansk University in Denmark in 2010. I was designated an expert in biopharmaceutics by the Ministry of Health, Iceland, in 1994, and as a Qualified Person in 2000 by the Icelandic Medicine Agency, amongst other special authorizations that I have received from various governmental agencies.

11. In all, I have over thirty years of hands-on research experience specializing in the formulation of intranasal therapeutics, including benzodiazepines.

12. Attached as Appendix C is a copy of my *curriculum vitae* in support of my opinions.

B. Bases for Opinions and Materials Considered

13. Materials I have relied on in preparing this declaration are referenced throughout, as well as listed in the attached Appendix B. My opinions are based on my education, on my experience, and on other bases such as articles and other

references, as well as other relevant knowledge. This declaration states my current opinions, which could change if additional information or analyses become available to me.

C. Previous Litigation Experience

14. I have served as an expert witness in a patent proceeding:

- Lannett Holdings, Inc. v. AstraZeneca AB (IPR2015-001629) (expert for Petitioner Lannett Holdings, Inc.)

D. Scope of Work

15. I have been retained by Neurelis as a technical expert in this matter to provide various opinions regarding the '876 Patent. I receive \$500 per hour for my services or \$750 per hour for depositions. No part of my compensation is dependent upon my opinions given or the outcome of this case.

II. Legal Standards

16. For my opinions in this declaration, I understand from patent owner Neurelis' counsel that this requires applying various legal principles. As I am not an attorney, I have been informed about various legal principles that involve my analysis. I have used my understanding of those principles in forming my opinions. I summarize these principles as I understand them below.

17. For example, I have been told by Neurelis' counsel that the Petitioner, in this case Aquestive, bears the burden of proving unpatentability in this proceeding by a preponderance of the evidence. I am informed that this preponderance of the evidence standard means that Petitioner must show that unpatentability is more probable than not.

18. I have also been told by counsel that when I review and consider the claims, the claims should be construed in light of the specification from the perspective of a person of ordinary skill in the art ("POSA"). I discuss who qualifies as the person of ordinary skill in the art in more detail below. *See* Section III.

19. I have been asked by counsel to consider the question of obviousness/non-obviousness. I am told by counsel that this analysis must be from the perspective of the person of ordinary skill in the art, and whether the skilled artisan would consider any differences between the prior art and what is claimed to have been obvious. To make this assessment, I have been informed by Neurelis' counsel that the concept of patent obviousness involves four factual inquiries: (1) the scope and content of the prior art; (2) the differences between the claimed invention and the prior art; (3) the level of ordinary skill in the art; and (4) secondary considerations of non-obviousness. I further note that I have been instructed by counsel that one cannot use an existing patent as a guide to select from prior art elements, or otherwise engage in

hindsight. Rather, the better approach is to consider what the POSA knew, and what the art taught, suggested, or motivated the person of ordinary skill in the art to further pursue, and to differentiate between steps that were routinely done (such as in response to known problems, steps or obstacles), and those which, for example, may have represented a different way of solving existing or known problems.

20. I am also informed by counsel that there must be some motivation or rationale for a POSA to combine references, and that the combination of the references to arrive at the claimed elements must have a reasonable expectation of success to a POSA at the time of filing.

21. I understand from counsel that before reaching any final conclusion on obviousness, the obviousness analysis requires consideration of objective indicia of non-obviousness. These must be considered to ensure that, for example, there were not some unanticipated problems, obstacles or hurdles that may seem easy to overcome in hindsight, but which were not readily overcome prior to the relevant invention date of the patents/claims at issue here. I understand from counsel that these objective indicia are also known as “secondary considerations of non-obviousness,” and may include long-felt but unmet need and unexpected results, among others. I also understand, however, that any offered evidence of secondary considerations of non-obviousness must be comparable with the scope of the challenged claims. This

means, from my understanding, that for any offered evidence of secondary considerations of non-obviousness to be given substantial weight, I understand from counsel that the proponent of that evidence must establish a “nexus” or a sufficient connection or tie between that evidence and the merits of the claimed invention, which I understand specifically incorporates any novel element(s) of the claimed invention. I also understand from counsel it is the patentee that has the burden of proving that a nexus exists.

22. With respect to long-felt need, I understand from Neurelis’ counsel that the evidence must show that a particular problem existed for a long period of time. More specifically, I understand that for a “need” to be long-felt and unmet: 1) the need must be persistent and recognized by those of ordinary skill in the art, 2) the need must not be satisfied by another before the alleged invention, and 3) the claimed invention itself must satisfy the alleged need. I also understand from counsel that long-felt need is analyzed as of the date that the problem is identified. Furthermore, I understand from Neurelis’ counsel that long-felt need should be based upon inadequacies in the technical knowledge of those skilled in the art, not due to business-driven market forces.

23. With respect to failure of others, I understand from counsel that the focus of the analysis is on the prior failure of others in the relevant industry, not the

inventors. I further understand from Neurelis' counsel that, absent a showing of a long-felt, unmet need or the failure of others, the mere passage of time without the claimed invention is not evidence of non-obviousness.

24. With respect to unexpected results, I understand from counsel that any results upon which a patentee wishes to rely as an indicator of non-obviousness must be based on a comparison of the purported inventions with the closest prior art.

III. Person of Ordinary Skill in the Art

25. As above, I have been informed by Neurelis' counsel that the analysis is to be conducted from the perspective of a POSA at the time of the invention.

26. I have also been informed by counsel that in defining a person of ordinary skill in the art the following factors may be considered: (1) the educational level of the inventor; (2) the type of problems encountered in the art; (3) prior art solutions to those problems; (4) rapidity with which innovations are made; and (5) sophistication of the technology and educational level of active workers in the field.

27. I understand that Petitioner's expert, Dr. Nicholas Peppas, submitted the following definition of a POSA:

It is my opinion that as of the earliest priority date that the '876 Patent as a whole is entitled to (i.e., no earlier than March 27, 2009), as discussed in ¶¶68-70, above) a POSITA would have been a medicinal chemist, pharmaceutical chemist, chemist, or biologist involved in the research

and development of pharmaceutical formulations for the treatment of epilepsy and related diseases/disorders. Such an individual would have at least a B.S. degree in chemical, biological, or pharmaceutical sciences or a medical degree and several years of experience in the field of transmucosal (including intranasal, rectal, vaginal, ocular, lacrimal, nasolacrimal, buccal, sublingual, urethral, inhalation, and auricular) pharmaceutical formulation development, the amount of post-graduate experience depending upon the level of formal education. The individual would also have some experience in design and testing of formulations for mucosal delivery (and particularly in intranasal formulations) of systemic-acting drugs.

Peppas Decl. (EX1041), ¶74.

28. I disagree with Dr. Peppas' definition on several points. As I explain in detail below, the formulation of a benzodiazepine for intranasal administration, as the claims recite, is difficult and complex science. The physiological constraints of active ingredient uptake due to the nasal anatomy, as well as the very low solubility of benzodiazepines requires a higher skill set and knowledge than a POSA with a bachelor's degree "with several years of experience."

29. Instead, in my opinion and experience, a person of ordinary skill in the art related to the '876 Patent should at least have held a Masters degree with many

years of experience, or a Ph.D. or Pharm.D degree⁵ with several years of experience, or its equivalent research experience.⁶ The reason is because there is a difference between how a person with a graduate degree and training processes scientific information, as compared to a person with only a bachelor's degree. A person of ordinary skill in the art with the requisite educational background above and the direct experience in intranasal formulations and benzodiazepines, could appreciate the difficult task of first formulating benzodiazepines to obtain a clinically-relevant dose

⁵ Dr. Peppas cites to a “medical degree” as within the educational background of a POSA. It is unclear if he is referring to an “MD”, or generally a degree in the medical field, which could be other types of healthcare professionals (for example, a dentist (DMD)). In my experience a health-care focused degree would likely not have provided the training necessary for a POSA in the context of the '876 patent.

⁶ I include “or its equivalent research experience” because in Iceland, there is the possibility that a professorship could be obtained by working in the relevant field for an extended period of time. That time period would be equivalent to the length of time it takes to obtain the information and knowledge needed to receive a graduate degree and obtain the relevant experience for the academic position. This is seldom awarded, and can be difficult to obtain.

in the formulation, while ensuring that sufficient uptake occurs in the nasal cavity. In my experience, a person with a bachelor's degree would be hard-pressed to succeed at this difficult task.

30. I also disagree with Dr. Peppas' list of the scientific background of one of ordinary skill in the art. Dr. Peppas contends that a POSA "would have been a medicinal chemist, pharmaceutical chemist, chemist, or biologist involved in the research and development of pharmaceutical formulations for the treatment of epilepsy and related diseases/disorders." Peppas Declaration (EX1041), ¶74. It is difficult to ascertain what role a medicinal chemist would play in the research and development of benzodiazepine pharmaceutical formulations for intranasal administration. Chemists (medicinal chemists in particular) are primarily concerned with chemical structures and synthesizing new chemical compounds. The chemical structures are known here.

31. Instead, in my opinion the POSA would have had knowledge of benzodiazepine structure and function, including solubility issues with benzodiazepines in general. The POSA would also have knowledge and practical experience working with intranasal formulations, including knowledge of the physiology and anatomy of the nasal cavity, with relevant experience in developing intranasal formulations.

32. I also disagree with Dr. Peppas' statement that the POSA could have had experience in what he deems as related fields, including "rectal, vaginal, ocular, lacrimal, nasolacrimal, buccal, sublingual, urethral, inhalation, and auricular." While those fields can be informative, the pathway to successfully formulating an intranasal product can be distinguishable from the mucosal systems above. For example, as I explain below, the use of rectal formulations of diazepam (a commercially available product) for intranasal administration would not work.

33. I also note that the experience may come from the POSA's own experience, or may come through research or work collaborations with other individual(s) with experience in the medical, pharmaceutical or biotech industry, *e.g.*, as members of a research team or group. For example, the person of ordinary skill in the art may work as part of a team or collaboration to develop a benzodiazepine formulation for intranasal administration, including consulting with others to select the benzodiazepine for use in the intended treatment, in this case a quick-acting formulation for use in patients experiencing an epileptic seizure, as well as subsequent testing of the intranasal benzodiazepine formulation.

IV. Summary of Opinions

34. I have been asked to provide my opinions regarding claims 1-36 of the '876 Patent, from the perspective of a POSA at the time of the '876 Patent's earliest

filing date. While I understand that petitioner Aquestive asserts that this date should be March 27, 2009, I understand from Neurelis' counsel that there are legal arguments that establish that the '876 Patent is entitled to the priority date of March 28, 2008, the filing date of the '558 Provisional Application. I do not provide any opinions on the legal argument at issue here; however, it is my opinion that the '558 Provisional Application, which incorporated by reference the 1988 SIGMA catalogue excerpt [EX2006], disclosed alkyl glycosides, and thus a POSA would have known and recognized from the incorporation by reference that the '558 Provisional Application highlighted alkyl glycosides as part of the claimed invention.

35. Moreover, it is also my opinion that claims 1-16 and 24-36 are not obvious in view of Gwozdz [EX1014] and Meezan [EX1011] (Ground 2 of Dr. Peppas' Declaration [EX1041]) and claims 17-23 are not obvious in view of Gwozdz, Meezan and Cartt'784 [EX1015] (Ground 3 of Dr. Peppas' Declaration [EX1041]). Instead, Aquestive and Dr. Peppas failed to provide in my opinion a motivation to combine or reasonable expectation of success to achieve an intranasal formulation of benzodiazepines as claimed in claims 1-36.

36. In addition, it is also my opinion that the unexpected and surprising success of the '876 Patent at formulating an intranasal non-aqueous diazepam formulation as claimed in claims 1-36, especially in view of the failure of others to

successfully formulate an intranasal diazepam or benzodiazepine formulation, for intranasal administration, further supports the non-obviousness of the '876 Patent's claims. The eventual approval of Neurelis' NDA for NRL-1 (Valtoco[®]), which will fill a long-felt and unmet need for an alternative to rectal and intravenous diazepam products, only serves to strengthen the non-obviousness of Neurelis' challenged claims.

V. The '876 Patent [Ex. 1001]

37. The '876 Patent, titled "Administration of Benzodiazepine Compositions", was filed on October 29, 2014 as U.S. Patent Application No. 14/527,613. *See* EX1001, pg. 0001. The '876 Patent issued on September 19, 2017. The '876 Patent is a continuation of U.S. Patent Application No. 13/495,942 (now U.S. Patent No. 8,895,546), which was filed on June 13, 2012, which is a continuation-in-part of U.S. Patent Application No. 12/413,439, which was filed on March 27, 2009. *Id.* The '876 Patent claims priority to U.S. Provisional Application No. 61/040,558, which was filed on March 28, 2008, U.S. Provisional Application No. 61/497,017, which was filed on June 14, 2011 and U.S. Provisional Application No. 61/570,110, which was filed on December 13, 2011. *Id.* The abstract, which comports with the title of the patent, states that the patent "relates to pharmaceutical

compositions comprising one or more benzodiazepine drugs for nasal administration, methods for producing and for using such compositions.” *Id.*

38. The claims of the '876 Patent also comport with the subject matter stated. Claim 1, the sole independent claim, recites:

A method of treating a patient with a disorder which is treatable with a benzodiazepine drug, comprising: administering to one or more nasal mucosal membranes of a patient a pharmaceutical solution for nasal administration consisting of a benzodiazepine drug, one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); ethanol and benzyl alcohol in a combined amount from about 10% to about 70% (w/w); and an alkyl glycoside.

EX1001, 63:26-34. The dependent claims provide further details of the tocopherols or tocotrienols, alkyl glycoside, benzodiazepine and ethanol and benzyl alcohol claimed. For example, claims 2, 7, 11 and 12 relate to specific tocopherols or tocotrienols (claims 2 and 7), or narrower ranges of the tocopherols or tocotrienols (claims 11 and 12). Claims 3-6, 9-10 and 17 relate to the benzodiazepine claimed in claim 1. Claims 8 and 13-15 relate to the ethanol and benzyl alcohol amounts claimed in claim 1. Claims 24-26 relate to specific amounts of alkyl glycosides and dodecyl maltoside, and claims 16 and 18-23 relate to the claimed solution formulation of claim 1 used in

a pharmaceutically acceptable spray formulation, and the administration thereof. *See* EX1001, 63:35-64:55.

39. Claims 27-36 relate to specific combinations of the claimed components in the pharmaceutical solution for nasal administration of claim 1. For example, claim 27 recites “wherein the solution consists of diazepam, vitamin E, ethanol, benzyl alcohol and dodecyl maltoside.” EX1001, 64:56-58. Claim 28 recites amounts of each component, reciting “wherein the solution consists of about 56.47% (w/v) vitamin E, about 10.5% (w/v) benzyl alcohol, about 10% (w/v) diazepam, about 0.25% (w/v) dodecyl maltoside, q.s. dehydrated ethanol.” *Id.*, 64:59-62. Claims 34-36 relate to bioavailability ranges of the claimed nasal solution pharmaceutical formulations as compared to drug administered intravenously.

40. A list of the claims is provided in Appendix A of my declaration.

VI. Claim Construction

A. “Consisting Of”

41. I understand from Neurelis’ counsel that the phrase “consisting of,” which is referred to as a “transitional phrase,” is a close-ended term that limits the claim to contain only what is recited in the claim. The practical effect of this interpretation, in my understanding, is that the claims would exclude any excipient or other ingredient not explicitly included in the claim, including water. This means that

the challenged claims of the '876 Patent relate to a non-aqueous solution containing a benzodiazepine drug, one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); ethanol and benzyl alcohol in a combined amount from about 10% to about 70% (w/w); and an alkyl glycoside, and excludes any other active ingredient or excipient, including water. Dr. Peppas acknowledges this understanding as well. *See* Peppas Depo. Tx. [EX2011], 137:16-138:6.

B. “In a Combined Amount”

42. I have been asked by Neurelis’ counsel to consider the meaning to a POSA of the claim term “in a combined amount” when used in the context of the claim. In the context of claim 1, the claim reads “ethanol and benzyl alcohol in a combined amount from about 10% to about 70% (w/w).” In my opinion, this means that both ethanol and benzyl alcohol are present in an amount that is greater than 0%. This interpretation agrees with the specification as well as what Neurelis had represented to the patent office during prosecution of this application. In particular, Neurelis argued that “[n]owhere does Sonne or Meezan teach solutions consisting of benzodiazepine, 30-90% tocopherol or tocotrienol, an alkyl glycoside and both ethanol and benzyl alcohol in a combined concentration of 10-70% (w/w).” *See*

EX1004, 2148-49 (emphasis in original). Accordingly, the claim term “in a combined amount” means that both ethanol and benzyl alcohol are present in the claimed range.

43. In my opinion and experience, all other claim terms can be understood by a POSA by its plain and ordinary meaning.

VII. Background

A. Epilepsy and Acute Seizure Treatment

44. Epilepsy, which is defined as two or more seizures not caused by illnesses or circumstance, is a prevalent disease, resulting in altered awareness, abnormal behavior, and/or involuntary movements. *See* French and Pedley [EX2019], 166. While epilepsy is a brain disorder, its cause is generally unknown. Epilepsy may have many etiologies, including developmental disorders, brain injury, illness and infection. *Id.*, 166. Characterized by violent seizures that are unpredictable in nature and frequency, epilepsy affects individuals of all ages, with onset most often occurring in childhood and older adulthood. *Id.* Epilepsy is one of the most common serious neurological disorders, affecting 6 to 8 per 1000 persons in the United States. Living with epilepsy, particularly for people with refractory seizures, can involve challenges in school, uncertainties about social and employment situations, limitations on driving, and questions about independent living.

45. Immediate ceasing of epileptic seizures is essential to treating this life-threatening condition; without treatment there is a significant increase in morbidity and mortality rate. *See* Cole [EX2015], 220. There is an increased likelihood for progression into status epilepticus if a seizure lasts longer than 5 minutes. *See id.* Past studies have highlighted the benefits of administering benzodiazepines such as diazepam for treatment of epileptic seizures, especially in the young and elderly, including decreasing seizure intensity as well as avoiding expensive hospital stays. *Id.* Other benzodiazepines, such as clobazam, clonazepam, lorazepam and midazolam can be used prophylactically to treat epilepsy cluster events or as a rescue agent in seizure events. *Id.*; French [EX2019], 174.

46. While benzodiazepine formulations had been developed for intravenous administration by 2008, the need for medical professionals to administer these therapeutic products greatly limited their use for epileptic patients requiring an immediate cessation of the seizure symptoms outside of a hospital or clinic setting. *See, e.g.,* Cole [EX2015], 220. A rectal formulation (Diasat[®]) was also available, but again its use was also limited to specific situations, and not conducive to administration in a public setting. Terry [EX2016], 1135. Limitations on development of new therapeutic formulations were hampered by technical challenges

posed by benzodiazepine formulations that were well known to POSAs in 2008, as I explain below.

B. Benzodiazepine Solubility

47. As above, my extensive experience working with benzodiazepines, specifically for treating cluster seizures in patients, agrees with the Background of the Invention of the '876 Patent, which explains why there was a lack of convenient and effective benzodiazepine products available for use as a rescue medication for epileptic seizures:

Current formulations of benzodiazepine drugs can be administered orally, rectally, or parenterally. The ability to utilize these and other types of formulations has been significantly limited due, in many cases, to solubility challenges.

I fully agree with this statement that while benzodiazepine drugs are highly useful in the treatment of neurological disorders, such as epileptic seizures and status epilepticus, the challenge of administering a high enough dose of benzodiazepine (clinical dose) to act as a rescue agent during a seizure could not be overcome in many instances because of its low solubility. *See, e.g.,* Riss [EX2013].

48. As such, developing benzodiazepine formulations has proven not to be a straightforward task, in contrast to Dr. Peppas' opinion, in part because of the difficulty in solubilizing sufficient amounts of the drug for use in treatment of

patients. Moreover, while the degree of solubility for benzodiazepines vary depending upon the lipophilicity of the benzodiazepine molecule, the clinical dose threshold needed for treatment of an epileptic seizure event was also at issue, which varied depending upon the benzodiazepine used. Thus, POSAs, including my work in the field, required evaluating the ratio between the threshold clinical dose needed for treatment and the solubility of the benzodiazepine drug; this ratio in turn determined the margin by which a POSA could safely and effectively use the benzodiazepine agent without risk of precipitation of the drug in the nasal cavity, and thus its suitability for development as an anti-epileptic seizure medication.

49. My work focused on this very issue, where we published a study in 1997 that evaluated the ratio between the threshold clinical dose and the solubility of benzodiazepines in two different lipophilic vehicles: polyethyleneglycol 200 (PEG200) and Glycofurolum 75 (GF). *See* Bechgaard [EX2007], Table 2.

50. I note that because of the high clinical threshold dose needed for treatment with diazepam, Diastat[®] (a formulation for rectal use) administered intranasally would not have been clinically possible and would not have worked. In my experience and opinion, a POSA would have recognized not only the issues posed by the high alcohol content and thus irritation potential in Diastat[®], but also the

diazepam amount was far too low and the administration volume far too high for effective intranasal administration and uptake to occur.

C. Treatment of Epileptic Patients with Benzodiazepine

51. Accordingly, despite its therapeutic promise in stopping and preventing seizures in patients, benzodiazepine use was not widespread in 2008 because of the significant solubility challenges experienced by POSAs. This was compounded by issues related to administration of therapeutic agents to a seizing patient. As I explained above (*see* Section VIIA) although intravenous benzodiazepine formulations were approved by the FDA well before the priority date of the '876 Patent, administration of this therapeutic product could only be accomplished in a hospital or clinic setting by a medical professional. Many groups attempted to develop formulations for use outside of the hospital setting to increase usability and effectiveness of benzodiazepine drugs.

52. One such treatment was developed specifically for use by, for example, parents to administer to children in a home setting. Diastat[®], which was approved by the FDA in 1997, is a rectally administered diazepam formulation that allows caregivers outside of a hospital or clinic to administer diazepam to seizing patients. Diastat[®], which contains 5 mg/mL diazepam, propylene glycol, ethyl alcohol (10%), hydroxypropyl methylcellulose, sodium benzoate, benzyl alcohol (1.5%), benzoic acid

and water, with a pH between 6.5 – 7.2, was shown in clinical studies to significantly reduce seizure frequency as well as a prolonged time to next seizure event, as compared to placebo. *See* Diastat[®] Label (2005) [EX2017]. Although effective and relatively safe to use, the inconvenience of rectal administration, especially in public settings, hampered widespread adoption and use of this therapeutic treatment. However, with all of these issues, Diastat[®] was still the only FDA-approved benzodiazepine product on the market in 2008 (or 2009) that could be used outside of a hospital or clinic setting for treatment of epileptic seizures.

53. The ability to administer therapeutic drugs intranasally was first realized by experiments performed in 1980 related to the administration of propranolol, an adrenergic β -receptor-blocking agent used for treating angina pectoris and managing hypertension. *See* Hussain [EX2008], 1240. The researchers were able to demonstrate that intranasal administration of propranolol approached similar rapid uptake and serum levels as with the equivalent propranolol amount in intravenous administration. *See* Hussain, 1240 (“The nasal route for propranolol administration appears to be superior to the oral route and as effective as the intravenous route.”).

54. While Hussain successfully demonstrated the viability of intranasal administration as a rapid-uptake alternative to intravenous formulations, application to other therapeutic agents was not straightforward. Intranasal formulations are

particularly difficult to develop as therapeutic agents because of the relatively small delivery volume, as well as the active elimination mechanisms in the nasal cavity to clear foreign materials. In my opinion and experience, POSAs would have realized that these technical challenges would have been demanding for highly water-soluble therapeutic agents, such as propranolol, much less for drugs such as benzodiazepines that are difficult to solubilize in a concentrated form, as I explain below.

D. Challenges of Developing Intranasal Formulations

55. While the experiments by Hussain proved promising for intranasal administration, many technical challenges and obstacles to developing intranasal formulations existed and were known to POSAs well prior to 2008. These include: 1) limitation on delivery volume; 2) mucosal and ciliary clearance mechanisms; and 3) nasal cell anatomy.

1. Delivery Volume Limited to About 200 μ l (100 μ l Per Nostril)

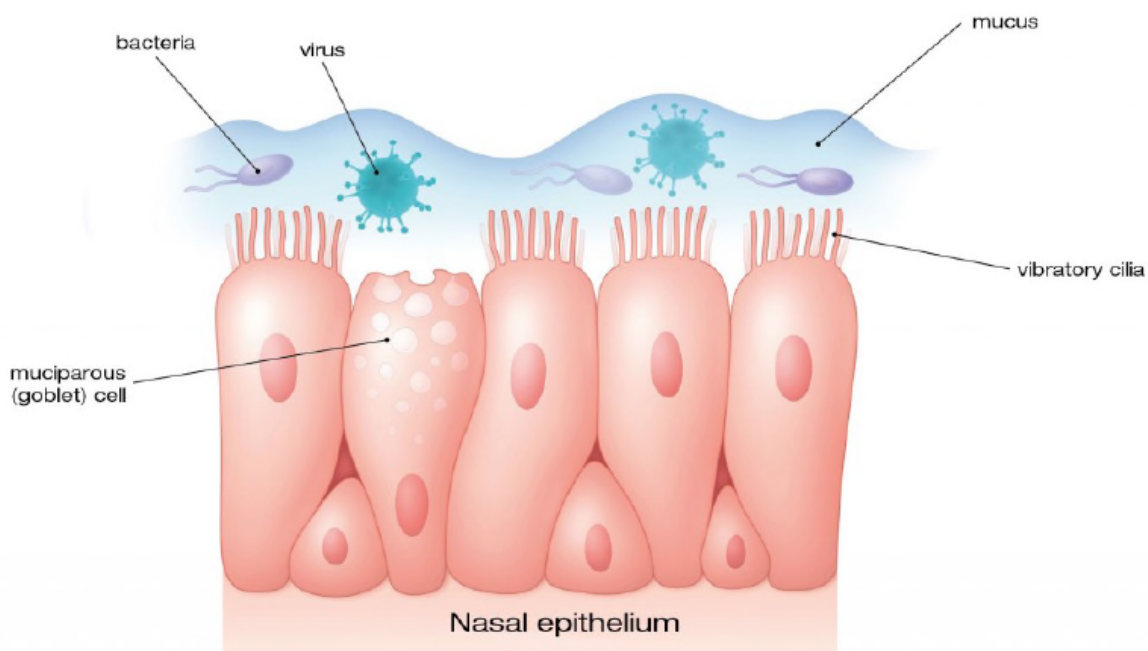
56. Because of the small volume of the nasal cavity, only 100 μ l of solution can be administered to a nostril at one time.⁷ This means that if an effective clinical dose must be captured in the 100 μ l volume (200 μ l for both nostrils), the effective

⁷ The maximum volume for an adult in my experience is about 150 μ l per nostril (300 μ l total volume).

intranasal administration dose will be 5-10 times more concentrated than an intravenous route of administration (with an average administration volume of 1 ml, for example), and about 50-100 times more concentrated than a rectal route of administration (with an average administration volume of 5-10 ml, for example). Accordingly, a POSA would have known and readily recognized that therapeutic agents which are already solubility-challenged would have even more difficulty exploiting in an intranasal formulation.

2. *Residence Time of Therapeutic Agents is Decreased Significantly Because of Defense Mechanisms to Clear Foreign Agents*

57. Unlike other mucosal systems, including ocular, lacrimal, rectal and buccal/sublingual systems, the nasal cavity has anatomical mechanisms to quickly remove foreign materials from the nasal cavity and destroy them through swallowing and breakdown in gastric juices. Corbo [EX2020], 546. There are several levels of defense mechanisms present in the nasal cavity, including a thick mucosal layer, forming a substantial carpet layer on the surface that can trap foreign agents (such as bacteria and viruses) and prevent them from reaching the cellular wall, as well as beating or vibratory cilia, which actively migrate foreign agents trapped in the mucus layer towards the gastric/stomach cavity.



From <https://www.fitonasal2act.com/how-does-the-nose-work/the-nasal-mucosa/>
(accessed November 4, 2019) [EX2021].

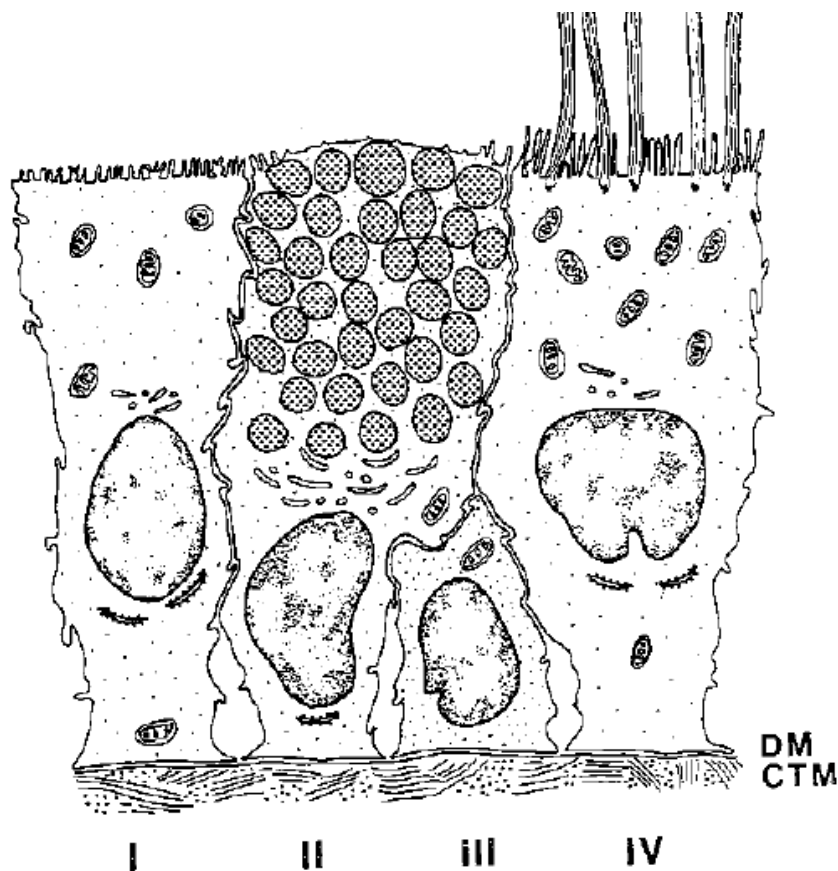
58. As a result of these defense mechanisms, the residence half-life of a solution placed in the nasal cavity is approximately 15 minutes, a short residence time in the nasal cavity. Accordingly, any therapeutic agent for intranasal administration must not only penetrate the thick mucosal layer to reach the nasal cell wall for absorption, it must also do so quickly before the therapeutic agent is effectively swallowed and instead orally absorbed by the subject.

59. In my opinion and experience, many therapeutic formulations developed for intranasal administration are actually orally absorbed, rather than absorbed through

the nasal mucosa, effectively delaying absorption of the therapeutic agent in the patient. While this may not matter in some therapeutic applications, a fast absorption and systemic availability for treatment of epileptic seizures is essential to “minimize mortality as well as reduc[e] neurological sequelae caused by prolonged seizure activity.” Lau and Slattery [EX2009], 171.

3. *Cellular Structures Within the Nasal Cell Wall Prevent Influx of Therapeutic Agents*

60. In addition to the defense mechanisms for removing foreign agents from the nasal cavity as quickly as possible, tight junctions and other intracellular structures, as well as specialized nasal epithelial cells (*see* figure below non-ciliated columnar cell (I), goblet cell (II), basal cell (III) and ciliated columnar cells (IV)) are present that increase the integrity of the cellular barrier to physically block foreign agents from entering through the cell wall and into the subject.



From Mygind [EX2022], 9. This means that therapeutic agents must also maneuver through the cellular wall, often through breaking junctions and physical bonds between or through the cells. POSAs recognized that balancing cellular wall breakdown, while avoiding irritation to the nasal mucosa and other adverse effects, must be addressed in order to successfully deliver therapeutic agents intranasally.

4. Difficulty in Developing Intranasal Benzodiazepine Formulations

61. Thus, obtaining true intranasal absorption, rather than eventual oral uptake, can be difficult, and in the case of some therapeutic agents insurmountable.

This was seen in the studies by Lau and Slattery for diazepam and lorazepam in 1989. *See* Lau [EX2009], 171, Abstract. Lau first recognized the primary challenge of administering benzodiazepines for treatment of status epilepticus because of their poor water solubility characteristics (diazepam 0.05 mg/ml and lorazepam 0.08 mg/ml). *See id.*, 171. Lau attempted to overcome these challenges by first solubilizing the benzodiazepines in an organic non-aqueous vehicle, including triacetin, dimethyl sulfoxide, polyethylene glycol 400, Cremophor EL (polyoxyethylated castor oil), Lipal-9-LA (laureth-9(polyoxyethylene-9 lauryl ether), isopropyl adipate and azone 1-dodecylazacycloheptane-2-one. *Id.*, 171-172. Of the seven organic vehicles, only Cremophor EL, a non-ionic surfactant, was found to be “quite well tolerated” by human subjects. *Id.*, 172.

62. Lau then administered diazepam and lorazepam solubilized in Cremophor EL in human patients to measure uptake (peak concentration) and amount (serum levels) as compared to intravenous administration. Lau found that time to peak concentration (1 hour for diazepam and 0.5 to 4 hours for lorazepam) was significantly delayed as compared to intravenous administration (immediate peak concentration at first timepoint of the study). *Id.*, 173-174, Figure 1 (reproduced below).

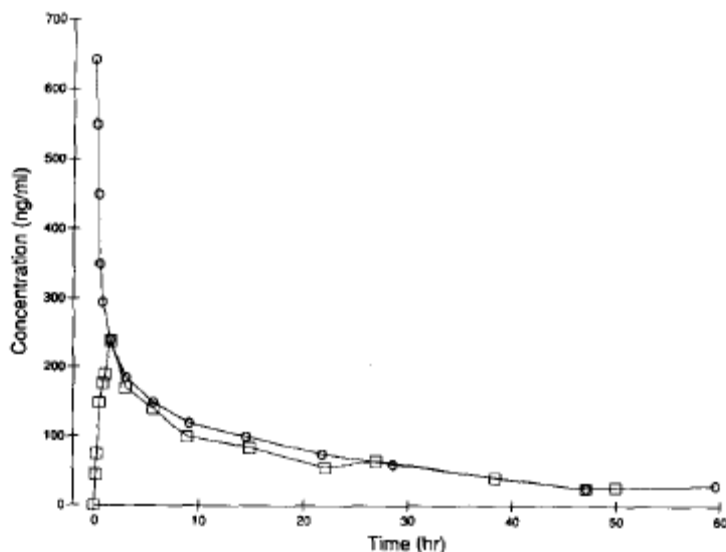


Fig. 1. Time course of diazepam concentration in plasma of subject 1 following i.v. (○) and intranasal (□) administration.

Lau, 172, FIG. 1.

63. Lau also found that bioavailability (peak concentration) was significantly less than with intravenous administration, less than 240 ng/ml for intranasal administration as compared to 647 ng/ml for intravenous administration. *Id.* Similar results were obtained for lorazepam, even though approximately $\frac{1}{2}$ of the dose was administered intravenously as compared to intranasally. *See* Lau, 174, FIG. 2 (reproduced below).

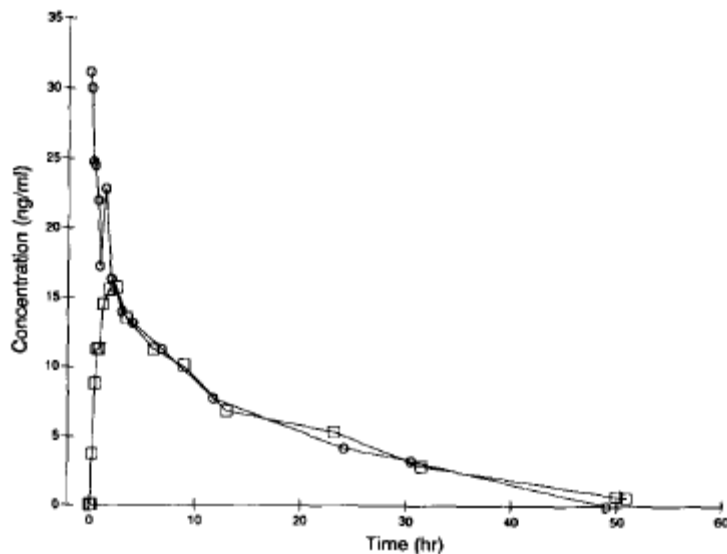


Fig. 2. Time course of lorazepam concentration in plasma of subject 6 following i.v. (○) and intranasal (□) administration.

Lau, 173, FIG. 2. Lau made two important conclusions:

- The time course and peak concentration following intranasal absorption is “rather slow for the treatment of a medical emergency such as status epilepticus” (Lau, 173); and
- Even with the addition of a non-ionic surfactant at “neat” (*i.e.*, 100%) concentration in order to “maximize contact of the solution with the biological barrier” and “disrupting the mucosal barrier” (*i.e.*, as a penetration enhancer), “[i]t appears that there is little room between the poor aqueous solubility of these compounds and the potential for solvent irritation (and toxicity, not addressed in this study) to achieve a satisfactory formulation.” (*Id.*).

Lau thus observed that the difficulties posed by both the intranasal administration route, as well as benzodiazepines specifically, may prove too much for successful development into a therapeutic drug:

Although diazepam and lorazepam cross the nasal mucosa and are absorbed into the systemic circulation, absorption is rather slow and peak concentration is low relative to that found after i.v. administration. **It would appear that this route of administration may be of limited utility for benzodiazepines in the treatment of status epilepticus where rapid onset of effect is essential.**

Lau, 173 (emphasis added). Other researchers have had similar difficulties administering clonazepam in dimethyl- β -cyclodextrin. *See* Schols-Hendriks [EX2010], Abstract.

64. I have personal experience in the difficulties of developing an intranasal benzodiazepine formulation for use as a rescue agent in epileptic seizures. I authored a review article in 1999, explaining the difficulties of developing intranasal benzodiazepine formulations due to its low solubility:

For intranasal application, however, the solubility problem is very critical, since one clinical dose needs to be dissolved in a volume not exceeding about 300 μ l for administration into two nostrils.

Bechgaard [EX2007], 293 (referencing 1993 article). The solubility issue was not only critical because of the threshold clinical dose needed to obtain effectiveness in

treating cluster seizures in a rapid manner, but also because of the risk of precipitates forming that could not only further irritate the nasal cavity, but also reduce uptake of therapeutic agent through the nasal mucosa and cellular wall. In my experience, drug precipitate and particulates have difficulty overcoming the integrity of the cellular wall present in the nasal cavity. Moreover, drug particulates and precipitates are more readily trapped in the thick mucosal layer, and thus cleared quickly through to the gastric system and orally absorbed.

65. This tendency to precipitate with lower solubility benzodiazepines means that the clinical dose should not overlap or be close to the saturation dose of the agent. To determine this threshold, we measured the solubility index for the following benzodiazepines: clonazepam, desmethyldiazepam, diazepam, flunitrazepam, lorazepam, lormethazepam, midazolam, nitrazepam and triazolam. Table 2 of the article summarizes our findings:

Table 2

Solubility of Various Benzodiazepines at 25°C in Polyetheneglycol 200 (PEG200) and Glycofurolum 75 (GF). The Indexes Show How Many Maximal Clinical Doses That May be Dissolved in 200 µl Solvent. The Clinical Dose Used is iv (unless otherwise expressed).

Drug	Clinical Dose (mg)	Solubility (mg/ml)		Index	
		PEG200	GF	PEG200	GF
Clonazepam	1	21	51	4.2	10.2
Desmethyldiazepam	15 ^a	17	29	0.2	0.4
Diazepam	10	61	101	1.2	2.0
Flunitrazepam	2	14	42	1.4	4.3
Lorazepam	4	168	391	8.4	19.6
Lormethazepam	1	17	48	3.4	9.6
Midazolam	5	140	202	5.6	8.1
Nitrazepam	5 ^a	37	84	1.5	3.4
Triazolam	0.125 ^a	6.7	14	10.7	22.4

^aExpresses the peroral dose.

Id., 295. Our study found that for some agents, such as diazepam, the clinical dose (10 mg) was close to the solubility of the drug in either PEG200 (61 mg/200 µl) or GF (101 mg/200 µl) as co-solvents. In contrast, midazolam has a much wider gap, or ratio, between the threshold clinical dose (5 mg) and solubility of the drug in either PEG200 (140 mg/200 µl) or GF (202 mg/200 µl). From this, a POSA would note that developing certain benzodiazepines such as diazepam would be more difficult than, for example, midazolam because the saturation dose of diazepam is close to the clinical dose, thereby risking precipitation of the drug within the nasal cavity:

The solubilities of various benzodiazepines in polyethyleneglycol 200 and glycofurol are shown in Table 2. The solubility index is introduced because it directly shows how many intravenous doses can be dissolved

in an application volume of 200 μ l (100 μ l into each nostril). The volume, 200 μ l, has been chosen because 300 μ l is considered to be the upper limit with respect to keeping the formulation in the nasal cavity. How large the index should be is not known. Ideally it should be more than 2-3, depending on the bioavailability of the benzodiazepine and the exponential solubility lowering effect of water from mucus in the nasal cavity. **In clinical situations it may not be favorable to use concentrations close to saturation. The risk of precipitation in the humid nasal cavity may be very much increased.**

Bechgaard [EX2007], 295 (emphasis added).

66. As a result of our work from this article, we pursued the development and eventual approval this year of NAYZILAM[®], a proprietary mixture of midazolam, ethanol, PEG-6 methyl ether, polyethylene glycol 400, propylene glycol and water. Midazolam was chosen specifically because of the high solubility index, *i.e.*, ratio between the clinical dose and saturation dose of midazolam. In fact, from our work in 1997, I would have been discouraged from pursuing lower solubility index benzodiazepines for development since this would have been, in my opinion, a potential set-up for failure. Thus, as I explain in more detail below, it was surprising and unexpected to me that the '876 Patent was successful in formulating a non-aqueous intranasal diazepam formulation as seen in Examples 1-11.

67. The ability to formulate diazepam into an intranasal formulation for use in the treatment of epilepsy is not just reflected in patent examples. I have been active in this work for over three decades, and follow the successes and failures of the benzodiazepine field very closely. The intranasal diazepam formulation developed by Neurelis is currently in Phase III clinical studies, and I understand that it is close to approval by the Food & Drug Administration. See <https://www.neurelis.com/neurelis-news/neurelis-files-new-drug-application-fda-valtoco™-nasal-spray-investigational-treatment-pediatric> (accessed November 1, 2019) [EX2023]. Besides NAYZILAM®, there has been no other successful intranasal benzodiazepine formulation that has been FDA approved. This, along with the prior art references cited by Dr. Peppas, in my opinion reinforce the unexpected nature of the challenged claims, and the fact that a POSA would not have been motivated to combine the cited references, as I explain in detail below.

VIII. All Challenged Claims Of The '876 Patent Are Valid

A. The Provisional Application Incorporates By Reference Alkyl Glycosides as Claimed

68. I understand from Neurelis' counsel that U.S. Provisional Application Serial No. 61/040,558 ('558 Provisional Application) [EX1008], which the '876 Patent claims priority to (*see* EX1001, pg. 0001), includes an incorporation by

reference to a 1988 SIGMA Catalog excerpt [EX2006]. The “incorporation by reference” phrase reads:

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

EX1008, ¶[152]. I reviewed the SIGMA catalogue excerpt in the context of this paragraph, as well as the provisional application as a whole. In my opinion, a POSA reading this phrase, and reviewing the SIGMA catalogue, would have recognized and understood that alkyl glycosides were disclosed and supported in the provisional application.⁸

69. First, the term “biological detergents” as used in the ’558 Provisional Application has a specific meaning to a POSA. While a detergent is an agent that is amphipathic, that is a molecule that has both a nonpolar tail region and a polar head group, not all detergents can be biological detergents. I agree with Dr. Peppas’

⁸ As I mentioned above, I do not provide an opinion with regards to legal arguments related to the incorporation by reference of the SIGMA Catalogue excerpt [EX2006] into the ’558 Provisional Application. *See* Section IV.

definition of a “biological detergent” as “a detergent and surfactant that can be used in biological applications.” *See* Peppas Depo. Tx [EX2011], 106:8-13. Surfactants (also known as surface active agents) make up a subset of detergents that is named after its functional ability to reduce the surface tension of a liquid when dissolved, allowing rapid spreading and wetting of liquids on a surface. Detergents and surfactants are classified by the charge characteristics of the polar head group in the molecule, including anionic (negatively charged), cationic (positively charged) and non-ionic (neutral charge). Depending on that charged group, the detergent could be potentially harmful to a patient or useful, as is the case in the ’876 Patent, as an enhancing agent.

70. In the context of an intranasal pharmaceutical formulation, as is the case for the ’876 Patent, biological detergents would have been limited to detergents that are appropriate for administering to the nasal cavity of a human or other animal subject. Generally, non-ionic detergents (*i.e.*, the polar head group is “non-ionic” or neutral), including alkyl glycosides, would be the specific detergent class that would be useful for intranasal administration. This is supported earlier in paragraph [152], which includes “non-ionic materials” as preferable surface-active agents (*i.e.*, surfactants); other detergents or surfactants, such as anionic detergents (sodium dodecyl sulfate (SDS), for example), would have been potentially irritating or even toxic to the nasal lining. Moreover, detergents that may be appropriate for topical

administration may not be useful for intranasal administration because of the cutaneous layer that protects and excludes agents from entering into the bloodstream.⁹

71. The incorporated text of the 1988 SIGMA catalog includes a limited number of biological detergents within the six pages that are specifically cited to. This section includes 4 different categories: Anionic, Cationic, Zwitterionic and Non-Ionic. *See* EX2006, 316. Within the category of non-ionic detergents, there are ten listed non-ionic biological detergents on pg. 316 of the document: 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 and Triton X-100. I note that 9 of the 11 non-ionic detergents listed are alkyl glycosides. Additional alkyl glycosides are listed within pages 319-321 of the SIGMA catalog excerpt, including n-Heptyl β -D-thio-glucopyranoside, n-Hexyl β -D-glucopyranoside and Octyl β -D-thioglucopeyranoside. Thus, alkyl glycosides, which are non-ionic biological

⁹ Dr. Peppas also recognizes that ointments, which are generally topical formulations used on the skin, “may [have] different priorities of different characteristics.” *See* Peppas Depo. Tx [EX2011] 106:25-107-3.

detergents, are prominently represented within the 1988 SIGMA Catalog pages incorporated into the '558 Provisional Application.

72. It is my own experience and opinion that alkyl glycosides were prevalent as a biological detergent, and this would have been well known and recognized to a POSA in 2008. This is demonstrated by the fact that 9 of the 11 non-ionic detergents, together with the critical micellar concentration (CMC; concentration at which micelles are formed) and other characteristics, listed on pg. 316 of the 1988 SIGMA catalog are alkyl glycosides. The SIGMA Catalog excerpt specifically included these select biological detergents as advantageous for biological use because of its CMC values. *Id.* This means that the vast majority of the listed non-ionic biological detergents were well-studied with known characteristics, indicating the importance and interest in this compound class.

73. Dr. Peppas also considered alkyl glycosides to be well known to a POSA by at least 2008. In his deposition, Dr. Peppas testified that alkyl glycosides are “something I have in my laboratory and I’ve used it from time to time.” Peppas Depo. Tx [EX2011], 99:17-18. Dr. Peppas further characterized alkyl glycosides as

surfactants and furthermore that a “large number” of alkyl glycosides can be classified as a biological detergent. *See id.*, 104:6-11 and 107:10-13.¹⁰

74. Moreover, Dr. Peppas also agreed that the SIGMA catalog [EX2006] includes alkyl glycosides, specifically identifying dodecyl maltoside (specifically claimed in claims 26-28 and 30-33) as disclosed within the SIGMA catalog. *See* Peppas Depo. Tx [EX2011], 125:9-127:5. Dr. Peppas also agreed that the SIGMA catalog, which disclosed alkyl glycosides, was in fact incorporated by reference in the specification.¹¹ *Id.*, 153:8-25.

¹⁰ “Q: Got it. So would alkyl glycoside fall in the category of a biological detergent?

A [Dr. Peppas]: A large number of alkyl glycosides can fall into the biological detergents, but not all.”

¹¹ “Q: Now let’s go back to [SIGMA Catalog, EX2006]. Is this document incorporated by reference into the document that we looked at earlier? Is the rest of your testimony about that correct?

A [Dr. Peppas]: This document is incorporated in one of the patents that you showed me this morning, which we have over there.

Q: It is incorporated by reference into –

75. It is thus my opinion that a POSA would have understood that the SIGMA Catalog excerpt from 1988 [EX2006], which as I understand and what Dr. Peppas corroborates, was incorporated by reference in the '558 Provisional Application. The 1988 SIGMA Catalog's biological detergents section highlights non-ionic detergents, specifically alkyl glycosides. Moreover, a POSA would have immediately appreciated that the predominant, functionally-characterized non-ionic detergents in the SIGMA Catalog excerpt were alkyl glycosides, specifically because they were advantageous for biological use. As such a POSA would have known and recognized from the incorporation by reference that the '558 Provisional Application [EX1008] highlighted alkyl glycosides, and that the inventors were in possession of alkyl glycosides as a key part of the claimed inventive concept.

B. The Cited References Do Not Provide the Requisite Motivation or Reasonable Expectation of Success Needed to Support an Obviousness Case

A: By reference into that patent.

Q: -- into the patent that is in dispute in this matter; correct?

A: Yes, it is.

Q: And does it disclose what we discussed earlier?

A: It does disclose alkyl glycosides --"

76. I was also asked to evaluate Dr. Peppas' opinion in Ground 2 of his declaration [EX1041] of whether challenged claims 1-16 and 24-36 are obvious over the combination of Gwozdz [EX1014] and Meezan [EX1011]. Claim 1 recites:

A method of treating a patient with a disorder which is treatable with a benzodiazepine drug, comprising: administering to one or more nasal mucosal membranes of a patient a pharmaceutical solution for nasal administration consisting of a benzodiazepine drug, one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); ethanol and benzyl alcohol in a combined amount from about 10% to about 70% (w/w); and an alkyl glycoside.

EX1001, 63:26-34.

77. I disagree with Dr. Peppas that the challenged claims are obvious in view of Gwozdz and Meezan. For the reasons below, it is my opinion that a POSA, in view of Gwozdz and Meezan would not have had a motivation to combine, nor a reasonable expectation of success in combining the two references to come to the challenged claims. Instead, both Gwozdz and Meezan provide no motivation to either: 1) modify Gwozdz to include alkyl glycosides; or 2) combine Gwozdz with Meezan, a reference that relates to the use of *surfactants* to include in an aqueous intranasal formulation. Similarly, there is no reasonable expectation of success in adding the disclosure of

Meezan to Gwozdz because it is not known what the surfactants of Meezan would have done in the non-aqueous environment of Gwozdz.

78. In addition, non-ionic surfactants combined with alcohols and benzyl alcohol are incompatible with regards to maintaining antimicrobial and preservative activity, as well as the combination of tocopherols and benzyl alcohol. Moreover, the use of at least benzyl alcohol and ethanol in nasal formulations was not recommended by POSAs because of the potential for damaging the nasal mucosa and ciliary epithelial cells.

79. In coming to his conclusion that the claims are obvious, Dr. Peppas assumes two points that a POSA would have come to in order to combine the excipients in the specific combination claimed:

- A POSA would have “Increas[ed] the Drug Solubility to Allow More Drug to Dissolve Per Unit Solvent/Formulation”; *see* Peppas Decl. [EX1041], section XI.D (Solution #1)
- A POSA would have also “Us[ed] Penetration Enhancers to Increase the Permeability of the Nasal Mucosa With Respect to the Drug”; *see id.*, section XI.E (Solution #2).

In my experience and opinion, these solutions are mutually exclusive. In fact, Dr. Peppas provides no reason why a POSA would have combined both solutions, rather

than pursuing one or the other. A POSA would have instead, for example, considered not sacrificing drug solubility by removing co-solvent necessary for maximizing solubility of the benzodiazepine drug. For this, and the detailed reasons below, Dr. Peppas' combination of Gwozdz and Meezan fail to render obvious the challenged claims.

1. Claim 1 is Not Obvious Over Gwozdz and Meezan

a. There is No Motivation for a POSA to Modify Gwozdz

80. Dr. Peppas relies on Gwozdz to provide Solution #1, *i.e.*, that a POSA would have sought to “increase[e] the drug solubility to allow more drug to dissolve per unit solvent/formulation.” *See* Peppas Decl. [EX1041], section XI.D Heading (Solution #1). Dr. Peppas states that “Gwozdz teaches that pharmaceutical solutions containing 30-99% tocopherols, 1-70% alcohols (including combinations of ethanol and benzyl alcohol), and benzodiazepines (such as diazepam) can be created.” *Id.*, ¶203. Dr. Peppas also claims that Gwozdz “solved the [solubility] problem with respect to diazepam (“combining tocopherol and ethanol has been found to provide solubility of the Diazepam approaching the 10% level.”[)]. *Id.*, ¶194, citing to Gwozdz [EX1014], 7:14-16.

81. Gwozdz [EX1014], which claims priority to a provisional application (U.S. Provisional Application Serial No. 61/040,281) (*see* EX1014, pg. 0000), that

was filed on the same day as the '558 Provisional Application (*i.e.*, March 28, 2008), relates to non-aqueous hydrophobic or lipophilic “pharmaceutical solutions . . . produced by dissolving therapeutic agent in one or more tocopherols or tocotrienols and one or more alcohols or glycols.” *See* Gwozdz [EX1014], pg. 0000, Abstract. In particular, Gwozdz is concerned with the solubilization of hydrophobic/lipophilic pharmaceutical agents, including therapeutic agents such as “ibuprofen, diazepam, griseofulvin, cyclosporin, cortisone, proleukin, etoposide and paclitaxel.” Gwozdz [EX1014], pg. 0001, lns. 18-20. Gwozdz distinguishes its formulations from prior art formulations containing “[o]ne or more surfactants [which] are used to stabilize the emulsion, and excipients are added to render the emulsion more biocompatible, stable and less toxic,” as well as micellar formulations using the non-ionic surfactants TWEEN 80, BRIJ 58 and HCO-60. *Id.*, pg. 0002, lns. 6-8 and 24-25. Gwozdz also states that “the resulting pharmaceutical solution is not an emulsion or vesicle, and can be used directly in the production of pharmaceutical compositions.” *Id.*, pg. 0004, ln. 34 – pg. 0005, ln. 2 (emphasis added).

82. Gwozdz furthermore discloses a specific example for diazepam:

As a non-limiting example, the solubility of Diazepam at room temperature is less than or equal to 6.67% in 190 proof ethanol.¹² However, combining tocopherol and ethanol has been found to provide solubility of the Diazepam approaching the 10% level. By way of illustration, at 70% tocopherol:30% ethanol (200 proof), Diazepam is soluble to greater than or equal to 8% and at 95% tocopherol:5% ethanol (200 proof), Diazepam is soluble at greater than or equal to 9%.

Gwozdz [EX1014], pg. 0007, lns. 12-19. While Dr. Peppas in relying on this paragraph contends that “Gwozdz solved the (solubility) problem with respect to diazepam,” and implying that a POSA would simply then add a penetration enhancer to Gwozdz, I cannot agree with his position. From my calculations, Gwozdz’s solubility level for diazepam, a benzodiazepine, is close to the same amount as the clinical dose (10 mg) in 100 µl needed for therapeutic effect. *See* Bechgaard [EX2007], 295, Table 2.

¹² I note that the comparison of the 6.67% in 190 proof ethanol to the tocopherol/ethanol combination (which uses 200 proof ethanol) and improvement in solubility levels is not equal. The “190 proof ethanol” comparison includes 5% water, while the tocopherol:200 proof ethanol is a non-aqueous system. To make a fair comparison, the control “190 proof ethanol” should also be in 200 proof ethanol.

83. This is important because Gwozdz in fact discloses that increasing the amount of tocopherol from 70% to 95% and decreasing the amount of ethanol from 30% to 5% increases the solubility of diazepam to 9%, or 9 mg/100 µl of solvent (18 mg/200 µl solvent). Since the clinical dose of diazepam is 10 mg, this means that at this high, maximum amount of tocopherol of 95% as claimed, and minimal amount of ethanol of 5%, the solubility index (ratio between the clinical dose and saturation concentration) would be less than 2. *Id.*, 295 (suggesting a solubility index of more than 2-3 to avoid precipitation of the benzodiazepine formulation). A POSA would have thus known and realized that there is little room to modify Gwozdz without affecting its ability solubilize diazepam.

84. Gwozdz instead discloses that adding less tocopherol *reduces* the solubility of diazepam. *Compare* Gwozdz diazepam formulation with 70% tocopherol and 95% tocopherol [EX1014], pg. 0007, lns. 12-19. Because of the already low solubility index of Gwozdz's diazepam formulation, in my opinion there would have been no reason or motivation for a POSA to modify at least the exemplary formulation even further by adding either benzyl alcohol or an alkyl glycoside as claimed in claim 1. Doing so would potentially take away the amount of either or both of the tocopherol and ethanol, and as observed by Gwozdz, decrease the solubility of diazepam. Accordingly, for this reason alone, there would have been no reason to

reduce the amount of tocopherol even further, thereby risking less than a therapeutic amount of diazepam being administered to a subject.

85. As such, it is my opinion that there would have been no motivation, nor a reasonable expectation of success, to modify Gwozdz by adding benzyl alcohol and alkyl glycoside to Gwozdz's invention as claimed in claim 1.

b. Benzyl Alcohol is Incompatible with Tocopherols and Tocotrienols

86. Dr. Peppas uses the Handbook of Pharmaceutical Excipients [EX1031] ("Handbook") to explain that the solvents ethanol and benzyl alcohol were known to POSAs. *See* Peppas Dec. [EX1041], ¶¶ 123 and 124. However, the Handbook also provides other useful and practical information to POSAs, including with regards to incompatibilities of excipients with other excipients and/or active ingredients. A review of the Handbook entry for Benzyl Alcohol, for example, includes this guidance to POSAs with regards to the combination of Benzyl Alcohol with fats:

Benzyl alcohol is incompatible with oxidizing agents and strong acids. It can also accelerate the autoxidation of fats.

EX1031, pg. 0010 (emphasis added). In my opinion and experience, this would have at least cautioned a POSA to not combine benzyl alcohol with tocopherols or tocotrienols, which are fat-soluble compounds. *See, e.g.*, EX1031, pg. 0006. The

Handbook, in fact, cautions against using conditions that would result in the autoxidation of tocopherol. *Id.* Doing so would negate the anti-oxidation properties of tocopherol, and degrade the compound such that undesirable by-products may exist in the formulation.

87. As such, for this separate reason, a POSA would have had no motivation to combine and no reasonable expectation of success in combining a tocopherol or tocotrienol with benzyl alcohol. I accordingly disagree with Dr. Peppas that a POSA would have modified Gwozdz further by combining benzyl alcohol with the invention of Gwozdz.

c. Benzyl Alcohol and Ethanol are Incompatible with Alkyl Glycosides

88. The Handbook also discloses that benzyl alcohol and ethanol are incompatible with nonionic surfactants, such as alkyl glycosides.¹³ Specifically, the Handbook states that the antimicrobial activity of ethanol and benzyl alcohol is reduced or eliminated in the presence of nonionic surfactants. *See* EX1031, pg. 004 (“Ethanol is inactivated in the presence of nonionic surfactants and is ineffective

¹³ Dr. Peppas confirmed alkyl glycosides are non-ionic surfactants. Peppas Depo. Tx [EX2011], 106:5-6.

against bacterial spores”) and pg. 0010 (benzyl alcohol) (“Although antimicrobial activity is reduced in the presence of nonionic surfactants, such as polysorbate 80, the reduction is less than is the case with hydroxybenzoate esters or quaternary ammonium compounds.”).

89. Especially with regards to multidose intranasal uses, the inactivation of the antimicrobial activity of ethanol and/or benzyl alcohol could have consequences in the successful approval of this intranasal formulation. Accordingly, for this separate reason, it is my opinion that a POSA would have had no motivation to combine and no reasonable of success in combining an alkyl glycoside (a non-ionic surfactant) with a combination of benzyl alcohol and ethanol as claimed.

d. Benzyl Alcohol was a Known Irritant in Intranasal Formulations

90. It was also known that benzyl alcohol is a known irritant to the nasal cavity. As such, POSAs knew that because of the presence of benzyl alcohol, which is used as a preservative in pharmaceutical formulations, injectable compositions containing benzyl alcohol could not be used in intranasal formulations. This was seen, for example, with regards to the benzodiazepine lorazepam, where a lorazepam injectable composition, which was approved and sold by Wyeth Laboratories under

the brand name ATIVAN[®], was recognized by POSAs as unsuitable for intranasal formulations.

A commercially available injectable composition approved by the FDA and sold by Wyeth Laboratories under the brand name Ativan[®], includes 2 mg of lorazepam in 0.18 mL of polyethylene glycol 400 in propylene glycol with 2.0% benzyl alcohol as a preservative. This composition was not acceptable for intranasal spray administration because benzyl alcohol is irritating to the mucosa.

See U.S. Patent No. 6,610,271 [EX2014], 6:31-39 (emphasis added).

91. I note that Dr. Peppas appears to argue that the claim phrase “ethanol and benzyl alcohol in a combined amount from about 10% to about 70% (w/w)” includes combinations where either ethanol or benzyl alcohol is set to 0%, *i.e.* no benzyl alcohol or ethanol added in the limitation “ethanol and benzyl alcohol in a combined amount.” *See, e.g.,* Peppas Dec. [EX1041], ¶187. As I explained above, “in a combined amount” would be construed by a POSA to necessarily include both ethanol and benzyl alcohol in some amount to come to a total in the claimed range. *See* Section VI. As such, to the extent that Dr. Peppas may argue that benzyl alcohol may not be included in the claimed formulation, and thus no nasal irritation would occur, this would be incorrect. Instead, because the claimed formulation includes benzyl alcohol, a POSA would be surprised at the inclusion of this excipient.

92. POSAs, thus, prior to 2008 recognized and knew that the combined use of ethanol and benzyl alcohol would not have been advised in an intranasal formulation because it was a well known irritant to the nasal mucosa.¹⁴ Accordingly, I disagree with Dr. Peppas when he states that “[c]oncentrations of 5% v/v or more are employed as a solubilizer”. Peppas Dec. [EX1041], ¶124. A POSA would not have used this high concentration of benzyl alcohol in intranasal formulations because it would have potentially harmed the patient when applied to the nasal mucosa. For this separate reason, it is my opinion that a POSA would have had no motivation to combine nor a reasonable expectation of success in using benzyl alcohol in an intranasal benzodiazepine formulation as claimed.

e. Dr. Peppas’ Own Work Would Have Discouraged a POSA to Use a Penetration Enhancer in an Intranasal Formulation

93. Moreover, from Dr. Peppas’ own work, there would have been no reason to add a nasal enhancer to the formulation as claimed. During his deposition, Dr. Peppas pointed to a senior-authored publication as support for the importance of adding nasal penetration enhancers (bioadhesives) to active ingredients to enhance

¹⁴ I note that Diastat[®] also includes 1.5% benzyl alcohol, a separate reason why a POSA would not have applied it for intranasal use. See ¶52, above.

absorption through the nasal mucosa. *See* Peppas Depo. Tx., 33:24-34:8. However, EX1045, which relates to a pharmacokinetic modeling study comparing intranasal versus ocular formulations, actually concludes that penetration enhancers should not be added to intranasal formulations:

The results indicate that use of a nasal enhancer (increase of parameters κ_1 and κ_2) is **not the best delivery method**. Instead, use of a viscous delivery carrier (low κ_4 value) is a much more efficient method of nasal delivery.

Maitani [EX1045], 191 (emphasis added). When asked about this statement, Dr.

Peppas explained that this statement relates not only to intranasal administration, but to ocular and lacrimal as well. *See* Peppas Depo. Tx [EX2011], 134:10-135:4.

However, the pharmacokinetic models presented in Dr. Peppas article clearly differentiates between intranasal, ocular and lacrimal systems. *See, e.g.,* Maitani, FIG.

1. Moreover, the statement above plainly reads that the “use of a viscous delivery carrier is a much more efficient method of **nasal** delivery,” not ocular or lacrimal delivery systems. Dr. Peppas’ deposition statement is also not supported because POSAs would have known in my experience not to use viscous delivery vehicles with ocular and lacrimal systems. As such, it appears that Dr. Peppas encouraged POSAs before 2008 that nasal enhancers (not ocular or lacrimal enhancers) should not be used to deliver active ingredients, but instead a viscous delivery system was superior.

94. As such, it is my opinion that Gwozdz fails to provide a motivation to modify its disclosure to include a surfactant molecule, such as an alkyl glycoside, to the formulation. Gwozdz distinguishes itself from prior art solutions containing surfactants or micellar formulations. Gwozdz, in fact, exemplifies a maximized tocopherol formulation necessary for achieving solubility levels that could approach levels needed for clinical relevance. As such, there would have been no motivation for a POSA to further modify Gwozdz such that the tocopherol and/or ethanol levels were potentially decreased by adding benzyl alcohol and alkyl glycoside as claimed. Moreover, a POSA would have known from the Handbook regarding the incompatibility of benzyl alcohol with tocopherols/tocotrienols, and ethanol and benzyl alcohol with non-ionic surfactants, such as alkyl glycosides. A POSA would also have been cautioned regarding benzyl alcohol's known properties as a nasal irritant. Finally, even Dr. Peppas' own reference states that a nasal enhancer should not be added to an intranasal (ocular or lacrimal) formulation.

95. For these reasons, it is my opinion that a POSA would not have been motivated to modify Gwozdz to further include benzyl alcohol (or a second alcohol) and an alkyl glycoside as claimed.

f. There is No Motivation to Combine Meezan with Gwozdz

96. Dr. Peppas relies on Meezan [EX1011] to provide Solution #2, *i.e.*, that a POSA would have “us[ed] penetration enhancers to increase the permeability of the nasal mucosa with respect to the drug.” *See* Peppas Decl. [EX1041], section XI.E Heading (Solution #2). Dr. Peppas states that Meezan “discloses intranasal solutions (which could include sprays) for the administration of various drugs, including small organic molecules and a couple of anti-seizure agents.” *Id.*, ¶222. Meezan et al. [EX1011] was concerned with increasing absorption and decreasing adverse effects of water-soluble therapeutic drugs through non-intravenous routes of administration, including “oral, ocular, nasal, nasolacrimal, inhalation or pulmonary, oral cavity (sublingual or Buccal cell) or cerebral spinal fluid (CSF) delivery route[s],” as well as increasing stability of protein and peptide formulations, by addition of surfactants, including alkyl glycoside and/or saccharide alkyl esters. *See* EX1011, ¶[0004]. In particular, Meezan discloses the formulation and use of surfactants, including alkyl glycosides and saccharide alkyl esters, in an aqueous setting to administer peptides and protein therapeutic agents, including insulin, glucagon and exendin-4, to treat diabetes. *See, e.g.*, Meezan, ¶¶[0146]-[0172] (Examples 1-7).

97. While Dr. Peppas goes on to admit that benzodiazepines are not specifically named in Meezan, Dr. Peppas concludes that “a POSITA would readily expect that Meezan ‘962 would be applicable to benzodiazepines because

benzodiazepines are small organic molecules and are known to be anti-seizure agents.” *See* Peppas Decl. [EX1041], ¶222. This statement is a stretch, at best, and likely incorrect. The reason is because the genus of “small organic molecules” is practically infinite. In my review, Meezan gives no guidance as to how a POSA can determine what group, if any, of small organic molecules would benefit from Meezan’s disclosure. Instead, Meezan relates to, and provides numerous examples for, peptides and proteins, specifically “insulin, glucagon and exendin-4.” Meezan [EX1011], Abstract. The therapeutic agents disclosed in Meezan moreover primarily relate to water-soluble compounds, including the “anti-seizure agents” topiramate and zonisamide that Dr. Peppas relies on for support from Meezan. Thus, none of the anti-seizure agents which Dr. Peppas points to as relevant in Meezan, or the exemplified compounds of Meezan are poorly water soluble therapeutic agents as with benzodiazepines.

98. In addition, Dr. Peppas acknowledged during his deposition that alkyl glycosides as used in Meezan are solubilized in water, which is not the case for the claimed formulation.¹⁵ Peppas Depo. Tx [EX2011], 140:13-23. Dr. Peppas also

¹⁵ This understanding comports with the language of “consisting of,” which excludes additional excipients from the claim term, including water. *See* Section VI.

acknowledged that he did not know how Meezan's alkyl glycosides function in the absence of water, as it is claimed in the '876 Patent.¹⁶ During this exchange, Dr. Peppas provided information that would be needed in order to determine how the alkyl glycosides of Meezan would function with the non-aqueous solutions of Gwozdz, including "[s]olubility of the glycoside in other solvents, other – other solvents, other carriers ... [p]robably a number of other parameters; pH, pH sensitivity, concentrations." *Id.*, 141:14-18. Dr. Peppas also could not answer how and if Meezan, which he admitted provides a stabilizing function to the active pharmaceutical ingredient, could function to stabilize a compound in a non-aqueous environment.¹⁷

Dr. Peppas also agreed and understood that the challenged claims of the '876 Patent excluded water. *Id.*, citing to Peppas Depo. Tx. [EX2011], 137:16-138:6.

¹⁶ "Q: Do you have any understanding of how the formulations of Meezan would function if the water was removed?

A [Dr. Peppas]: Not from Meezan per se." Peppas Depo. Tx. [EX2011], 141:8-11.

¹⁷ I note that Meezan employs alkyl glycosides as micelles in order to stabilize and enhance penetration of the peptides and proteins exemplified in its application. For example, experimental Example 3 uses 14.3 mM dodecyl- β -D-maltoside with insulin

99. I agree with Dr. Peppas' statements that a POSA would not have known how alkyl glycosides from Meezan would function in the non-aqueous environment of Gwozdz, and thus what to expect when they are combined. This level of uncertainty, in my opinion, supports that the claims were not obvious. Claim 1 of the '876 Patent excludes water from the benzodiazepine solution. By doing so, claim 1 creates a milieu not conducive for a surfactant to function, either to stabilize or act as a traditional penetration enhancer in solution. Surfactants align themselves at the air- or oil-interface; without water, surfactants would have lacked the substrate needed to orient itself and function as a surface-active/tension-reducing agent. All of this, in my opinion, would have likely discouraged a POSA from using the alkyl glycosides of Meezan in the non-aqueous formulations of Gwozdz.

100. It is thus my opinion that claim 1 of the '876 Patent is not obvious over the combination of Gwozdz and Meezan.

(see EX1011, ¶[0156] (0.5% dodecyl- β -D-maltoside; referring to Table I)) to increase bioavailability in eye drops, which is 90X more than the CMC for this alkyl glycoside. See 1988 SIGMA Catalog excerpt [EX2006], 316 (CMC of 0.16 mM for n-dodecyl- β -D-maltoside).

2. *Claims 2, 7, 11 and 12 are Not Obvious Over Gwozdz and Meezan*

101. Claims 2, 7, 11 and 12 recite tocopherol or tocotrienol variants. *See* Appendix A (claim chart). For the same reasons as in claim 1, Gwozdz and Meezan do not render these claims obvious. Gwozdz and Meezan fail to provide a motivation to combine Gwozdz, and its disclosed tocopherol compositions with Meezan, nor would a POSA have a reasonable expectation of success in formulating an intranasal benzodiazepine as claimed because a POSA would not have known how the aqueous alkyl glycoside of Meezan would function in the non-aqueous environment of Gwozdz. *See* Section VIII.B.1. For this reason, it is my opinion that claims 2, 7, 11 and 12 are not obvious over Gwozdz and Meezan.

3. *Claims 3-6 and 9-10 are Not Obvious Over Gwozdz and Meezan*

102. Claims 3-6 and 9-10 recite specific benzodiazepines and/or ranges of benzodiazepines. *See* Appendix A (claim chart). For the same reasons as in claim 1, Gwozdz and Meezan do not render these claims obvious. Gwozdz and Meezan fail to provide a motivation to combine Gwozdz and Meezan, where Meezan does not even teach, suggest or disclose the use of a benzodiazepine compound. Accordingly, there is no motivation to combine, nor would a POSA have a reasonable expectation of success in formulating an intranasal benzodiazepine as claimed because a POSA. *See*

Section VIII.B.1. For this reason, it is my opinion that claims 3-6, and 9-10 are not obvious over Gwozdz and Meezan.

4. *Claims 8 and 13-15 are Not Obvious Over Gwozdz and Meezan*

103. Claims 8 and 13-15 recite different amounts of the benzyl alcohol and ethanol combinations. *See* Appendix A (claim chart). For the same reasons as in claim 1, Gwozdz and Meezan do not render these claims obvious. Gwozdz and Meezan fail to provide a motivation to combine Gwozdz, and its disclosed general alcohols, nor would a POSA have a reasonable expectation of success in formulating an intranasal benzodiazepine as claimed because a POSA would not have known how the aqueous alkyl glycoside of Meezan would function in the non-aqueous environment of Gwozdz. *See* Section VIII.B.1.

104. For this reason, it is my opinion that claims 8 and 13-15 are not obvious over Gwozdz and Meezan.

5. *Claims 16 and 24-33 are Not Obvious Over Gwozdz and Meezan*

105. Claims 16 and 24-33 recite specific amounts and pharmaceutical forms of the claimed intranasal benzodiazepine formulation of claim 1. *See* Appendix A (claim chart). For the same reasons as in claim 1, Gwozdz and Meezan do not render these claims obvious. Gwozdz and Meezan fail to provide a motivation to combine Gwozdz with Meezan, much less the specific amounts of excipients recited in these claims, nor

would a POSA have a reasonable expectation of success in formulating an intranasal benzodiazepine as claimed because a POSA would not have known how the aqueous alkyl glycoside of Meezan would function in the non-aqueous environment of Gwozdz. *See* Section VIII.B.1. For this reason, it is my opinion that claims 16 and 24-33 are not obvious over Gwozdz and Meezan.

C. Claims 17-23 of the '876 Patent are Not Obvious Over Meezan and Gwozdz, and Further In View of Cartt'784

106. Dr. Peppas provides a separate ground of invalidity for claims 17-23 which recite specific benzodiazepine amounts as well as modes of administration. *See* Exhibit A (claim chart). For the same reasons as in claim 1, the combination of Meezan and Gwozdz fail to render obvious claims 17-23. Cartt'784 [EX1015] does not fix the many deficiencies of Meezan and Gwozdz, including the failure to provide a motivation to combine or reasonable expectation of success that such a combination would work.

107. A POSA instead would have recognized that Gwozdz [EX1014] distinguished its non-aqueous lipophilic and hydrophobic formulations from Cartt'784 [EX1015], which provides the same emulsions and particulates that Gwozdz distinguished its invention from: “Advantageously, the resulting pharmaceutical solutions is not an emulsion or vesicle, and can be used directly in the production of pharmaceutical compositions.” Gwozdz [EX1014], pg. 0004, ln. 34 – pg. 0005, ln. 2

(emphasis added). Accordingly, a POSA would have recognized the lack of motivation to combine with Cartt’784, with Gwozdz instead teaching that it is a superior alternative over the teachings of Cartt’784.

108. While Dr. Peppas appears to primarily use Cartt’784 for dosage and pharmaceutical form and administration disclosure, *see, e.g.*, Peppas Dec. [EX1041], ¶253, Dr. Peppas ignores that applying a particulate formulation, especially with regards to dosage and method of administration, may not be translatable and applicable in a solution formulation.¹⁸ In addition, a POSA would have found it

¹⁸ Dr. Peppas cited to paragraphs 178, 179, 180 and 181 in Cartt’784 to support his statement during the deposition that while the Abstract of Cartt’784 discusses particulate pharmaceutical formulations, Cartt’784 does disclose solution-based formulations. *See* Peppas Depo. Tx [EX2011], 144:12-14. A review of paragraphs 178, 179, 180 and 181, however, does not support Dr. Peppas’ argument. Instead, these paragraphs relate to solvents used for making the particulate formulations disclosed in Cartt’784. For example, paragraphs 178 and 179 discuss the use of “first solvents” and “second solvents.” This ties back to sections in Cartt’784 that discusses the making of the particulates of the patent application:

difficult, if not nearly impossible, to combine the exact same excipients, including a combined amount of benzyl alcohol and ethanol, given the large lists of solvents present. Such a list would provide no reasonable expectation of success given the disparate lists, and no POSA would have had a motivation to combine these references. Dr. Peppas agrees with me on this point.¹⁹

109. As such, it is my opinion that claims 17-23 are not obvious over the combination of Gwozdz, Meezan and Cartt’784.

[0156] Small particle dispersions can also be prepared by precipitation techniques. In some embodiments, the small particle dispersions are formed by a microprecipitation method, which includes: (i) dissolving the organic compound in a water-miscible first solvent; (ii) preparing a solution of polymer and an amphiphile in an aqueous second solvent and in which second solvent the organic compound is substantially insoluble ...

Cartt’784 [EX1015], paragraph [0156] (emphasis added). As such, Dr. Peppas’ conclusion at deposition that Cartt’784 discloses aqueous solutions of benzodiazepines is not supported and incorrect.

¹⁹ “Q: How many combinations of two solvents do you think you could make out of the excipients listed in paragraph 182?

A: I could make too many combinations.” Peppas Depo. Tx 147:21-148:2.

IX. Secondary Considerations

110. I understand from Neurelis' counsel that a patent owner may submit "secondary considerations of obviousness" to refute an assertion of obviousness of a patent claim. *See* Section II, above. There are several categories of secondary considerations from my understanding from counsel, including findings of unexpected results, failure of others and a long-felt but unmet need.

111. As discussed above, there have been numerous instances of failure of others to develop an intranasal benzodiazepine product, such as Neurelis' NRL-1 (Valtoco[®]) intranasal diazepam product, and in fact explicit statements by POSAs on the difficulty of diazepam to be formulated into an intranasal benzodiazepine product. Lau and Slattery's study in 1989 [EX2009], which recognized the primary challenge of benzodiazepines to formulate into an intranasally administered product because of their poor water solubility characteristics (diazepam at 0.05 mg/ml and lorazepam at 0.08 mg/ml). *See* Section VII.D.4, above. Despite some success by Lau in solubilizing diazepam and lorazepam in a "neat" non-ionic surfactant organic vehicle, Lau found that for both diazepam and lorazepam, the time to peak concentration was significantly delayed, and the uptake amount was significantly less as compared to intravenous administration. *See* Lau [EX2009], 173-174, Figures 1 and 2. Lau concluded:

Although diazepam and lorazepam cross the nasal mucosa and are absorbed into the systemic circulation, absorption is rather slow and peak concentration is low relative to that found after i.v. administration. **It would appear that this route of administration may be of limited utility for benzodiazepines in the treatment of status epilepticus where rapid onset of effect is essential.**

Lau, 173 (emphasis added). As I also observed, other researchers have had similar difficulties administering clonazepam in dimethyl- β -cyclodextrin. *See* Schols-Hendriks [EX2010], Abstract.

112. Lau's experience mirrored my own work in the benzodiazepine intranasal formulation field. As I discussed, the difficulty in solubilizing benzodiazepines reflects directly to an intranasal formulation to deliver the drug across the nasal mucosa. *See* Section VII.D.4. This is because benzodiazepines with solubility indices that are close to its clinical dose, such as diazepam, may form precipitates in the nasal mucosa during delivery. *Id.* This tendency to precipitate with lower solubility benzodiazepines, such as diazepam, means that there is a risk the diazepam drug once it enters the nasal cavity will be trapped in the mucosal layer and washed through to the gastric system to be swallowed and absorbed through an oral route. *Id.*

113. Thus I was surprised to see that Neurelis had succeeded in formulating diazepam into an intranasal formulation by 2008, as disclosed in the examples of the

'876 Patent. *See* Section VII.D.4, above. The difficulty in formulating an intranasal formulation is evidenced by the fact that for over 20 years, Diastat® is the only alternative to intravenous diazepam. *See* Peppas Depo. Tx. [EX2011], 120:20-24. This is because, as I mentioned above, diazepam's solubility index is low, with the solubility level close to the clinical dose required for treatment. *See* Section III, above. Diazepam is one of the drugs of choice for acute first-line management of epileptic seizures, and as such is an important tool in the treatment of seizures, especially in pediatric patients as evidenced by the efficacy of Diastat®. Because of its importance, I understand that Neurelis received an orphan drug designation in 2015 by the U.S. Federal Food & Drug Administration (FDA) for the treatment of acute repetitive seizures. *See* <https://www.neurelis.com/neurelis-news/fda-orphan-drug-designation> (accessed November 1, 2019) [EX2024]. Once approved, Neurelis' NRL-1 intranasal diazepam product will provide the long-felt needed "alternative to either rectal diazepam or an emergency room visit" for pediatric, adolescent and adult epilepsy patients. *See id.*

X. Conclusion

114. For the reasons above, it is my opinion that from the perspective of a POSA at the time of the '876 Patent's earliest filing date of March 28, 2008, that the '558 Provisional Application, which incorporated by reference the 1988 SIGMA

catalogue excerpt [EX2006], disclosed alkyl glycosides, and thus a POSA would have known and recognized from that incorporation by reference that the '558 Provisional Application highlighted alkyl glycosides as part of the claimed invention.

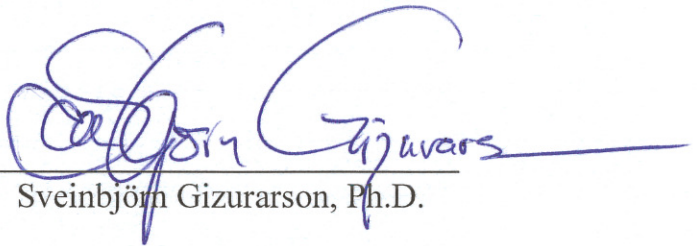
115. Moreover, it is also my opinion that claims 1-16 and 24-36 are not obvious in view of Gwozdz [EX1014] and Meezan [EX1011] (Ground 2 of Dr. Peppas' Declaration [EX1041]) and claims 17-23 are not obvious in view of Gwozdz, Meezan and Cartt'784 [EX1015] (Ground 3 of Dr. Peppas' Declaration [EX1041]). Instead, Aquestive and Dr. Peppas failed to provide in my opinion a motivation to combine or reasonable expectation of success to achieve an intranasal formulation of benzodiazepines as claimed in claims 1-26.

116. In addition, it is also my opinion that the unexpected and surprising success of the '876 Patent at formulating an intranasal non-aqueous diazepam formulation as claimed in claims 1-36, especially in view of the failure of others to successfully formulate an intranasal diazepam or benzodiazepine formulation, for intranasal administration, further supports the non-obviousness of the '876 Patent's claims. The eventual approval of Neurelis' NDA for NRL-1 (Valtoco®), which will fill a long-felt and unmet need for an alternative to rectal and intravenous diazepam products, only serves to strengthen the non-obviousness of Neurelis' challenged claims.

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

Dated: November 4th 2019

By: _____


Sveinbjörn Gizurarson, Ph.D.

APPENDIX A

Challenged Claims of the '876 Patent

CLAIM	
1	A method of treating a patient with a disorder which is treatable with a benzodiazepine drug, comprising: administering to one or more nasal mucosal membranes of a patient a pharmaceutical solution for nasal administration consisting of a benzodiazepine drug, one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); ethanol and benzyl alcohol in a combined amount from about 10% to about 70% (w/w); and an alkyl glycoside.
2	The method of claim 1, wherein the natural or synthetic tocopherols or tocotrienols is Vitamin E.
3	The method of claim 1, wherein 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, lorazepam, prazepam, quazepam, triazolam, temazepam, loprazolam, or any pharmaceutically-acceptable salts thereof, and any combinations thereof.
4	The method of claim 3, wherein the benzodiazepine drug is diazepam, or a pharmaceutically-acceptable salt thereof.
5	The method of claim 1, wherein the solution contains about 1 to

	about 20% (w/v) of benzodiazepine.
6	The method of claim 5, wherein the solution contains about 1 to about 20% (w/v) of diazepam.
7	The method 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.
8	The method of claim 1, wherein the solution contains ethanol from 1 to 25% (w/v) and benzyl alcohol from 1 to 25% (w/v).
9	The method of claim 8, wherein the benzodiazepine drug is present in the pharmaceutical solution in a concentration of from about 10 mg/mL to about 250 mg/mL.
10	The method of claim 9, wherein the benzodiazepine drug is present in the pharmaceutical solution in a concentration of from about 20 mg/mL to about 50 mg/mL.
11	The method 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).
12	The method claim 11, 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).
13	The method of claim 1, wherein the ethanol and benzyl alcohol is in a combined amount from about 15% to about 55% (w/w).

14	The method of claim 13, wherein the ethanol and benzyl alcohol is in a combined amount from about 25% to about 40% (w/w).
15	The method of claim 1, wherein the solution comprises ethanol from 10 to 22.5% (w/v) and benzyl alcohol from 7.5 to 12.5% (w/v).
16	The method of claim 1, wherein the solution is in a pharmaceutically-acceptable spray formulation.
17	The method of claim 16, wherein the benzodiazepine is administered in a therapeutically effective amount from about 1 mg to about 20 mg.
18	The method of claim 17, wherein said pharmaceutical solution is in a pharmaceutically-acceptable spray formulation having volume from about 10 μ L to about 200 μ L.
19	The method of claim 18, wherein the administration of the pharmaceutical solution comprises spraying at least a portion of the therapeutically effective amount of the benzodiazepine into at least one nostril.
20	The method of claim 18, wherein the administration of the pharmaceutical solution comprises spraying at least a portion of the therapeutically effective amount of the benzodiazepine into each nostril.
21	The method of claim 20, wherein the administration of the pharmaceutical solution comprises spraying a first quantity of the pharmaceutical solution into the first nostril, spraying a second quantity of the pharmaceutical solution into a second nostril, and optionally after a pre-selected time delay, spraying a third quantity

	of the pharmaceutical solution into the first nostril.
22	The method of claim 21, further comprising, optionally after a pre-selected time delay, administering at least a fourth quantity of the pharmaceutical solution to the second nostril.
23	The method of claim 21, wherein nasal administration of the pharmaceutical solution begins at any time before or after onset of symptoms of a disorder which is treatable with the pharmaceutical solution.
24	The method of claim 1, wherein the solution contains at least about 0.01% (w/w) of an alkyl glycoside.
25	The method of claim 24, wherein the solution contains about 0.01% to 1% (w/w) of an alkyl glycoside.
26	The method of claim 25, wherein the solution contains about 0.01% to 1% (w/w) of dodecyl maltoside.
27	The method of claim 1, wherein the solution consists of diazepam, vitamin E, ethanol, benzyl alcohol and dodecyl maltoside.
28	The method of claim 1, wherein the solution consists of about 56.47% (w/v) vitamin E, about 10.5% (w/v) benzyl alcohol, about 10% (w/v) diazepam, about 0.25%(w/v) dodecyl maltoside, q.s. dehydrated ethanol.
29	The method of claim 1, wherein the solution consists of diazepam, alkyl glycoside, vitamin E, ethanol, and benzyl alcohol.
30	The method of claim 1, wherein the solution consists of diazepam from 5 to 15% (w/v), dodecyl maltoside from about 0.01 to 1% (w/v), vitamin E from 45 to 65% (w/v), ethanol from 10 to 25%

	(w/v) and benzyl alcohol from 5 to 15% (w/v).
31	The method of claim 1, wherein the solution consists of diazepam from 5 to 15% (w/v), dodecyl maltoside from 0.01 to 1% (w/v), vitamin E from 45 to 65% (w/v), ethanol from 10 to 25% (w/v) and benzyl alcohol from 5 to 15% (w/v).
32	The method of claim 1, wherein the solution consists of diazepam from 9 to 11% (w/v), dodecyl maltoside from 0.1 to 0.5% (w/v), vitamin E from 50 to 60% (w/v), ethanol from 15 to 22.5% (w/v) and benzyl alcohol from 7.5 to 12.5% (w/v).
33	The method of claim 1, wherein the solution consists of diazepam 10% (w/v), dodecyl maltoside from 0.15 to 0.3% (w/v), vitamin E from 50 to 60% (w/v), ethanol from 17 to 20% (w/v) and benzyl alcohol from 10 to 12% (w/v).
34	The method of claim 1, wherein said treatment achieves bioavailability that is from about 80 to 125% of that achieved with the same benzodiazepine administered intravenously.
35	The method of claim 34, wherein said treatment achieves bioavailability that is from about 90 to 110% of that achieved with the same benzodiazepine administered intravenously.
36	The method of claim 35, wherein said treatment achieves bioavailability that is from about 92.5 to 107.5% that obtained with the same benzodiazepine administered intravenously.

APPENDIX B

Exhibit No.	Description
2007	E. Bechgaard et al., “Solubilization of Various Benzodiazepines for Intranasal Administration, A Pilot Study,” <i>Pharmaceutical Development and Technology</i> 2:293-296 (1997)
2008	A. Hussain et al. “Nasal Absorption of Propranolol in Humans,” <i>Journal of Pharmaceutical Sciences</i> 69:1240 (1980)
2009	S. Lau and J. Slattery, “Absorption of Diazepam and Lorazepam Following Intranasal Administration,” <i>International Journal of Pharmaceutics</i> , 54:171-174 (1989)
2010	M. Schols-Hendriks et al., “Absorption of Clonazepam After Intranasal and Buccal Administration,” <i>British Journal of Clinical Pharmacology</i> 39:449-451 (1995)
2011	Dr. Nicholas Peppas Deposition Transcript, October 24, 2019.
2012	Declaration of Dr. Sveinbjorn Gizurarson, Ph.D.
2013	J. Riss et al., “Benzodiazepines in Epilepsy: Pharmacology and Pharmacokinetics,” <i>Acta Neurologica Scandinavica</i> 118:69-86 (2008)
2014	D. Wermeling, U.S. Patent No. 6,610,271, issued August 26, 2003
2015	C. Cole et al., “Community Survey of Carer’s: Individual Epilepsy Guidelines (IEG) for Rescue Medication,” <i>Seizure</i> 18:220-224 (2009)
2016	D. Terry et al., “Acceptance of the Use of Diazepam Rectal Gel in School and Day Care Settings,” <i>Journal of Child Neurology</i> 22:1135-1138 (2007)
2017	Diastat® Label (2005)
2018	“UCB announces NAYZILAM® (midazolam) nasal spray now approved by FDA to treat intermittent, stereotypic episodes of frequent seizure activity in people living with epilepsy in the U.S.,” UCB Press Release, https://www.biospace.com/article/releases/ucb-announces-nayzilam-midazolam-nasal-spray-now-approved-by-fda-to-treat-intermittent-stereotypic-episodes-of-frequent-seizure-activity-

	<u>in-people-living-with-epilepsy-in-the-u-s-/</u> (2019) (Accessed October 31, 2019)
2019	J. French and T. Pedley, “Initial Management of Epilepsy,” New England Journal of Medicine 359:166-176 (2008)
2020	G. Corbo et al. “Measurement of Nasal Mucociliary Clearance,” Archives of Disease in Childhood 64:546-550 (1989)
2021	“How does the nose work? The nasal mucosa,” <u>https://www.fitonasal2act.com/how-does-the-nose-work/the-nasal-mucosa/</u> (Accessed November 5, 2019)
2022	N. Mygind, “Nasal Allergy,” 9 (Blackwell Scientific Publications, 1979)
2023	“Neurelis Files New Drug Application With The FDA For VALTOCO™ (Diazepam Nasal Spray), An Investigational Treatment For Pediatric, Adolescent And Adult Epilepsy Patients,” <u>https://www.neurelis.com/neurelis-news/neurelis-files-new-drug-application-fda-valtocotm-nasal-spray-investigational-treatment-pediatric</u> (2018) (Accessed November 1, 2019)
2024	“Neurelis Receives FDA Orphan Drug Designation for NRL-1 in the Treatment of Acute Repetitive Seizures,” <u>https://www.neurelis.com/neurelis-news/fda-orphan-drug-designation</u> (2015) (Accessed November 1, 2019)

APPENDIX C

CURRICULUM VITAE



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School of Health Sciences

University of Iceland

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Web-page: <http://www.uni.hi.is/sveinbj>

Education

1990	Ph.D. in Pharmacy	University of Copenhagen
1986	MS Pharmacy	University of Copenhagen

Special authorization

2000	Qualified Person	Icelandic Medicine Agency
1994	Expert in Biopharmaceutics	Ministry of Health, Iceland
1991	Laboratory Animal Sciences	ScanLAS
1990	Biohazards	Natl. Inst. Health. Japan
1988	Radiopharmaceuticals	August Krogh Institute
1986	Chemical Warfare – analysis & emergency	Ministry of defense, Denmark

Employment

1991-:	Assistant (1991), Associated (1993) and Full Time Professor (1996) at the Faculty of Pharmaceutical Sciences, University of Iceland
1991-2005:	CEO of Lyfjapróun biopharmaceuticals.
1990-1991:	PostDoc at National Institute of Health, Tokyo, Japan
1986-1990:	Project manager at Novo Nordisk A/S, Denmark

Awards

2007	Innovation Award. University of Iceland
2004	Innovation Award. Trade Council of Iceland
1996	Young Investigator Research Achievement Award. National Research Council.

Opponent

Iceland:	University of Iceland: 2017, 2014, 2013 and 2010;
Denmark:	University of Copenhagen: 2005;
Sweden:	Uppsala University: 2004 (Jan) and 2004 (Dec).

Accreditation service

Iceland:	Prepare Faculty of Pharmaceutical Sciences, University of Iceland for their Accreditation: 2010, 2015, 2019
Denmark:	Auditing Syd-Dansk University, Faculty of Pharmaceutical Sciences: 2010

Start-ups

1. Lyfjapróun hf (accredited by EU) – founded in 1991 and was acquired by Actavis in 2007
2. LipoMedica ehf – founded in 1998 and merged with BioGels in 2005
3. Hananja ehf. (accredited by EU (FP-7)) – founded in 2001
4. Mentis Cura ehf – founded in 2004
5. Nepson ehf – founded in 2005
6. Capretto ehf – founded in 2015
7. Calor ehf – founded in 2016
8. Eclampsin ehf – founded in 2019

Developed products

1. Nayzilam (Intranasal midazolam): A rescue drug for cluster seizures. FDA has accepted the IND Application in August 2018. The product will be marketed by UCB
2. Monolipids for antimicrobial therapy (Medical Device), developed by Capretto ehf – Expected to reach market in 2019.

Charity

1. Responsible pharmacist at Hlaðgerðarkot - a Christian alcohol and drug addiction rehabilitation center.
2. Working on establishing a not-for-profit organization in Malawi, focusing on manufacturing drugs to treat children under 5 years of age.

Supervision of M.Sc. and PhD students

BSc Students (Biology) from Iceland: 2
BSc Students (Veterinary Medicine) from Denmark: 1
MSc Students (Pharmacists) from Denmark: 10
MSc Students (Engineering) from Denmark: 1
MSc Students (Pharmacists) from Spain (Barcelona): 6
MSc Students (Pharmacists) from Poland (Jagiellonian): 2
MSc Students (Pharmacists) from France (Lyon): 1
MSc Students (Pharmacists) from Germany: 2
MSc Students (Pharmacists) from Iceland: 71
MSc Students (Pharmaceutical Sciences) from Iceland: 2
MSc Students (Biology) from Iceland: 1
MSc Students (Medicine) from Iceland: 5
PhD Students (Pharmaceutical Sciences) from Denmark: 1
PhD Students (Pharmaceutical Sciences) from Iceland: 2
PhD Students (Pharmaceutical Sciences) from Iceland (supervisory committee): 3
PhD Students (Pharmaceutical Sciences) currently working on their thesis: 4

PATENTS

Filed by Dr. Sveinbjörn Gizurarson

AFRICA – AIPO

1. OA-10564: Gizurarson S, Heron I. Pharmaceutical preparation for topical administration of antigens and/or vaccines to mammals via a mucosal membrane (Priority date: February 15 1993)

AUSTRALIA

2. AU-7880991: Bechgaard E, Gizurarson S, Hjortkjær RK. Pharmaceutical preparation containing n-glycofurols and n-ethylene glycols. (Priority date: May 10, 1990)
3. AU-7643591: Bechgaard E, Gizurarson S, Hjortkjær RK. A pharmaceutical preparation. (Priority date: May 10, 1990)
4. AU-1358695: Bechgaard E, Gizurarson S, Hjortkjær RK. Nasal administration. (Priority date: May 10, 1990).
5. AU-668290: Gizurarson S, Heron I. Pharmaceutical preparation for topical administration of antigens and/or vaccines to mammals via a mucosal membrane (Priority date: February 15 1993)
6. AU-8102298: Gizurarson S. Method for administration of active substances to the olfactory region (Priority date: July 1, 1997)
7. AU-8459898: Gizurarson S, Guðmundsdóttir V. Antigen delivery system comprising monoglyceride or diglyceride derivatives as adjuvant (Priority date: July 9, 1997).
8. AU-7816400: Skúlason S, Holbrook WP, Kristmundsdóttir Þ, Gizurarson S. Pharmaceutical composition for treatment of mucosal epithelial ulceration and/or erosion (Priority date: October 22, 1999)
9. AU-2002333194: Gizurarson S, Hau J. A method of producing antibodies ex-vivo. (Priority date: August 16, 2001)
10. AU2003215884: Gizurarson S. A bioadhesive agent (Priority date: February 25th 2002)
11. AU-2003215885: Gizurarson S, Ólafsdóttir S, Kristinsson JL, Hrafnkelsdóttir K, Ólafsson DR, Ingólfsson O, Ingimundardóttir ER. Absorption promoting agent. (Priority date: February 25, 2002)
12. AU-2003205979: Gizurarson S, Ólafsdóttir S. An immunological adjuvant. (Priority date: February 25, 2002)
13. AU-2008206105: Gizurarson S. Methods and compositions for the delivery of a therapeutic agent (Priority date: January 19 2007)
14. AU-2013203271: Gizurarson S. Methods and compositions for the delivery of a therapeutic agent. (Priority date: January 18, 2008)
15. AU-2016210731: Gizurarson S. Methods and compositions for the delivery of a therapeutic agent (Priority date: April 9, 2013)
16. AU-2018202245: Gizurarson S. Methods and compositions for the delivery of a therapeutic agent (Priority date: April 9, 2013)
17. AU-2017283276: Gizurarson S, Helgadóttir H, Kristmundsdóttir Þ. Thermostable formulation of biologically active substances (Priority date: June 20 2016)

AUSTRIA

18. AT-164080: Bechgaard E, Gizurarson S, Hjortkjær RK. Pharmaceutical preparation containing n-glycofurols and n-ethylene glycols. (Priority date: May 10, 1990)
19. AT-126711: Bechgaard E, Christoffersen PB, Hjortkjær RK, Gizurarson, S. Nasal dispenser actuated by nose contact (Priority date: May 31, 1991).
20. AT-195077: Gizurarson S, Heron I. Pharmaceutical preparation for topical administration of antigens and/or vaccines to mammals via a mucosal membrane (Priority date: February 15 1993)
21. AT-307676: Gizurarson S. Method for administration of active substances to the olfactory region (Priority date: July 1, 1997)
22. AT-329617: Gizurarson S, Guðmundsdóttir V. Antigen delivery system comprising monoglyceride or diglyceride derivatives as adjuvant (Priority date: July 9. 1997).
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BRAZIL

24. BR-9810568: Gizurarson S, Guðmundsdóttir V. Antigen delivery system comprising monoglyceride or diglyceride derivatives as adjuvant (Priority date: July 9. 1997).
25. BR-0307913: Gizurarson S, Ólafsdóttir S, Kristinsson JL, Hrafnkelsdóttir K, Ólafsson DR, Ingólfsson O, Ingimundardóttir ER. Absorption promoting agent. (Priority date: February 25. 2002)

CANADA

26. CA-2082495: Bechgaard E, Gizurarson S, Hjortkjær RK. Pharmaceutical preparation containing n-glycofurols and n-ethylene glycols. (Priority date: May 10, 1990)
27. CA-2156084: Gizurarson S, Heron I. Pharmaceutical preparation for topical administration of antigens and/or vaccines to mammals via a mucosal membrane (Priority date: February 15 1993)
28. CA-2298596: Gizurarson S. Method for administration of active substances to the olfactory region (Priority date: July 1, 1997)
29. CA-2295237: Gizurarson S, Guðmundsdóttir V. Antigen delivery system comprising monoglyceride or diglyceride derivatives as adjuvant (Priority date: July 9. 1997).
30. CA-2386422: Skúlason S, Holbrook WP, Kristmundsdóttir Þ, Gizurarson S. Pharmaceutical composition for treatment of mucosal epithelial ulceration and/or erosion (Priority date: October 22, 1999)
31. CA-2457595: Gizurarson S, Hau J. A method of producing antibodies ex-vivo. (Priority date: August 16, 2001)
32. CA-2477321: Gizurarson S, Ólafsdóttir S, Kristinsson JL, Hrafnkelsdóttir K, Ólafsson DR, Ingólfsson O, Ingimundardóttir ER. Absorption promoting agent. (Priority date: February 25. 2002)
33. CA-2476958: Gizurarson S, Ólafsdóttir S. An immunological adjuvant. (Priority date: February 25. 2002)
34. CA-2676010: Gizurarson S. Methods and compositions for the delivery of a therapeutic agent (Priority date: January 19 2007)

35. CA-3028927: Gizurarson S, Helgadóttir H, Kristmundsdóttir Þ. Thermostable formulation of biologically active substances (Priority date: June 20 2016)

CHINA

36. CN-1056812: Bechgaard E, Gizurarson S, Hjortkjær RK. Pharmaceutical preparation containing n-glycofurols and n-ethylene glycols. (Priority date: May 10, 1990)
37. CN-1262626: Gizurarson S, Guðmundsdóttir V. Antigen delivery system comprising monoglyceride or diglyceride derivatives as adjuvant (Priority date: July 9. 1997).
38. CN-1642576: Gizurarson S, Ólafsdóttir S, Kristinsson JL, Hrafnkelsdóttir K, Ólafsson DR, Ingólfsson O, Ingimundardóttir ER. Absorption promoting agent. (Priority date: February 25. 2002)
39. CN-101678112: Gizurarson S. Methods and compositions for the delivery of a therapeutic agent (Priority date: January 19 2007)
40. CN-106389330: Gizurarson S. Methods and compositions for the delivery of a therapeutic agent (Priority date: January 19 2007)
41. CN-106420614: Gizurarson S. Methods and compositions for the delivery of a therapeutic agent (Priority date: January 19 2007)

CZECHOSLOVAKIA

42. CS-136191: Bechgaard E, Gizurarson S, Hjortkjær RK. Pharmaceutical (Priority date: May 10, 1990)

DENMARK

43. DK-0532546: Bechgaard E, Gizurarson S, Hjortkjær RK. Pharmaceutical preparation containing n-glycofurols and n-ethylene glycols. (Priority date: May 10, 1990)
44. DK-19910001031 19910531: EP-0587668: Bechgaard E, Christoffersen PB, Hjortkjær RK, Gizurarson, S. Nasal dispenser actuated by nose contact (Priority date: May 31, 1991).
45. DK-0682528: Gizurarson S, Heron I. Pharmaceutical preparation for topical administration of antigens and/or vaccines to mammals via a mucosal membrane (Priority date: February 15 1993)
46. DK-0991479: Gizurarson S. Method for administration of active substances to the olfactory region (Priority date: July 1, 1997)
47. DK-2121025: Gizurarson S. Methods and compositions for the delivery of a therapeutic agent (Priority date: January 19 2007)
48. DK-2651430: Gizurarson S, Meiri H. Biological activity of placental protein 13 (Priority date: December 14 2010)

EUROPE

49. EU-0532546: Bechgaard E, Gizurarson S, Hjortkjær RK. Pharmaceutical preparation containing n-glycofurols and n-ethylene glycols. (Priority date: May 10, 1990)
50. EP-0587668: Bechgaard E, Christoffersen PB, Hjortkjær RK, Gizurarson, S. Nasal dispenser actuated by nose contact (Priority date: May 31, 1991).

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54. EP-1267826: Skúlason S, Holbrook WP, Kristmundsdóttir Þ, Gizurarson S. Pharmaceutical composition for treatment of mucosal epithelial ulceration and/or erosion (Priority date: October 22, 1999)
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60. EP-3150230: Gizurarson S. Methods and compositions for the delivery of a therapeutic agent (Priority date: January 19 2007)
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GERMANY

62. DE-69129110: Bechgaard E, Gizurarson S, Hjortkjær RK. Pharmaceutical preparation containing n-glycofurols and n-ethylene glycols. (Priority date: May 10, 1990)
63. DE-69425427: Gizurarson S, Heron I. Pharmaceutical preparation for topical administration of antigens and/or vaccines to mammals via a mucosal membrane (Priority date: February 15 1993)
64. DE-69832070: Gizurarson S. Method for administration of active substances to the olfactory region (Priority date: July 1, 1997)
65. DE-69834921: Gizurarson S, Guðmundsdóttir V. Antigen delivery system comprising monoglyceride or diglyceride derivatives as adjuvant (Priority date: July 9. 1997).

GREECE

66. GR-3034727: Gizurarson S, Heron I. Pharmaceutical preparation for topical administration of antigens and/or vaccines to mammals via a mucosal membrane (Priority date: February 15 1993)

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ICELAND

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70. IS-5329: Gizurarson S, Guðmundsdóttir V. Antigen delivery system comprising monoglyceride or diglyceride derivatives as adjuvant (Priority date: July 9. 1997).
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73. IS-7421: Gizurarson S, Ólafsdóttir S, Kristinsson JL, Hrafnkelsdóttir K, Ólafsson DR, Ingólfsson O, Ingimundardóttir ER. Absorption promoting agent. (Priority date: February 25. 2002)
74. IS-7422: Gizurarson S. A bioadhesive agent. (Priority date: February 25. 2002)
75. IS-6282: Gizurarson S, Ólafsdóttir S. An immunological adjuvant. (Priority date: February 25. 2002)
76. IS-8593: Gizurarson S. Methods and compositions for the delivery of a therapeutic agent (Priority date: January 19 2007)
77. IS-8940: Gizurarson S, Meiri H. Biological activity of placental protein 13 (Priority date: December 14 2010)
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ISRAEL

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87. JP-2003512310: Skúlason S, Holbrook WP, Kristmundsdóttir Þ, Gizurarson S. Pharmaceutical composition for treatment of mucosal epithelial ulceration and/or erosion (Priority date: October 22, 1999)
88. JP-2005509598: Gizurarson S, Hau J. A method of producing antibodies ex-vivo. (Priority date: August 16, 2001)
89. JP-2005519075: Gizurarson S. A bioadhesive agent. (Priority date: February 25. 2002)
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- 104. ES-2117642: Bechgaard E, Gizurarson S, Hjortkjær RK. Pharmaceutical preparation containing n-glycofurols and n-ethylene glycols. (Priority date: May 10, 1990)
- 105. ES-2150982: Gizurarson S, Heron I. Pharmaceutical preparation for topical administration of antigens and/or vaccines to mammals via a mucosal membrane (Priority date: February 15 1993)
- 106. ES-2255165: Gizurarson S. Method for administration of active substances to the olfactory region (Priority date: July 1, 1997)
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Dr. Sveinbjörn Gizurarson, professor

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