UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AQUESTIVE THERAPEUTICS, INC.,
Petitioner,

v.

NEURELIS, INC.,
Patent Owner.

Case IPR2019-00451
Patent 9,763,876

PATENT OWNER RESPONSE
37 C.F.R. §42.120

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I. PRECISE REQUESTED RELIEF

Treatment of epilepsy and epileptic seizures through the intranasal route of administration has been a long-sought alternative to intravenous and rectal medications in the market. Conventional medications are not only harder to administer during a seizure but are also not appropriate in most environments (requiring professional administration or a private setting). Despite this long-felt, unmet need for an effective intranasal treatment – particularly intranasal benzodiazepine treatment – no one prior to the patent owner (Neurelis) was able to develop an effective intranasal diazepam formulation – the invention claimed in the involved 9,763,876 patent ('876 patent).[1] The petitioner (Aquestive) attempts to prove obviousness of this claimed formulation, but fails for various reasons, most importantly because the references are not actually prior art to the '876 patent. Indeed, Aquestive relies on the ***wrong*** priority date as the entire basis for its obviousness analysis – depending solely on a lack of written description theory that even Aquestive's expert, Dr. Peppas, could not substantiate during his

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[1] Indeed, the U.S. Food & Drug Administration granted Patent Owner Orphan Drug status and Fast Track Review for its formulation for this very reason, as further detailed *infra*.

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deposition. Neurelis preserves its arguments that the petition never made out a prima facie case and that the various theories of institution rest on misapprehension of controlling law and improper burden shifts.

Yet, even if the Board considers the merits of Aquestive's prior-art references – which the Board should not – Aquestive fails to establish a motivation to combine the references and a reasonable expectation of success in doing so. Instead, Aquestive shows a misunderstanding of its cited references and, importantly, an oversimplification of the art at issue (which Dr. Peppas ultimately demonstrates). Additionally, a review of the long-felt yet unmet need for a diazepam intranasal formulation (considering also the failure of others in developing such a formulation) further supports a finding of non-obviousness.

Accordingly, Neurelis requests termination of this review or at least a final written decision denying the IPR2019-00451 petition and holding that Aquestive has failed to prove that any challenged claim is unpatentable.

II. STATEMENT OF REASONS TO DENY THE PETITION

A. BACKGROUND

1. Epilepsy and epilepsy treatment

Epilepsy is a general term for conditions with recurring seizures, involving abnormal electrical activity in the brain that causes an involuntary change in body movement or function, sensation, awareness, and/or behavior. A seizure may last

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from a few seconds to a few minutes. While epilepsy is known as a brain disorder, its cause is still unknown and may have many etiologies, including developmental disorders, brain injury, illness and infection. EX2012, ¶44; EX2019, 166.

Epilepsy actively affects over 3.4 million people in the United States (about 1.2% of the total population) and ranks as the second most burdensome neurological disorder worldwide in terms of disability-adjusted life years, with associated stigma, psychiatric co-morbidity and high economic costs. EX2004, 3; EX2001; EX2005, 296. Nearly half a million children in the United States alone have active epilepsy. EX2001. Medications exist to help prevent seizures, but success varies and about one-third of epileptics receiving care still experience seizures. EX2004, 3.

Moreover, there are no quick, simple and effective treatments available to control and treat epileptic seizures once they occur. Immediate cessation is essential to treating epileptic seizures as they significantly increase morbidity and mortality rates – with an increased likelihood for progression into an epileptic state when a seizure lasts longer than 5 minutes. EX2012, ¶45. Benzodiazepines proved to be a promising treatment – with past studies highlighting the benefits of administering benzodiazepines (*e.g.*, diazepam) for treatment of epileptic seizures, especially in the young and elderly. *Id.*, ¶45. By 2008, benzodiazepine formulations were developed for intravenous administration (Valium®) and rectal

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administration (Diastat®).[2] *See* EX1042; EX2012, ¶46. However, their use was still limited to specific situations, and not conducive to administration in a public setting. EX2012, ¶¶51-52.

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[2] Throughout his declaration, Dr. Peppas refers to formulations directed to other routes of administration – *e.g.*, intravenous formulations and rectal formulations such as Valium® and Diastat® – as being informative of what a POSA would know regarding intranasal formulation. *See* EX1041, ¶133; *see also* ¶136 (comparing topical preparations to transmucosal preparations). This fails to appreciate the unique characteristics of each given therapeutic agent and intricacies of each administration route. *See* EX2012, ¶¶28-32, Section VII.D. Dr. Peppas ultimately agrees. When asked whether Diastat® could be reformulated for nasal administration, Dr. Peppas acknowledged that he would need more information (*e.g.*, other ingredients, form, delivery method, bioavailability, etc.) and would need to conduct additional studies, including human studies. EX2011, 118:18-120:19; *see also* EX2012, ¶52 (re-formulating Diastat® to intranasal administration would not have been clinically possible and would not have worked).

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2. *Benzodiazepine for intranasal administration*

With these concerns in mind, nasal sprays became a promising method of administering benzodiazepines. EX2012, ¶¶53-54; EX2008. However, the known solubility challenges of benzodiazepines thwarted efforts to treat epilepsy with intranasal benzodiazepines. EX2012, ¶54; *see also*, ¶¶47-50. Specifically, before 2008, benzodiazepines were known to pose challenges in administering a high enough clinical dose to act as a rescue agent during a seizure because of their low solubility. *Id.*, ¶47; EX2013. For example, benzodiazepine's low solubility created a challenge for administering a high enough dose (clinical dose) to act as a rescue agent during a seizure. EX2012, ¶47. An additional challenge was dealing with variances in clinical dose threshold for a given benzodiazepine used – with diazepam, specifically, requiring a high clinical dose for treatment. *Id.*, ¶48. Thus, a POSA would need to consider the ratio between the threshold clinical dose needed for treatment and the solubility of the benzodiazepine drug. But 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, it was also critical because of the risk of precipitates forming. *Id.* Precipitates could not only further irritate the nasal cavity, but also reduce uptake of a therapeutic agent through the nasal mucosa and cellular wall. *Id.* The known tendency to precipitate with lower solubility benzodiazepines meant that the clinical dose could not

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overlap or be close to the saturation dose of the agent. *Id.*, ¶¶64-65; EX2007, 293. Dr. Peppas does not address any of these concerns in his declaration and instead oversimplifies a POSAs ability, as of 2008-2009, to develop benzodiazepine formulations. While Dr. Peppas makes blanket assertions that "there simply is no criticality to (or unexpected results stemming from) the specific types or amounts of . . . benzodiazepines" (EX1041, ¶51) and that "benzodiazepines . . . have been known for decades, and their effects on the human body are generally predictable" (*id.*, ¶63), he admitted in deposition testimony that he has ***zero experience*** working with benzodiazepines (directly or indirectly). *See* EX2011, 13:3-18, 22:16-21, 24:10-15, 25:2-21, 26:19-22, 34:21-35:8; 44:5-8, 47:19-24.

As Neurelis' expert Dr. Gizurarson explains, developing benzodiazepine formulations has proven ***not*** to be a straightforward task. EX2012, ¶48. Despite its therapeutic promise in stopping and preventing seizures in patients, benzodiazepine use was not widespread in 2008 because of its known challenges. *Id.*, ¶51. Even today, the only FDA approved intranasal benzodiazepine formulation is NAYZILAM® (an aqueous midazolam formulation[3]), which was

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[3] Midazolam has a higher solubility index than diazepam. EX2012, ¶¶66-67. As Dr. Gizurarson, who developed NAYZILAM®, opines, a POSA would have been

approved this year. EX2012, ¶67; *see also* EX2011, 49:9-13 (admitting he could not identify any FDA-approved intranasal benzodiazepine formulations).

Additional technical challenges and obstacles to developing intranasal formulations existed and were known to POSAs prior to 2008. EX2012, ¶55. These included at least: (1) limited delivery volume because of the small volume of the nasal cavity – requiring an effective dose 5-10 times more concentrated than with intravenous administration (EX2012, ¶56); (2) mucosal and ciliary clearance mechanisms – limiting residence time of a solution placed in the nasal cavity (*id.*, ¶¶57-59); and (3) nasal cell anatomy – known to physically block foreign agents from entering through the cell wall (*id.*, ¶60).

Thus, by 2008, POSAs knew obtaining true intranasal absorption to be difficult, and in the case of some therapeutic agents insurmountable. Benzodiazepines were such known therapeutic agents due to their poor water solubility characteristics, as shown in at least one study (Lau, EX2009) conducted on diazepam (0.05mg/ml) and lorazepam (0.08mg/ml) in 1989. EX2012, ¶61. Lau's studies on intranasal administration of diazepam and lorazepam showed

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discouraged from pursuing a lower solubility index benzodiazepine for development since this would have been a potential set-up for failure. *Id.*, ¶66.

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(1) time to peak concentration was significantly delayed as compared to intravenous administration (EX2012, ¶62); and (2) bioavailability was also significantly less than with intravenous administration (*id.*, ¶63). Lau ultimately concluded that "[i]t would appear that this [intranasal] route of administration may be of limited utility for benzodiazepines in the treatment of status epilepticus where rapid onset of effect is essential." EX2009, 173; EX2012, ¶63. Other researchers had similar difficulties in administering benzodiazepines. *See* EX2012, ¶¶63-67.

3. The challenged patents and claims[4]

The application for the '876 patent, titled "Administration of Benzodiazepine Compositions", was filed on October 29, 2014. EX1001. The

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[4] While Dr. Peppas provides his rendition of the prosecution history of the '876 patent (EX1041, ¶¶29-37), his alleged "expert opinions" regarding statements and decisions made by the applicant during prosecution should not be considered as they are improper legal opinions. *See* 37 C.F.R. §42.65(a). Indeed, Dr. Peppas admitted that he was not an expert on this subject matter during deposition testimony. *See* EX2011, 70:13-89:6 ("I agree with you I did express on a matter that I was not an expert on.").

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abstract 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.*, Abstract. The inventors realized that while nasal delivery would address the drug-administration problem, known solubility problems could be especially difficult using a nasal administration route. The inventors thus developed the use of vitamin E-analogs and alcohols as substantial fractions of the formulation to address the solubility problem, while still providing an acceptable nasal-delivery formulation. The alkyl glycoside functions as a penetration enhancer to improve bioavailability. EX1001, 16:55-56, 34:45-48.

Challenged claim 1, from which all the other challenged claims depend, defines the invention as (EX1001, 63:26-34):

> 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

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about 70% (w/w); and

an alkyl glycoside.

The challenged ’876 patent issued in 2017 but claims benefit back to 2008. EX1001, cover.

4. The ’876 patent’s chain of priority

The ’876 patent claims priority to U.S. Provisional Patent Application No. 61/040,558 (’558 Provisional) (EX1008), filed on March 28, 2008. The ’558 Provisional discloses alkyl glycosides as part of the formulation claimed. Specifically, the ’558 Provisional provides:

> In some embodiments, the drug delivery system of the invention may advantageously comprise an absorption enhancer . . . . In some embodiments, enhancing agents that are appropriate include . . . acyl glycerols, fatty acids and salts, tyloxapol and ***biological detergents listed in the SIGMA Catalog, 1988, page 316-321 (which is incorporated herein by reference)***.

EX1008, [150]-[152] (emphasis added). The excerpt from the 1988 SIGMA Catalog lists biological detergents and includes alkyl glycosides such as

n-dodecyl β-D-maltoside,

n-dodecyl-β- D-glucopyranoside,

n-heptyl- β-D-glucopyranoside,

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n-hexyl- β-D- glucopyranoside,

n-nonyl- β-D-glucopyranoside,

n-octyl- β-D-glucopyranoside,

n-octyl- β-D-thioglucopyranoside,

among others. EX2006, 319-320. Notably, of the 10 non-ionic biological detergents[5] listed on page 316 of the catalog, 9 of them are alkyl glycosides. EX2012, ¶71. Additional alkyl glycosides are listed within pages 319-321 of the excerpt – showing, overall, a prominent representation within the 1988 SIGMA catalog pages incorporated by reference into the '558 Provisional. *Id.* As Dr. Gizurarson states – and as Aquestive's expert (Dr. Peppas) confirms – alkyl glycosides were known to fall in the category of "biological detergents", as listed in the 1988 SIGMA catalog. EX2012, ¶¶69-75; EX2011, 107:10-13. Thus, Dr. Peppas ultimately agreed that the 1988 SIGMA catalog teaches alkyl glycosides.

Applicants to the Patent Office routinely employ the long-established and

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[5] A POSA would have understood that in the context of pharmaceutical formulations, biological detergents would have been limited to detergents appropriate for administering to the nasal cavity of a human or other animal subject – which, in such a case, would have been non-ionic detergents. EX2012, ¶70.

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recognized method of incorporation by reference to avoid repeating information contained in a publicly available document, such as the SIGMA catalog. *See* MPEP §§608.01(p)(1)(B), 2163.07(b) (9th ed., rev. R-08.2017, Jan. 2018). The inclusion of the SIGMA catalog disclosure of non-ionic detergents, preponderantly including numerous alkyl glycosides, thus would have reasonably conveyed to a POSA that the inventor possessed at the time of filing the claimed alkyl glycosides as part of the invention. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1564-67 (Fed. Cir. 1991) (reversing judgment of no support under 35 U.S.C. §120) (citing *In re Heinle*, 342 F.2d 1001, 1007 (C.C.P.A. Apr. 8, 1965) (reversing rejection, explaining that incorporating drawing dimensions into specification would not constitute new matter and therefore properly support the claims). Indeed, Dr. Peppas testified an incorporation by reference is an admission of fact by the applicant. *See* EX1041, ¶¶148-150; *see also* EX2011, 117:9-19.

Accordingly, the '876 patent properly claims priority to the '558 Provisional, including its inherent disclosure of alkyl glycosides.

B. CLAIM CONSTRUCTION

1. "consisting of"

The '876 patent has one independent claim – claim 1 – which discloses "a pharmaceutical solution for nasal administration ***consisting of***" a list of elements. EX1001, 63:25-34 (emphasis added). The transitional phrase "consisting of" is a

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close-ended exclusive term that limits the claimed invention to contain "only what is expressly set forth in the claim." *Multilayer Stretch Cling Film Holdings, Inc. v. Berry Plastics Corp.*, 831 F.3d 1350, 1358 (Fed. Cir. 2016) (citation omitted). The prosecution history of the parent application, U.S. Patent Application No. 13/495,942 ('942 Application), suggests the same: in amending independent Claim 1 in response to an Office action, Neurelis argued that the "transitional phrase 'consisting of' excludes any element, step, or ingredient not specified in the claim. Thus, the pending claims exclude such additional ingredients as water, poloxamer and benzalkonium chloride, which Sonne teaches." EX1004, 2148-2149 (citing MPEP § 2111.03.). Accordingly, the "consisting of" language should be construed to limit the pharmaceutical solution to "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" to the exclusion of any other excipients. *See also* EX2012, ¶41.

2. "in a combined amount"

Independent claim 1 additionally discloses "ethanol and benzyl alcohol ***in a combined amount*** from about 10% to about 70% (w/w)." EX1001, 63:25-34 (emphasis added). The use of the conjunctive "and" with "in a combined amount" requires that each of ethanol and benzyl alcohol be present in an amount >0%

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(w/w). *Medgraph, Inc. v. Medtronic, Inc.*, 843 F.3d 942, 949 (Fed. Cir. 2016) (giving "and" its plain meaning requiring both conditions when not mutually exclusive). The prosecution history supports this construction. For example, during prosecution of the parent '942 Application, Neurelis amended independent claim 1 from requiring "one or more alcohols or glycols, or any combination thereof, in an amount from about 10% to about 70% (w/w)" to "ethanol and benzyl alcohol in a combined amount from about 10% to about 70% (w/w)" (EX1004, 2139) and argued that "[n]owhere does Sonne or Meezan teach solutions consisting of benzodiazepine, 30-90% tocopherol or tocotrienol, an alkyl glycoside and <u>both</u> ethanol and benzyl alcohol in a combined concentration of 10-70% (w/w)" (EX1004, 2148-49 (emphasis in original)). Thus, construing "in a combined amount" to include 0% (w/w) of either ethanol or benzyl alcohol would render the "combined" term meaningless.[6] *See Gemstar-TV Guide Int'l, Inc. v. Int'l Trade*

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[6] Strangely, and without opining that "in a combined amount" means anything other than adding two or more ingredients, Dr. Peppas states that a disclosure in Gwozdz of 10% ethanol and 0% benzyl alcohol meets the claim limitation of a combined total of 10-30%. *E.g.*, EX1041, ¶397. Dr. Peppas' interpretation of this claim term is unsupported by the claim language or the law.

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Comm'n, 383 F.3d 1352, 1375 (Fed. Cir. 2004) ("The ordinary meaning of 'combining,' which is a present participle of 'combine,' is 'to cause (as ***two or more*** things or ideas) to mix together: MINGLE: BLEND.") (emphasis added) (quoting *Webster's Third New Int'l Dictionary* 452 (1993)). Additionally, the specification ***only*** discloses examples of benzyl alcohol and ethanol in amounts >0%. EX1001, *passim*. Accordingly, "in a combined amount" should be construed to mean "in a combined amount from about 10% to about 70% (w/w), where each of ethanol and benzyl alcohol is present in an amount >0%". *See also* EX2012, ¶42.

C. THE LEVEL OF ORDINARY SKILL IN THE ART

Neurelis disputes certain aspects of Aquestive's description of the level of ordinary skill in the art. First, Aquestive and its expert – Dr. Peppas – describe the POSA as one having at least a bachelor's degree in chemical, biological, or pharmaceutical sciences or a medial degree and "several years of experience in the field of transmucosal . . . pharmaceutical formulation development." EX1041, ¶74. As Neurelis' expert Dr. Gizurarson explains and as further detailed below, the formulation of a benzodiazepine for intranasal administration is a difficult and complex science requiring a higher skill set and knowledge than a POSA with a bachelor's degree "with several years of experience." EX2012, ¶¶28-29. Specifically, the POSA would be working against physiological constraints of

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active ingredient uptake due to the nasal anatomy, as well as the very low solubility of benzodiazepines in formulating the pharmaceutical composition disclosed in the '876 patent. *Id.*

Accordingly, a POSA would at least have held a Master's degree with many years of experience, or a Ph.D. or Pharm.D degree with several years of experience, or its equivalent research experience. *Id.*, ¶29.

Second, Aquestive and Dr. Peppas describe the POSA as 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." EX1041, ¶74. Chemists are primarily concerned with chemical structures and synthesizing new chemical compounds and Dr. Peppas does not explain what role a medicinal chemist would play in the research and development of benzodiazepine pharmaceutical formulations for intranasal administration – especially where, as here, the chemical structures were all known. EX2012, ¶30.

Accordingly, a POSA would have had knowledge of benzodiazepine structure and function, including solubility issues with benzodiazepines in general. *Id.*, ¶31. The POSA would further 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. *Id.* Notably, Aquestive and Dr. Peppas' description of a POSA having experience in "rectal, vaginal, ocular, lacrimal, nasolacrimal, buccal, sublingual, urethral, inhalation, and auricular" delivery as "related fields" does not take into consideration the differences in formulating an intranasal product and complexities of the intranasal pathway. *Id.*, ¶32; *see also* EX2011, 118:18-120:19.

D. AQUESTIVE'S UNPATENTABILITY ANALYSIS AND THE INSTITUTION DECISION HINGE ON INCORRECT THEORIES OF PATENT PRIORITY

Aquestive's entire theory of unpatentability rests on an alleged lack of written description in the '558 Provisional. Compare Pet. 6 (arguing prior art Gwozdz (EX1011) entitled to 28 March 2008 priority) and 18-20 (arguing challenged patent not entitled to its 28 March 2008 priority). Specifically, Aquestive and Dr. Peppas represent that the '876 patent cannot claim priority to the '558 Provisional because the '876 patent requires the presence of an alkyl glycoside and "the presence of any alkyl glycoside (either generally or particularly) – regardless of amount – was not disclosed, described, or enabled by '558 Provisional." Pet. 20; *see also* EX1041, ¶¶64-70. Aquestive needs this theory to be true because its primary reference, Gwozdz (EX1011), has the same filing date as the '876 patent and, thus, would not otherwise qualify as prior art. Yet, as detailed below, Aquestive facially failed to consider the entire disclosure of the provisional application, ***including the most relevant disclosure for what Aquestive alleged***

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was missing from the description. Pet., *passim*. For a separate reason not raised by Aquestive, the Board concluded that the '876 patent was not entitled to the '558 Provisional priority date based on a flawed understanding of prosecution formality. Neither theory of priority is supported in law or in fact.

1. *Aquestive Never Met its Burden to Establish a Facially Reasonable Likelihood of Unpatentability*

Under 35 U.S.C. §314(a), the Director may not institute an IPR unless:

> the information presented in the petition filed under section 311 and any response filed under section 313 shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition.

Aquestive's attempt to establish this likelihood pivotally depended on showing that Neurelis was not entitled to its earliest priority date. Pet. 6. To do so, Aquestive argued that Neurelis was not entitled priority to the '558 Provisional (EX1008). *Id.* at 18-20. Specifically, Aquestive maintains that the '876 patent claim limitation for "alkyl glycosides" was not met until the filing of U.S. Application No. 12/413,439 ('439 Application) (EX1007) on March 27, 2009. *Id.* Yet the petition makes no attempt to account for the '558 Provisional's discussion of enhancers, including the express statement "enhancing agents that are appropriate include…***biological detergents listed in the SIGMA Catalog, 1988, page[s] 316-321 (which is incorporated herein by reference)***." EX1008, ¶152 (emphasis added).

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As Dr. Gizurarson explains, a POSA would have recognized and understood that alkyl glycosides were disclosed and supported in the '558 Provisional through this incorporation by reference. *See* EX2012, ¶68. As detailed, *supra* (Section II.A.4), the 1988 SIGMA catalog included a limited number of biological detergents, one category of which were non-ionic detergents. Of the non-ionic detergents listed throughout pages 316-321, alkyl glycosides were prominently represented.[7] EX2012, ¶¶71-72. Notably, Aquestive agrees that the claimed alkyl glycosides were known as enhancers. *E.g.*, Pet. 69. Aquestive's expert further testified that a "large number" of alkyl glycosides can be classified as a biological detergent. EX2011, 107:10-13. Thus, Aquestive and Dr. Peppas statements support Dr. Gizurarson's opinion (EX2012, ¶¶34, 114) that the 1988 SIGMA catalog discloses alkyl glycosides, as claimed in the '876 patent.

Yet, Aquestive provided no legal or technical rationale for failing to address this disclosure. Pet., *passim.* Because a lack of written description argument seeks to prove a negative, it must account for the ***entire*** disclosure before asserting that

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[7] Dr. Peppas agreed that the 1988 SIGMA catalog includes alkyl glycosides, specifically identifying dodecyl maltoside (claimed in claims 26-28 and 30-33) as disclosed within the catalog entry. *See* EX2011, 125:9-127:5.

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something is not taught and may not just summarily declare that written description is lacking. *Hyatt v. Dudas*, 492 F.3d 1365, 1370-71 (Fed. Cir. 2007) (examiner accounted for every limitation in the specification and why they were not disclosed in combination). Here in an inter partes proceeding with an expert witness, Aquestive mentions '558 Provisional ¶152 [EX1008], but conspicuously ignores the incorporated disclosure therein. Pet., 20 (never mentioning the incorporated material). The supporting declaration from Dr. Peppas does not even mention ¶152, much less the incorporated material.[8] Indeed, after testifying that he had considered the 1988 SIGMA catalog pages (EX2011, 124:4-125:19), Dr. Peppas provided redirect testimony "clarifying" that he had actually ***not*** considered those pages in forming his opinion (*id.*, 154:4-11).[9] *Cf. In re Edwards*, 568 F.2d 1349, 1354 (C.C.P.A. Jan. 18, 1978) (requiring consideration of the disclosure "as a whole" to determine whether the written-description requirement

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[8] Written description is a question of fact, so attorney argument must have evidentiary support and expert testimony must have basis.

[9] This, despite the fact that Dr. Peppas, in another section of his declaration, relies on an incorporation by reference in the '876 patent and labels it an admission of fact by the patent owner. *See* EX1041, ¶¶148-150.

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is satisfied) (reversing rejection).

The record at the time of institution provided no evidence that the specification ***when considered as a whole—including incorporated pages from the SIGMA catalog***—failed to support Aquestive's bare assertion of no written description. It is incidental to this portion of the response that both experts agree that the SIGMA catalog provides the allegedly missing description because even considering that fact involves an improper burden shift to the patent owner to prove patentability. 35 U.S.C. §316(e). The petition was facially defective and insufficient to provide a reasonable likelihood of unpatentability from the start. Any attempt to resuscitate Aquestive's defective petition arguments in reply would simply heap due-process violations on improper burden shifts. *Cf. Carbino v. West*, 168 F.3d 32, 34-35 (Fed. Cir. 1999) (new argument—even on question of law—improper); *Intelligent Bio-Systems, Inc. v. Illumina Cambridge, Inc.*, 821 F.3d 1359, 1369-70 (Fed. Cir. 2016) (new evidence properly not considered). This IPR should be terminated for this reason, alone.

2. Misplaced Reliance on Rule 57 Cannot Save the Petition

Despite the facial evidentiary insufficiency of the petition, the Director instituted anyway based on a legal argument that appeared nowhere in the petition. The problems with this new theory were detailed in a request for rehearing that was denied. Papers 10 & 14. Those arguments are repeated in this section to avoid

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waiver. Paper 9, 7. As a threshold matter, this belated intervention of the Director on Aquestive's behalf was inappropriate and a violation of due process; on the merits, it was wrong.

The Board regularly states that it is merely an adjudicator. *See, e.g.*, *Telebrands Corp. v. Tinnus Enters., LLC*, PGR2017-00015, Paper 53, 5 & n.3 (P.T.A.B. Oct. 11, 2019) (citing *SAS Inst., Inc. v. Iancu*, 138 S. Ct. 1348, 1355 (2018) ("it's the petitioner, not the Director, who gets to define the contours of the proceeding")). In this case, however, the Director thumbed the scale by advancing an argument the petitioner did not make (and the patent owner never had a chance to refute). In doing so, this IPR became a Director-defined proceeding, contrary to the Board's representations about IPRs in other cases and forums. Moreover, by failing to provide an opportunity to refute the new theory before institution, the Director denied Neurelis of due process. 5 U.S.C. §557(c) (requiring due process even at institution). Furthermore, the Director's interpretation of the rule in this case creates an unconstitutional Catch-22 for Neurelis: a formal non-statutory requirement that cannot be addressed in this proceeding but would result in loss of a patent. *See* U.S. Const., amend. V; *McDonnell v. United States*, 136 S. Ct. 2355, 2373 (2016).

In any case, the Director erred in applying Rule 57 to the '558 Provisional because the overwhelming weight of authority—***including Patent Office***

guidance—refutes the position advanced in the institution decision. *Ex parte Maziere*, 27 U.S.P.Q.2d 1705, 1706-07 (B.P.A.I. Jan. 26, 1993); MPEP §608.01(p)(1)(B), *accord Harari v. Hollmer*, 602 F.3d 1348, 1354 (Fed. Cir. 2010). Even if the rule somehow applied to provisional applications, it is moot once the patent has issued. *Magnivision, Inc. v. Bonneau Co.*, 115 F.3d 956, 960 (Fed. Cir. 1997); *Aristocrat Techs. Austl. PTY Ltd. v. Int'l Game Tech.*, 543 F.3d 657, 663 (Fed. Cir. 2008); *Exxon Corp. v. Phillips Petroleum Co.*, 265 F.3d 1249, 1254 (Fed. Cir. 2001); *Exela Pharma Sciences, LLC v. Lee*, 781 F.3d 1349, 1353 (Fed. Cir. 2015) (Newman, J., concurring). Proceeding with an IPR on an issue that is legally wrong and outside the scope of the IPR to address in any case is a waste of party and Board resources. 35 U.S.C. §316(b). The institution decision arbitrarily departs from long-standing USPTO practice without notice or justification. The IPR should be terminated for this separate reason.

E. THE COMBINATION DOES NOT TEACH THE CLAIMED SUBJECT MATTER

Despite the reliance of Aquestive (and the institution decision) on references that do not properly predate the '876 patent's priority date, Aquestive nevertheless fails to show motivation to combine Gwozdz (EX1014), Meezan'962 (EX1011), and/or Cartt'784 (EX1015) and further fails to show a reasonable expectation of success for any such combinations. EX2012, ¶¶35, 115. As an initial matter,

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Aquestive has not satisfied its burden in showing (1) a motivation to modify Gwozdz in the manner disclosed by the '876 claims; and/or (2) a motivation to combine the non-aqueous solutions of Gwozdz with the aqueous solutions of Meezan'962 or the particulate formulations of Cartt'784. Aquestive otherwise has not satisfied its burden in showing that a POSA would have a reasonable expectation of success in modifying Gwozdz in this combined manner – considering the known complications and sensitivities associated with intranasal administration and potential negative interactions associated with the claimed excipients.

To understand the overgeneralizations in Aquestive's obviousness analysis, Neurelis first provides the following clarifications of the prior art disclosure (which are not addressed by Aquestive but critical to a POSAs understanding of the relevant art).

1. The Alleged Prior Art

Aquestive's primary reference for Grounds 1-2 is Gwozdz (EX1014), titled "Pharmaceutical Solutions and Methods for Solubilizing Therapeutic Agents." *See* Pet. 5. Aquestive relies on Gwozdz for its disclosure of a "pharmaceutical solution comprising a therapeutic agent dissolved in one or more natural or synthetic tocopherols or tocotrienols, or any combination thereof and one or more alcohols or glycols, or any combination thereof" (EX1014, 0004) and its disclosure that the

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solution could be used with various benzodiazepines, including diazepam (EX1014, 0007-0008). *See* Pet. 23; EX1041, ¶203. As the title suggests, the claimed pharmaceutical solution aims to assist in solubilizing therapeutic agents – such as diazepam. *See* EX1014, 0005. Gwozdz accomplishes this without an alkyl glycoside – as Gwozdz does not disclose use of alkyl glycosides in its solutions. Pet. 33-34, 41; EX1041, ¶192.

Aquestive relies on Meezan'962 (EX1011), titled "Absorption Enhancers for Drug Administration," for its disclosure of alkyl glycosides as an example of an absorption enhancer for use with intranasal solutions. Pet. 120-121; EX1041, ¶227. Aquestive and Dr. Peppas fail to note that Meezan'962 discloses use of alkyl glycosides as ***surfactants*** to solubilize compounds in ***aqueous*** intranasal formulations. EX2012, ¶77; EX2011, 140:20-23. For instance, Example 2 of Meezan'962 – specifically called out by Dr. Peppas (EX1041, ¶234) – tests MIACALCIN®, a calcitonin-salmon nasal spray containing sodium chloride, benzalkonium chloride, nitrogen, hydrochloric acid, and ***purified water***. *See* EX1042, 0006; *see also* EX1011, ¶¶[0146]-[0172] (Examples 1-7). Meezan'962 does not apply to non-aqueous solutions, such as those disclosed in Gwozdz and as the '876 patent claims require. EX1001, claims (requiring tocopherols or

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tocotrienols)[10]; *see* EX2012, Section VIII.B.1(f). Meezan'962 further does not disclose benzodiazepines (directly or indirectly).[11] Pet. 37; EX1041, ¶222.

Aquestive lastly relies on Cartt'784 for its disclosure of dosing regimens of ***particle formulations*** of benzodiazepines. Pet. 34, EX1041, ¶¶241-242. Aquestive and Dr. Peppas recognize that neither Gwozdz nor Meezan'962 disclose particulate formulations (instead disclosing solutions). *See* Pet. 34. While Dr. Peppas attempts to overcome this deficiency by pointing to sporadic references to liquids and solvents in the reference (*see* EX1041, ¶247; EX2011, 143:16-145:17), a closer look at these passages do not support Dr. Peppas' argument. EX2012, ¶107 n.18.

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[10] *See* EX1041, ¶248 ("a tocopherol would be such a non-aqueous medium").

[11] While Petitioner and Dr. Peppas provide that a POSA would readily expect Meezan'962 to apply to benzodiazepines, by reference to "small organic molecules" (EX1041, ¶222), Petitioner and Dr. Peppas assume too much. As an initial matter, the genus of "small organic molecules" is practically infinite. EX2012, ¶97. Furthermore, a POSA would find no guidance in Meezan'962 as to how to determine what group, if any, of small organic molecules would benefit from Meezan's disclosure – instead providing numerous examples for, *e.g.*, peptides and proteins. *Id.*

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Instead, the references relate to solvents used for making the particulate formulations disclosed in Cartt'784. *Id.* Additionally, the Cartt'784 disclosure related to solvents includes a large list of available solvents for use with its formulations – without particularly pointing out ethanol and benzyl alcohol (alone or in combination). EX2012, ¶108; *see also* EX2011, 147:21-148:2 ("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.").

Despite the above deficiencies, Aquestive argues that a POSA would (1) have a reason to modify Gwozdz to combine the teachings of Meezan'962 and Cartt'784; and (2) would have a reasonable expectation of success in doing so. Aquestive's fails to meet either requirement.

2. *Aquestive Fails to Demonstrate a Motivation to Combine the Disclosure of Gwozdz with that of Meezan'962 (Ground 1 Fails)*

Aquestive's entire obviousness case for Ground 1 hinges on Dr. Peppas' assertion that a POSA, familiar with the known permeation problems associated with intranasal administration – especially, intranasal administration of benzodiazepines – would have looked to ***both*** of the following solutions: (1) increasing drug solubility; and (2) using penetration enhancers to increase the permeability of the nasal mucosa. *See* EX1041, ¶¶121-168. As an initial matter, as Dr. Gizurarson provides, a POSA would not recognize the solutions as necessarily

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compatible and instead would look to pursue one or the other. EX2012, ¶79. In fact, this is ***exactly*** what the inventors of the '876 patent and the Gwozdz patent appeared to do – with Gwozdz approaching the first solution and the '876 patent approaching the second solution.

a. Gwozdz provides no motivation to modify its disclosed formulations; instead, Gwozdz teaches a different approach

Gwozdz provided an independent solution to the problem addressed in the '876 patent – bioavailability of benzodiazepines with intranasal administration. Gwozdz's approach to the problem was focused on solubility and left no room for modification in its precipitation sensitive formulations. *See* Pet. 28; *see also* EX1041, ¶194. Dr. Peppas provides, in addressing the "Problem to be Solved and Solution" in Gwozdz:

- Gwozdz recognized a problem with solubility of certain therapeutic agents and specifically recognized diazepam as one example of such therapeutic agent. EX1041, ¶193.
- Gwozdz "solved the problem with respect to diazepam" by combining tocopherol and ethanol, providing solubility of diazepam approaching 10% level. *Id.*, ¶194.

What Aquestive and Dr. Peppas fail to appreciate is that the solution to

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insolubility in Gwozdz was limited to its specific disclosure. Specifically, Gwozdz was concerned with the solubilization of hydrophobic and lipophilic pharmaceutical agents. EX2012, ¶81; EX1014, 0000 (Abstract)-0001. Specific to the pharmaceutical agent diazepam, Gwozdz states:

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

EX1014, 0007. A POSA, knowing that Gwozdz's solubility level for diazepam is close to the same amount as the clinical dose needed for therapeutic effect (10 mg), and combined with the above statement, would understand that increasing the amount of tocopherol and decreasing the amount of ethanol increases the solubility and approaches diazepam's saturation concentration. *See* EX2012, ¶83. This, in effect, brings the formulation of Gwozdz close to risk of precipitation in the humid nasal cavity. *Id.* Additionally, a POSA would learn from the teachings of Gwozdz that adding less tocopherol reduces the solubility of diazepam. *Id.*, ¶¶82-83; *see also*, ¶65. With concerns of the already low solubility index of Gwozdz's diazepam formulation in mind, a POSA would have no motivation – and instead would be

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turned away from – adjusting the formulation any further (let alone adding any additional excipient such as benzyl alcohol or an alkyl glycoside to the mix). *Id.*, ¶¶80-85. A POSA would understand that doing so would potentially take away from the amount of either or both of the tocopherol and ethanol and, in turn, ***decrease*** the solubility of diazepam – *i.e.*, he would not sacrifice drug solubility by removing or reducing a co-solvent necessary for maximizing solubility of the benzodiazepine drug. *Id.* Thus, a POSA would not be motivated to modify the formulations of Gwozdz.

b. There is further no reasonable expectation of success in modifying the intranasal formulations of Gwozdz

The claimed intranasal formulation of the '876 patent requires all the following excipients: ethanol, benzyl alcohol, tocopherol or tocotrienol, and alkyl glycosides. Aquestive's theory of obviousness lacks a showing of reasonable expectation of success in modifying Gwozdz to include all of these claimed excipients and in their claimed amounts. Aquestive instead presents blanket conclusions – through its expert, Dr. Peppas – that a POSA would "easily" adapt teachings of one reference to another (EX1041, ¶170). This, despite the fact that Dr. Peppas simultaneously recognizes the complexities of formulating for intranasal administration. EX1041, ¶¶115-120. Conclusory assertions where evidence of a reasonable expectation of success is necessary is a classic marker for

improper hindsight. *In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988). Again, the reply is not an opportunity for Aquestive to make its case in the first instance.

Alkyl Glycosides

First, Aquestive has not shown reasonable expectation of success in adding a penetration enhancer – and specifically, an alkyl glycoside – to the Gwozdz formulation. Alkyl glycosides are known nonionic surfactants. *See* EX1041, ¶169. The Handbook of Pharmaceutical Excipients ("Handbook") (EX1031) teaches that non-ionic surfactants interact to the detriment of the disclosed solvents. First, the Handbook provides that "[e]thanol is inactivated in the presence of nonionic surfactants and is ineffective against bacterial spores." EX1031, 0004. Second, the Handbook provides that "antimicrobial activity is reduced in the presence of nonionic surfactants…" *Id.*, 0010. A POSA would recognize that especially when dealing with multidose intranasal use, the inactivation of microbial activity of ethanol and/or benzyl alcohol could have consequences in the successful approval of an intranasal formulation. EX2012, ¶¶88-89. A POSA by 2008 would have been aware of such interactions and, thus, less likely to look to a nonionic surfactant to combine with a formulation that already included ethanol and benzyl alcohol. *Id.* Aquestive and Dr. Peppas do not provide a reasonable expectation of success for this additional reason.

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Interestingly, Dr. Peppas' own work discourages a POSA from using a penetration enhancer in an intranasal formulation. While Dr. Peppas points to his senior-authored publication as support for the importance of adding nasal penetration enhancers (bioadhesives) to active ingredients to enhance absorption through the nasal mucosa (EX2011, 33:24-34:8), a closer look at the conclusion of Dr. Peppas' paper suggests 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.

EX1045, 191 (emphasis added). Dr. Peppas' attempts to work around this contradictory statement proved ineffective. *See* EX2012, ¶¶83-94.

Moreover, Dr. Peppas admitted in deposition testimony that whether a surfactant or detergent (*e.g.*, alkyl glycosides) can work as a penetration enhancer in any given formulation depends on the system that a POSA is working with (*e.g.*, nasal, buccal, or sublingual, etc.). EX2011, 105:2-15. Thus, Dr. Peppas' representation of the ease with which a POSA would formulate the claimed formulations fails to address the intricacies of any given route of administration. For at least these reasons, a POSA would not have had reasonable expectation of

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success in modifying Gwozdz with the addition of an alkyl glycoside as claimed by the '876 patent.

Benzyl Alcohol

Second, Aquestive has not shown reasonable expectation of success in adding additional solvents – and specifically, benzyl alcohol – to the Gwozdz formulation. While Aquestive and Dr. Peppas rely on the fact that the solvents ethanol and benzyl alcohol were known to POSA (citing to the Handbook (EX1031)), neither address the incompatibilities of either solvent with the other excipients disclosed in Gwozdz. For example, the Handbook entry for benzyl alcohol provides the following regarding 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, 0010 (emphasis added). A POSA relying on the Handbook would have at least been cautioned not to combine benzyl alcohol with tocopherols or tocotrienols. EX2012, ¶¶86-87. A POSA would recognize that doing so would negate the anti-oxidation properties of tocopherols and, as a result, degrade the compound such that undesirable by-products could be introduced into the formulation. *Id.*

Furthermore, a POSA as of 2008 was well aware that solvents, including

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benzyl alcohol, were known irritants to the nasal cavity. *See* EX1041, ¶103(b); EX2012, ¶90. Yet, Dr. Peppas relies on, *e.g.*, Valium® diazepam injection as an example of solvents used for administration of diazepam. EX1041, ¶103(b) n.9. However, a POSA would understand 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 the case with a lorazepam (a benzodiazepine) injectable composition sold under the brand name Ativan®. EX2012, ¶90. The composition of Ativan® would specifically have been recognized by a POSA as unsuitable for intranasal administrations:

> 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***.

EX2014, 6:31-39 (emphasis added). Yet, Dr. Peppas opines that benzyl alcohol concentrations of 5% (v/v) or more could be employed as a solubilizer. EX1041,

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¶124.[12] A POSA would have known ***not*** to use this high concentration of benzyl alcohol in intranasal formulations because of its potential harmful effects on the patient when applied to the nasal mucosa. EX2012, ¶92.

For at least these reasons, a POSA would not have reasonable expectation of success in modifying Gwozdz with the addition of a benzyl alcohol (as claimed by the '876 patent).

c. Aquestive shows no motivation to combine the formulations of Gwozdz with the formulations of Meezan'962

As an initial matter, Aquestive provides no motivation for a POSA to increase bioavailability of Gwozdz's intranasal formulation with addition of a

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[12] Dr. Peppas otherwise appears to argue that combinations including 0% benzyl alcohol (*i.e.*, no benzyl alcohol) with ethanol meet the claim limitation of "ethanol and benzyl alcohol in a combined amount." *See e.g.*, EX1041, ¶187. The claimed inventions and prosecution history do not allow for such an interpretation, as detailed *supra* (Section II.B.2.). To the extent Dr. Peppas (or Aquestive) argues that benzyl alcohol may be not be included in the claimed formulation, and thus nasal irritation would be less likely, this would be an incorrect reading of the patent claims. EX2012, ¶91.

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penetration enhancer.[13]

Instead, Gwozdz distinguishes itself from prior art solutions containing surfactants or micellar formulations and exemplifies a maximized tocopherol formulation necessary for achieving increased solubility. EX2012, ¶82. There would have been no motivation for a POSA to modify Gwozdz by adding a surfactant – *e.g.*, an alkyl glycoside.

Yet, even if a POSA were to find motivation to add a penetration enhancer to the intranasal formulations of Gwozdz, Meezan'962 would not get him to the claimed formulation of the '876 patent. Specifically, Meezan'962 was concerned with increasing absorption and decreasing adverse effects of ***water-soluble*** therapeutic drugs through non-intravenous routes of administration and increasing stability of its peptide and protein formulations by addition of surfactants – listing alkyl glycosides as one such category of surfactants. EX2012, ¶96; EX1011, ¶[0004]. As discussed *supra*, the therapeutic agents disclosed in Meezan'962 do not necessarily apply to benzodiazepines and, instead, primarily relate to water-

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[13] Indeed, the only reference to penetration enhancers in Gwozdz is in the context of injections and topical applications – both unrelated to intranasal formulations. EX1014, 10:3-16; 12:12-27.

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soluble compounds, including the "anti-seizure agents" topiramate and zonisamide. EX2012, ¶97. Accordingly, a POSA would not find Meezan'962 relevant to poorly water-soluble therapeutic agents such as benzodiazepines. *Id.*

Furthermore, Meezan'962 disclosed the use of surfactants in an ***aqueous*** setting. *Id.*, ¶98; EX1011, ¶¶[0146]-[0172] (Examples 1-7). Notably, Dr. Peppas acknowledged in his deposition that alkyl glycosides as used in Meezan'962 are solubilized in water, and that such is not the case for the claimed non-aqueous formulation. *Id.*, ¶98; EX2011, 140:13-23. In light of this realization – which was not addressed in his declaration – Dr. Peppas further testified that he did not know how Meezan'962's alkyl glycosides would function in the absence of water (and as claimed in the '876 patent). EX2011, 141:8-11; *see also* EX2012, ¶99. Indeed, a POSA would need more information (outside of either Gwozdz or Meezan'962 disclosure) in order to determine how the alkyl glycosides of Meezan'962 would function including, *e.g.*, "[s]olubility of the glycoside in other solvents, [] other carriers . . . [p]robably a number of other parameters; pH, pH sensitivity, concentrations" etc. *Id.*, 141:14-18.[14]

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[14] Dr. Peppas otherwise points to the teachings of Kee and Shaw (EX1016) as identifying alkyl glycosides as preferred enhancers for nasal delivery. *See e.g.*,

Because independent claim 1 of the '876 patent excludes water from its benzodiazepine solution – through its "consisting of" language – it does not provide a vehicle for which a surfactant such as alkyl glycoside could work to stabilize or act as a traditional penetration enhancer in a solution. *See also* EX2011, 138:12-139:23 (agreeing that water is not disclosed in claim 1). For all these reasons, a POSA would have been discouraged from selecting the alkyl glycoside as disclosed and used in Meezan'962 to add to the non-aqueous formulations of Gwozdz. Thus, Aquestive fails to show motivation to combine Gwozdz and Meezan'962 in a manner that render sole independent claim, claim 1, of the '876 patent obvious. Aquestive's argument related to the dependent claims fail for the same reason. *See also*, EX2012, ¶¶101-105.

3. *Aquestive Fails to Demonstrate a Motivation to Combine the Formulation of Cartt'784 to the Gwozdz and/or Meezan'962 Formulations (Ground 2 Fails)*

Cartt'784 does not fix the deficiencies with Aquestive's combination of

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EX1041, ¶¶103(f); 153, 160-161. The teachings of Kee and Shaw, and its conclusion as to alkyl glycosides, is distinguishable for the same reason as for Meezan'962 – all examples in EX1016 are directed to aqueous solutions. *See* EX1016, 0006-0009 (Examples 1-12).

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Gwozdz and Meezan'962. First, Gwozdz distinguished its non-aqueous lipohilic and hydrophobic formulations from Cartt'784 by stating, "[a]dvantageously, the resulting pharmaceutical solution is not an emulsion or vesicle, and can be used directly in the production of pharmaceutical compositions." EX1014, 0004-0005; *see also* EX2012, ¶107. A POSA reading the disclosure of Gwozdz would recognize that Gwozdz taught it was a superior alternative over the teachings of Cartt'784, thus showing lack of motivation to combine Gwozdz with Cartt'784. EX2012, ¶¶106-107.

Nevertheless, while Aquestive appears to primarily rely on Cartt'784 for its disclosure of dosage of benzodiazepines (Pet. 35), Cartt'784 actually applies to particulate formulations of benzodiazepines. *Id.*, ¶108. As detailed *supra* (Section II.E.1), a POSA would not find particulate formulations of benzodiazepines as easily translatable to solutions of benzodiazepines, especially as it relates to dosing regimens. Indeed, Dr. Peppas testified in deposition that "[s]olutions and particulates don't go together." EX2011, 145:13-17. Thus, Aquestive fails to set forth motivation to combine the non-aqueous formulations of Gwozdz with Cartt'784 for disclosure of the claimed dosing regimens.

Additionally, while Aquestive further relies on Cartt'784 as providing motivation to combine benzyl alcohol and ethanol as claimed in the '876 patent, a POSA would have been lost in the large list of available solvents disclosed in

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Cartt'784. EX2012, ¶108. As Dr. Peppas acknowledged, Cartt'784 provides "too many combinations" of solvents and otherwise does not specifically call out ethanol and benzyl alcohol as a preferred combination of solvents. *Id.*; *see also* EX2011, 147:21-148:2. Aquestive accordingly fails to set forth a motivation to combine the formulations of Gwozdz with Cartt'784 for disclosure of the combined solvents.

For all these reasons, Aquestive has not shown motivation to combine the asserted prior art references sufficient to establish a valid claim of obviousness for either of Grounds 1 or 2.

III. SECONDARY CONSIDERATIONS OF NONOBVIOUSNESS

As detailed *supra*, Aquestive has failed to establish a *prima facie* case of obviousness. Objective evidence of the failure of others to formulate a diazepam intranasal spray and a long-felt but unmet need to do so further supports a finding of non-obviousness. EX2012, ¶¶36, 116. All such objective evidence must be considered before reaching a conclusion of obviousness – *i.e.*, it is not merely rebuttal evidence. *See In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1075-77 (Fed. Cir. 2012). A showing of long-felt need is particularly probative of obviousness when "it demonstrates that a demand existed for the patented invention, and that others tried but failed to satisfy that demand." *Millennium Pharm., Inc. v. Sandoz, Inc.*, 862 F.3d 1356, 1368-69

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(Fed. Cir. 2017) (reversing the district court's finding of obviousness, in part, on a finding of long-felt but unresolved need).

Benzodiazepines for the treatment of epilepsy have been tested as early as the 1980s. Despite its therapeutic promise in stopping and preventing seizures in patients, benzodiazepine use was not widespread in 2008. EX2012, ¶51. As of 2008 (or even 2009) benzodiazepine formulations had only been approved and commercially developed for intravenous and rectal administration. *See supra*, Section II.A.1. Yet, the need for (1) medical professional administration of intravenous formulations in a hospital or clinical setting; and (2) private setting and parental administration of rectal formulations greatly hindered efficient treatment of epileptic seizures. EX2012, ¶113. Thus, there was a well-known need in the market for immediate treatment of epileptic seizures – with intranasal administration of benzodiazepines – and more specifically, diazepam[15] – proving to be a promising solution. EX2012, ¶¶111-112.

Also detailed *supra*, while the ability to administer therapeutic drugs

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[15] Diazepam is recognized as 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. EX2012, ¶113.

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intranasally was first realized as early as 1980 (EX2008, 1240), intranasal formulation of benzodiazepines has been hampered by technical challenges posed by benzodiazepines. Indeed, the 1989 Lau study on diazepam and lorazepam concluded that the intranasal route of administration "may be of limited utility for benzodiazepines in the treatment of status epilepticus where rapid onset of effect is essential." EX2009, 173; EX2012, ¶111. Other researchers had similar difficulties administering other benzodiazepines, *e.g.*, clonazepam. EX2012, ¶111. Dr. Gizurarson's work on intranasal delivery of the benzodiazepines further evidenced the difficulties in developing an intranasal benzodiazepine formulation for the use as a rescue agent in epileptic seizures. *See* EX2007; EX2012, ¶112. Based on his work with different benzodiazepines, Dr. Gizurarson explains that a POSA would note that developing certain benzodiazepines such as diazepam would be more difficult than, for example, midazolam, in light of precipitation concerns.[16] EX2012, ¶112.

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[16] Dr. Gizruarson further opines that a POSA would have been discouraged from pursuing lower solubility index benzodiazepines for development in light of precipitation concerns, which would have been a potential set-up for failure. *Id.*, ¶66.

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Thus, the need for an intranasal diazepam formulation for use in the treatment of epilepsy still existed as of 2008. That the industry had failed to develop the benzodiazepine formulation of the '876 patent is evident from the fact that before Neurelis's pioneering invention, no company had ever commercialized an intranasal diazepam formulation. Indeed, only ***one*** company has commercialized an intranasal benzodiazepine formulation – NAYZILAM® (a midazolam formulation) – and even then, only did so this year. EX2012, ¶75; EX2018.

Neurelis submitted a New Drug Application ("NDA") with the U.S. Food and Drug Administration ("FDA") for Valtoco® (diazepam nasal spray that is representative of the '876 patent claims) as a treatment for epilepsy patients six years and older who experience increased bouts of seizure activity (cluster or acute repetitive seizures) to address this unmet need. EX2024. In fact, FDA granted Neurelis both Orphan Drug designation for Valtoco® in November 2015 and Fast Track designation in December 2016. EX2023; *see also* EX2002 (granting Neurelis "Fast Track development program the investigation of NRL-1 for the management of selected, refractory patients with epilepsy, on stable regimens of AEDs, who require intermittent use of diazepam to control bouts of increased seizure.").

Thus, the fact that Neurelis, with the Valtoco® formulation, met this long-

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felt but unmet need – especially in light of the failure of others – confirms the non-obviousness of the '876 patent. EX2012, ¶113; *see also In re Piasecki*, 745 F.2d 1468, 1475 (Fed. Cir. 1984); *see also Alco Standard Corp. v. Tenn. Valley Auth.*, 808 F.2d 1490, 1500 (Fed. Cir. 1986) (affirming a nonobviousness finding based on a showing of long-felt but unmet need in the industry).

IV. CONCLUSION

Aquestive has failed to demonstrate a reasonable likelihood that any challenged claim is unpatentable. Aquestive cannot remedy this failing in reply. The review should be terminated or, alternatively, the Board should enter a final written decision holding the claims not unpatentable.

Date: November 5, 2019

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EXHIBIT LIST

Exhibit	Description
2001	Epilepsy Fast Facts, CDC (Center for Disease Control and Prevetions), CDC 24/7: Saving Lives, Protection People™, Apr. 9, 2019, pp. 1-2.
2002	Grant Fast Track – Dept. of Health and Human Services re: IND 112621; NRL-1 (diazepam intranasal solution), Dec. 27, 2016, pp 1-2.
2003	Howard LeWine, M.D., "Quick Injection Helps Stop Epileptic Seizures," Harvard Health Blog, Feb. 23, 2012; p. 1
2004	"Managing Epilepsy Well Network and Selected Self-Management Programs; Putting Collective Wisdom to Work for People with Epilepsy," Prevention Research Centers (PRC), CDC , Nov. 2016, pp.1-17
2005	K.M. Fiest, et al., "Prevalence and Incidence of Epilepsy, A Systematic Review and Meta-Analysis of International Studies," NEUROLOGY 88, Jan. 17, 2017, pp.296-303
2006	SIGMA Chemical Company Catalog (1988)
2007	E. Bechgaard et al., "Solubilization of Various Benzodiazepines for Intranasal Administration, A Pilot Study," Pharmaceutical Development and Technology 2:293-296 (1997)
2008	A. Hussain et al. "Nasal Absorption of Propranolol in Humans," Journal of Pharmaceutical Sciences 69:1240 (1980)
2009	S. Lau and J. Slattery, "Absorption of Diazepam and Lorazepam Following Intranasal Administration," International Journal of Pharmaceutics, 54:171-174 (1989)
2010	M. Schols-Hendriks et al., "Absorption of Clonazepam After Intranasal and Buccal Administration," British Journal of Clinical Pharmacology 39:449-451 (1995)
2011	Dr. Nicholas Peppas Deposition Transcript, October 24, 2019.
2012	Declaration of Dr. Sveinbjorn Gizurarson, Ph.D.

Exhibit	Description
2013	J. Riss et al., "Benzodiazepines in Epilepsy: Pharmacology and Pharmacokinetics," Acta Neurologica Scandinavica 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," Seizure 18:220-224 (2009)
2016	D. Terry et al., "Acceptance of the Use of Diazepam Rectal Gel in School and Day Care Settings," Journal of Child Neurology 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-in-people-living-with-epilepsy-in-the-u-s-/ (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," https://www.fitonasal2act.com/how-does-the-nose-work/the-nasal-mucosa/ (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," https://www.neurelis.com/neurelis-news/neurelis-files-new-drug-application-fda-valtocotm-nasal-spray-investigational-treatment-

Exhibit	Description
	pediatric (2018) (Accessed November 1, 2019)
2024	"Neurelis Receives FDA Orphan Drug Designation for NRL-1 in the Treatment of Acute Repetitive Seizures," https://www.neurelis.com/neurelis-news/fda-orphan-drug-designation (2015) (Accessed November 1, 2019)

TYPE VOLUME CERTIFICATE

This paper contains 8826 words, as determined using the word-counting utility of Microsoft Word, less the sections excluded pursuant to 37 CFR §42.24(a).

Date: November 5, 2019

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CERTIFICATE OF SERVICE

I certify that on November 5, 2019 this paper and accompanying exhibits EX2007- EX2024 were served via email as follows:

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