Paper No. 6
Filed: June 20, 2023

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MARINUS PHARMACEUTICALS, INC.,
Petitioner,

v.

OVID THERAPEUTICS INC.,
Patent Owner.

Case PGR2023-00020
Patent 11,395,817 B2

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EXHIBIT LIST

Exhibit	Description
2001	Disclaimer in Patent Under 37 CFR 1.321(a) for claims 1-21 and 23-24 of U.S. Patent No. 11,395,817, filed June 16, 2023
2002	Marinus Corporate Presentation June 2023, https://s25.q4cdn.com/443656056/files/doc_financials/2023/Corporate-Deck-June-FINAL.pdf (last accessed June 19, 2023)
2003	H. Vaitkevicius et al., Intravenous ganaxolone for the treatment of refractory status epilepticus: Results from an open-label, dose-finding, phase 2 trial, 63 *Epilepsia* 2381-2391 (2022)
2004	Ovid Therapeutics Corporate Overview May 2023, https://s201.q4cdn.com/176459324/files/doc_presentation/2023/05/OVID-May-2023-Corporate-Deck-FINAL-FOR-POSTING-5-5-23-1.pdf (last accessed June 19, 2023)
2005	Marinus Pharmaceuticals Provides Business Update and Reports Fourth Quarter and Full Year 2021 Financial Results (March 21, 2022), https://ir.marinuspharma.com/news/news-details/2022/Marinus-Pharmaceuticals-Provides-Business-Update-and-Reports-Fourth-Quarter-and-Full-Year-2021-Financial-Results/default.aspx (last accessed June 19, 2023)
2006	Excerpts from the File History of Provisional App. No. 62/882,648
2007	Excerpts from the File History of U.S. Patent No. 11,679,117
2008	Excerpts from the File History of U.S. Patent No. 11,110,100
2009	Excerpts from the File History of U.S. Patent No. 10,799,485
2010	Excerpts from the File History of U.S. Patent No. 10,603,308
2011	Marinus Pharmaceuticals Announces Formation of Scientific Advisory Board (April 30, 2020), https://s25.q4cdn.com/443656056/files/doc_news/Marinus-Pharmaceuticals-Announces-Formation-of-Scientific-Advisory-Board-2020.pdf (last accessed June 19, 2023)

2012	Marinus Scientific Advisory Board, https://marinuspharma.com/about-marinus/scientific-advisory-board/ (last accessed June 19, 2023)
2013	Excerpt from the File History of U.S. Patent No. 11,395,817

I. Introduction

U.S. Patent No. 11,395,817 ("the '817 patent") discloses and claims methods of treating status epilepticus ("SE") with ganaxolone. SE is a difficult to treat seizure disorder with around 150,000 cases per year. Before the claimed inventions, several drugs were employed to treat SE but, in many cases, their efficacy decreased dramatically as the duration of SE increased, resulting in a complete loss of efficacy.

Despite this, Petitioner raises five grounds alleging that claims 22 and 25-31 of the '817 patent[1] are unpatentable for anticipation, obviousness, or lack of enablement based on references and arguments that have already been before the Office and considered during prosecution of the '817 patent through art submitted by the applicant or a Third-Party Submission:

Ground	Claims	Basis for Ground
1	**22 and 25-31**	Anticipation by Zhang[*†] (Ex. 1009)
2	**22 and 25-31**	Obviousness over Zhang[*†]
3	**22 and 25-31**	Obviousness over Zhang[*†] and Saporito P1 (Ex. 1013) and/or Saporito P2 (Ex. 1014)
4	**22 and 25-31**	Obviousness over Zhang[*†] and/or Marinus's Orphan Drug Press Release[†] (Ex. 1011) and Marinus's Phase I Press Release[†] (Ex. 1022)
7	**22 and 25-31**	Lack of enablement under 35 U.S.C. § 112

[*]Submitted in an IDS
[†]Raised in a Third-Party Submission

[1] As discussed below in Section II, Patent Owner has disclaimed claims 1-21 and 23-24 of the '817 patent. This disclaimer renders moot Petitioner's Grounds 1-4 and 7 for claims 1-3, 10-17, 19-21, and 23-24 and Petitioner's Grounds 5, 6, and 8 for all claims covered by those grounds.

Petitioner's primary reference, Zhang, does not anticipate the challenged claims at least because it fails to disclose several claim elements, expressly or inherently. It also requires one to pick and choose, without guidance, a disease and dosing regimen from among extensive lists of options. Specifically, Zhang does not disclose administering ganaxolone to treat a human patient suffering from SE (as required by claims 22 and 25-31), improvement to a patient after administration for more than 8 hours (as required by claim 22), or any of the specific dose ranges recited in claims 25-31. Zhang's general disclosure instead provides formulations of ganaxolone that could be used to treat a laundry list of over 30 different diseases and disorders using a wide variety of doses and dosing regimens. Zhang's examples fare no better: Example 8 in particular discloses administering low doses of ganaxolone only to rats having chemically induced SE and shows that any anti-seizure effect of ganaxolone begins to decrease after 5 hours, after which no additional data is provided.

Zhang also does not render obvious any of claims 22 and 25-31, alone or in combination with any of Petitioner's other asserted references. Petitioner fails to even articulate a legally sufficient motivation to arrive at the challenged claims, let alone with a reasonable expectation of success. Petitioner also fails to identify any prior-art reference that describes the clinical evaluation of ganaxolone in treating SE, pointing to, at most, a press release stating that phase 1 clinical trials evaluating

the safety (not the efficacy) of using intravenous ganaxolone in healthy human volunteers had begun.

Petitioner also fails to address the substantial objective evidence of unexpected results, a long-felt need for an effective treatment for SE, and failures of others to treat SE, which all support the nonobviousness of the challenged claims. Petitioner's statements during the prosecution of its own patent applications, which were filed three years after Patent Owner's '817 patent, establish the unexpected results brought about by the methods of treating SE with ganaxolone that are claimed in the '817 patent. In particular, Petitioner relied on its own phase 2 data, which demonstrates that the dose ranges of ganaxolone recited in the '817 patent unexpectedly resulted in seizure burden reduction and cessation in subjects diagnosed with SE. Petitioner, however, ignores this evidence and fails to address it in the Petition.

Petitioner's enablement challenge is also facially deficient, as Petitioner fails to address the *Wands* factors or provide any support for its conclusion that the specification does not enable the challenged claims.

For the reasons detailed below, Petitioner fails to show that it is more likely than not that any challenged claim is unpatentable. The Board should deny institution.

II. Patent Owner's Statutory Disclaimer Under 37 C.F.R. § 1.321(a) of Challenged Claims 1-21 and 23-24.

Patent Owner has disclaimed claims 1-21 and 23-24 of the '817 patent under 35 U.S.C. § 253(a) in compliance with 37 C.F.R. § 1.321(a) by submission of an appropriate disclaimer, a copy of which is included as Exhibit 2001. Accordingly, these claims may not be considered in deciding whether to institute a post-grant review of the '817 patent. 37 C.F.R. § 42.207(e).

The present statutory disclaimer does not constitute an admission or acquiescence by Patent Owner as to the Petition. Rather, Patent Owner disagrees with Petitioner's arguments in the Petition and makes the present disclaimer without prejudice to Patent Owner's ability to rebut such arguments (including characterizing and distinguishing the references cited in the Petition) with respect to any patents and/or patent applications assigned to Patent Owner in any forum. No adverse inferences result from the disclaimer and the disclaimer has no effect on the other claims of the '817 patent. *See Raytheon Techs. Corp. v. General Electric Co.*, 993 F.3d 1374, 1379 n.4 (Fed. Cir. 2021). Patent Owner is not seeking an adverse judgment as to the disclaimed claims. Patent Owner is not disclaiming the '817 patent or any of the remaining claims challenged in the Petition under 37 C.F.R. § 42.73(b).

III. Background and State of the Art

A. Status epilepticus ("SE")

Epilepsies and seizure disorders fall within the field of neurology and encompass a range of neurological disorders characterized by abnormal electrical activity in the brain that causes seizures. A seizure refers to an atypical electrical discharge in the brain that results in changes in consciousness, sensation, and behavior. Ex. 1004, 18285. Epilepsy is a chronic condition characterized by recurring unprovoked seizures. *Id.*

SE is a specific type of seizure disorder that is defined as continuous seizure activity or multiple seizures lasting longer than 30 minutes without regaining consciousness. Ex. 1004, 18287. SE is considered to be "a life-threatening condition, associated with high mortality and if not treated immediately, c[ould] result in brain damage, cognitive impairment and death." Ex. 1011, 1. As acknowledged by Petitioner, SE is known to be "the second most common neurologic emergency in the U.S." with "150,000 cases per year." Ex. 2002, 22.

Despite having distinct manifestations of seizure activity, SE can be caused by many of the same risk factors associated with epilepsy. SE, however, does not fall neatly within the category of seizure disorders—it is a neurologic emergency with limited and drastic treatment options. Ex. 2003, 2382. For example, antiseizure medicines are the first line of defense against this serious disorder, but 30-57% of

patients fail to respond to first-line therapy. *Id.* In fact, "53-55% of patients with SE do not respond to either first- or second-line treatment." *Id*. These patients are given another round of second-line antiseizure medicines or are placed in a medically-induced coma. *Id.*; *see also* Ex. 1004, 18287 (reporting up to 40% of SE patients suffer from what is referred to as "refractory SE" ("RSE") and fail to respond to standard antiepileptic treatments). SE patients resistant to treatment face dire outcomes with mortality rates as high as 35% and "nearly half of the surviving patients have subsequent neurologic deficits." Ex. 2003, 2382. Indeed, Petitioner's own CEO has stated that SE is a "difficult to treat seizure disorder with limited treatment options." Ex. 1011, 1. Thus, one of the "key areas of unmet clinical needs in epilepsy" included "new AEDs for drug-resistant seizures and SE." Ex. 1004, 18306.

B. Ovid's endeavors in epilepsy and seizure disorder treatment

Ovid is a pioneer at the forefront of therapies for challenging neurological disorders. Ex. 2004, 3. Its team of dedicated scientists has invested significant resources and expertise in conducting laboratory and clinical investigations to unravel the pathological complexities of seizures, epilepsies, and SE, to advance the understanding of these disorders and develop effective therapeutic interventions. Ovid's portfolio of clinical candidates and patented inventions underscores its commitment to this field. For example, Ovid has four candidates in various stages

of clinical development: Soticlestat (in phase 3 clinical trials for treating Dravet syndrome and Lennox-Gastaut syndrome), GV101 (in phase 1 clinical trials for treating brainstem cavernous malformations), OV329 (in phase 1 clinical trials for treating tuberous sclerosis complex, infantile spasms, and focal seizures), and OV350 & other KCC2 activators (in preclinical development for treating resistant epilepsies and other neuropathologies). *Id.*, 5. Ovid's research in this field extends beyond these clinical candidates. In addition to the '817 patent directed to treating SE, Ovid has obtained patents in this same family that further embody Ovid's research and development efforts, including for treating essential tremors with gaboxadol (Ex. 1025), CDKL5 deficiency disorder with ganaxolone (Ex. 1024), and PCDH19-related epilepsy with ganaxolone (Ex. 1023).

Ovid's contributions to the treatment of seizures and epilepsies have stimulated collaborative efforts in this field. Recognizing the significance and potential of Ovid's scientific advancements, Petitioner has employed Ovid's innovative epilepsy treatment findings and research as the foundation for its own development of ganaxolone products as therapeutics. In March 2022, for instance, Marinus entered an exclusive license agreement with Ovid to license patents and patent applications in the U.S., the European Union, and select European countries related to the use of ganaxolone for treating CDKL5 deficiency disorder. Ex. 2005, 2.

Similarly, Ovid's '817 patent is the bedrock of Marinus's clinical development. The results generated in Marinus's clinical trials involving SE aligns seamlessly with the treatment methods outlined in the '817 patent. This validation demonstrates that Ovid's groundbreaking endeavors in this field have provided a reliable roadmap upon which others can build upon, forging a promising path forward in SE treatment.

For example, in a June 22, 2022 research article published in *Epilepsia*, which describes a phase 2 clinical trial that studied the use of intravenous ganaxolone for the treatment of refractory SE that was "sponsored and supported by [Petitioner]," the authors reported that "[r]eductions in seizure burden occurred rapidly in all three ganaxolone dose cohorts" tested. Ex. 2003, 2381, 2388. During the study, the three ganaxolone dose cohorts studied included 500 mg/day (low), 650 mg/day (medium), and 713 mg/day (high). *Id.*, 2383. These three ganaxolone doses are each encompassed by one or more of the '817 patent's claims. The primary endpoint of the phase 2 study was "the number of patients who did not require escalation to a third-line IV anesthetic for RSE control within the first 24 h of ganaxolone initiation." *Id.*, 2383. All three dose cohorts met the primary endpoint: "No patient who received ganaxolone added to the standard-of-care ASMs required treatment with IV anesthetics within 24 h of ganaxolone initiation (Table 2)." *Id.*, 2385. 82% of the treated patients achieved the secondary endpoint and "did not require

treatment for SE with additional second-line IV ASMs or IV anesthetics through the 24h following completion of ganaxolone infusion." *Id.*, 2386. In the four-week follow-up period, "85% of evaluable patients did not have SE relapse." *Id.* The authors thus concluded that "IV ganaxolone treatment resulted in rapid seizure cessation in RSE" and that "[r]eductions in seizure burden occurred rapidly in all three ganaxolone dose cohorts." *Id.*, 2388.

C. Marinus touts the unexpected benefits of Ovid's invention

Notwithstanding Ovid's earlier-filed '817 patent, Marinus sought its own patent protection for the use of ganaxolone to treat SE. During prosecution of its applications, Petitioner relied on these phase 2 data to establish unexpected results. Specifically, three years after the priority date of the '817 patent, in August 2019, Petitioner filed U.S. Provisional Application No. 62/882,648 ("the '648 provisional application"), entitled "Ganaxolone for Use in Treatment of Status Epilepticus." *See* Ex. 2006, 1-2, 15, 18. In that provisional application, Petitioner stated that "[t]here is an unmet medical need for therapeutics effective against treatment-resistant form of SE," and that "[i]t is an object of the invention to provide a treatment for status epilepticus." *Id.*, 21. Marinus filed several applications claiming the benefit of this provisional application, including U.S. Application Nos. 17/186,569[2] and

[2] U.S. App. No. 17/186,659 later issued as U.S. Patent No. 11,110,100.

17/729,427.[3] During prosecution of these applications, the Office repeatedly rejected pending claims[4] as obvious over the U.S. national stage entry of Zhang (US2016/0228454), which is the primary reference asserted by Petitioner in this proceeding. To overcome those rejections, Applicant submitted identical declarations from a Marinus scientist. Ex. 2007, 29-32; Ex. 2008, 25-28. The Marinus scientist stated that "we initially believed that a high ganaxolone exposure for a long treatment period of at least 4 days duration, would be required to break SE, *i.e.*, stop seizures and prevent seizures from rapidly returning was ganaxolone was discontinued." Ex. 2007, 30 at ¶ 7; Ex. 2008, 26 at ¶ 7. Despite that belief, the Marinus scientist stated that it was "completely unexpected" that maintaining a plasma concentration of about 500 ng/mL to about 1000 ng/mL ganaxolone for about 8 to about 12 hours was able to achieve "rapid and persistent suppression of SE." Ex. 2007, 31 at ¶¶ 8-10; Ex. 2008, 27 at ¶¶ 8-10. This result was "completely contrary" to Marinus' expectations. Ex. 2007, 31 at ¶ 10; Ex. 2008, 27 at ¶ 10.

[3] U.S. App. No. 17,729,427 later issued as U.S. Patent No. 11,679,117.
[4] The claims pending at the time the declarations were submitted related to treating status epilepticus by administering an effective amount of ganaxolone "to produce and maintain a ganaxolone plasma concentration of about 500 ng/ml to about 1000 ng/ml for about 8 to about 12 hours." Ex. 2008, 15; *see also* Ex. 2007, 18.

IV. The ’817 Patent and Its Prosecution History

A. The specification and claims

The ’817 patent describes “[m]ethods of using allosteric modulators and/or gaboxadol or pharmaceutically acceptable salts thereof for the treatment of epileptic disorders in a subject in need thereof.” Ex. 1001, 1:24-26. Allosteric modulators include ganaxolone. *Id*., 6:22-23. In the detailed description of the invention, the specification discloses a specific embodiment: “a method of treating an epileptic disorder such as status epilepticus includes administering ganaxolone or a pharmaceutically acceptable salt thereof to a patient in need thereof.” *Id.*, 8:11-14.

There are four examples in the specification. Example 3 provides a detailed description of the “evaluation of the ability of allopregnanolone, ganaxolone, and gaboxadol to block benzodiazepine-resistant status epilepticus.” *Id.*, 35:31-37:15. As depicted in the timeline shown in Figure 2, allopregnanolone, ganaxolone, and gaboxadol were administered to rats with escalating doses (0.5 mg/kg, 2 mg/kg, 5 mg/kg, 10 mg/kg, or 20 mg/kg) at 30 min after the onset of pilocarpine-induced convulsive SE. *Id.*, Fig. 2, 35:59-61, 36:22-24. Blinded behavioral observations were performed for two hours after compound administration, and the results obtained with these compounds were compared to those obtained from vehicle-treated control rats. *Id.*, 35:61-67. As shown by Table 2 and Figures 3 and 4, administration of 20 mg/kg ganaxolone, but not that of allopregnanolone and gaboxadol, was effective to

induce significant protection against SE, characterized by no observation of further convulsive seizures after 10 min of drug administration. *Id.*, Table 2, Figs. 3 and 4. At a lower dose (10 mg/kg), ganaxolone also afforded protection against SE despite not reaching a statistically significant threshold. *Id.* Both 10 mg/kg and 20 mg/kg of ganaxolone treatment also promoted 24-hour survival of the experimental animals, although the effects were not statistically significant. *Id.* Furthermore, as shown in Figure 5, all doses of ganaxolone examined, except the lowest dose (0.5 mg/kg), reduced the number of observed seizures after treatment. *Id.*, Fig. 5.

Example 4 describes a "prospective study for the characterization of the ability of allopregnanolone, ganaxolone, and gaboxadol to block benzodiazepine-resistant status epilepticus." *Id.*, 37:17-22. This study builds upon Example 3 and is designed to further examine the potential synergistic effects of gaboxadol with other compounds, including ganaxolone, against benzodiazepine-resistant SE in the lithium-pilocarpine rat SE model. *Id.*, 37:28-32.

The claims challenged by Petitioner include dependent claims 22 and 25-31, which all depend from independent claim 21. Independent claim 21 recites:

> 21. A method of treating status epilepticus comprising administering to a patient in need thereof a pharmaceutical composition comprising ganaxolone or a pharmaceutically acceptable slat thereof wherein the pharmaceutical composition is administered intravenously.

Ex. 1001, claim 21. Claim 22 further recites that "the pharmaceutical composition provides improvement to the patient after administration for more than 8 hours." *Id.*, claim 22. Claims 25-31 further recite that "the patient is administered" specific dose ranges of ganaxolone (i.e., 500 to 1000 mg/day (claim 25); 625 mg to 650 mg/day (claim 26); 650 mg to 675 mg/day (claim 27); 675 to 700 mg/day (claim 28); 625 to 700 mg/day (claim 29); 700 mg to 725 mg/day (claim 30); 1025 mg to 1050 mg (claim 31)). *Id.*, claims 25-31.

B. Prosecution history

The application leading to the '817 patent was filed on September 17, 2020, as U.S. Patent Application No. 17/024,127. It claims the benefit of priority to five continuation applications and two U.S. provisional applications, the earliest filed on August 11, 2016. Ex. 1001, 1.

Two of the applications in this patent family resulted in patents that also claim the use of ganaxolone to treat other types of epileptic disorders, including CDKL5 disorder (Ex. 1024) and PCDH19-related epilepsy (Ex. 1023). The same Examiner who examined the application that led to the '817 patent, Primary Examiner Rei-Tsang Shiao, Ph.D, examined these two applications. These earlier applications were rigorously examined by Examiner Shiao, who considered the same references that were presented and considered during prosecution of the '817 patent, including Zhang (Ex. 2009, 4; Ex. 2010, 4), and issued multiple Office Actions with

obviousness, enablement, and double patenting rejections. Exs. 1026, 1027. By the time Examiner Shiao examined the application leading to the ’817 patent, he had extensive familiarity with the use of ganaxolone for treating seizures and with the relevant art in the field.

On January 6, 2021, the Applicant submitted an IDS that listed WO 2016/127170 A1 assigned to Petitioner, which is the same Zhang reference asserted in the Petition, and U.S. Patent App. Publication No. US2016/0228454 A1, which is the U.S. national stage entry of Zhang. Ex. 1002, 18, 19.

On February 8, 2021, an attorney from Hogan Lovells US LLP filed a “Third Party Pre-Issuance Submission Under 37 C.F.R. § 1.290” on behalf of an unidentified third party. Ex. 1002, 37-53. The Third-Party Submission and accompanying claim chart relied on eight documents that the third party contended “demonstrate that, well before the earliest possible filing date of U.S. Application No. 17/024,127 (the ‘’127 Application’), it was known in the art that ***ganaxolone*** can effectively ***treat status epilepticus*** (‘SE’).” *Id.*, 39. As shown in the chart below, three of the documents are being asserted here.

TPS Doc. #	Name	Ex. in PGR	Used in Grounds
1	Carter et al., Characterization of the Anticonvulsant Properties of Ganaxolone (CCD 1042; 3a-Hydroxy-3b-methyl-5a-pregnan-20-one), a Selective, High-Affinity, Steroid Modulator of the gamma-Aminobutyric $Acid_A$ Receptor, The Journal of Pharmacology and Experimental Therapeutics, 280(3): 1284-1295 (1997)	1028	N/A
2	WO 2016/127170 (International Application No.: PCT/US2016/016977) ("Zhang")	1009	1-4
3	WO 2007/062266 (International Application No.: PCT/US2006/045626) ("Shaw")	N/A	N/A
4	Saporito et al., Intravenous Administration of Ganaxolone Attenuates Electroencephalographic Seizures in a Diazepam Resistant Model of Status Epilepticus, Neurobiology, 86 (16 supplement), published April 4, 2016 ("Saporito A2")	1029	N/A
5	Saporito et al., Ganaxolone Administered Intravenously Prevents Behavioral Seizures and Promotes Survival in the Rat Lithium-Pilocarpine Model of Status Epilepticus, Neurobiology, 86 (16 supplement), published April 4, 2016 ("Saporito A1")	1030	N/A
6	"Marinus Pharmaceuticals Doses First Subject in Phase 1 Clinical Trial for Ganaxolone IV," Published on June 22, 2016, Available at: https://ir.marinuspharma.com/news/news-details/2016/Marinus-Pharmaceuticals-Doses-First -Subject-in-Phase-1-Clinical-Trial-for-Ganaxolone-IV/default.aspx ("Marinus's Phase I Press Release")	1022	4

7	"Marinus Pharmaceuticals Receives FDA Orphan Drug Designation for Ganaxolone IV to Treat Status Epilepticus," Published on April 15, 2016, Available at: https://ir.marinuspharma.com/news/news-details/2016/Marinus-Pharmaceuticals-Receives-FDA-Orphan-Drug-Designation-for-Ganaxolone-IV-to-Treat-Status-Epilepticus/default.aspx ("Marinus's Orphan Drug Press Release")	1011	4
8	Chez, "Ganaxolone Therapy Improves Interictal EEG and Seizure Control in Lennox Gastaut Syndrome in Patients with PCDH19 and CDKL5," Annals of Neurol. 80 (Suppl 20) published October 26, 2016	1031	N/A

On April 4, 2022, the Examiner issued a non-final Office Action, rejecting the then-pending claims for obviousness-type double patenting over claim 1 of U.S. Patent No. 10,799,485 and claims 1-13 of U.S. Patent No. 10,603,308. Ex. 1002, 87-91. On the same day, the Examiner also entered a PTO/SB/429 third-party submission form that had been signed by the Examiner on February 18, 2022. *Id.*, 95-97. The PTO/SB/429 form states that "all references considered except where lined through." *Id.* None of the references listed in the PTO/SB/429 form were lined through, indicating that the Examiner considered all the references of the Third-Party Submission—including, most notably, Zhang.

The Applicant filed terminal disclaimers on April 19, 2022, to obviate the double patenting rejections, and filed a supplemental response on May 11, 2022, to present eleven additional claims for examination. *Id.*, 139-141, 145-150.

On June 13, 2022, the Examiner issued a Notice of Allowance, allowing all pending claims. *Id.*, 160-167. The issue fee was paid on June 14, 2022. *Id.*, 181-182. On June 21, 2022, the Examiner entered another signed PTO/SB/429 third-party submission form, where documents 1 and 4-7 from the third-party submission were stricken through. *Id.*, 183-185. The Examiner did not, however, strike through documents 2 (Zhang), 3, and 8 on this form, indicating that at least these three documents were considered by the Examiner during prosecution. *Id.* Again, document 2 from the third-party submission is the same Zhang reference that the Petitioner asserts here. The Examiner did not provide any explanation in subsequent office communications as to why a new signed PTO/SB/429 form was entered;[5] nor did the Examiner indicate that the new PTO/SB/429 form would supersede the earlier entered PTO/SB/429 form.

On June 24, 2022, the Examiner issued another Notice of Allowance, allowing claims 1-20, and on June 28, 2022, the Examiner issued yet another Notice of Allowance, allowing pending claims 1-31. *Id.*, 186-190.

[5] According to the MPEP, when "an examiner believes a submission is non-compliant (e.g., the examiner believes a submitted document is not a publication), the examiner should immediately consult the screener or other appropriate TC point of contact. If as a result of such consultation it is determined that the examiner should not consider a listed document, the examiner should strike through the document to indicate that the examiner did not consider either the document or its accompanying concise description." MPEP § 1134.01.

V. Petitioner's Asserted References

A. Zhang (Ex. 1009)

Zhang (WO 2016/127170 A1) is a Marinus PCT publication titled "Intravenous Ganaxolone Formulations and Their Use in Treating Status Epilepticus and Other Seizures Disorders" and focuses on intravenous ganaxolone formulations. Specifically, Zhang's "disclosure provides an injectable ganaxolone formulation comprising ganaxolone, sulfobutyl ethyl-β-cyclodextrin; and water." Ex. 1009, ¶ [0005]; *see also id.*, ¶¶ [0064]-[0068] ("Lyophilized Beta-Cyclodextrin-Ganaxolone Formulations."). Zhang broadly identifies a variety of potential uses for the formulations, ranging from a seizure disorder to traumatic brain injury to seizures arising from neurodegenerative disorders, such as Parkinson's disease Ex. 1009, 1, ¶¶ [0005]-[0006]; *see also id.*, ¶¶ [0069]-[0073]. Zhang also contemplates combination treatment with its formulations. Ex. 1009, ¶¶ [0090]-[0103] ("Combination Treatment").

Zhang was identified to the Office by Patent Owner and is listed on the face of the '817 patent. Ex. 1001, 2; Ex. 1002, 19, 115, 183. Zhang is also the same as document 2 submitted in the Third-Party Submission filed during the '817 patent's prosecution. Ex. 1002, 38; *supra*, § IV.B.

As relevant to the challenged claims, Zhang does not disclose administering ganaxolone to treat a human patient suffering from SE (as required by claims 22 and

25-31), improvement to a patient after administration for more than 8 hours (as required by claim 22), or any of the specific doses recited in claims 25-31.

Instead, Zhang broadly indicates that its ganaxolone formulations can be used to treat the following 31 diseases or disorders: status epilepticus, refractory status epilepticus, or super-refractory status epilepticus; PCDH19 female pediatric epilepsy; seizures including acute repetitive seizures, cluster seizures, infantile spasms, Lennox-Gastaut syndrome, West syndrome, catamenial epilepsy; provoked seizures resulting from low blood sugar, electrolyte imbalance, high fever, brain infection (such as brain infections due to encephalitis, malaria, meningitis, toxoplasmosis, or amoebic infection), adverse reaction of prescription drugs, or alcohol or drug overdose; seizures arising from neurodegenerative disorders including Parkinson's disease, Alzheimer's Disease, Amyotrophic Lateral Sclerosis, and Huntington's disease; seizures arising from inflammatory disorders such as multiple sclerosis; and seizure disorders arising from lysosomal storage disorders, including Neimann-Pick-C, Tay Sachs, Batten, Sandhoff, and Gaucher disease. Ex. 1009, ¶¶ [0069]-[0073].

Zhang includes eight examples that discuss formulations of ganaxolone (examples 1-6), studies of the plasma levels of ganaxolone in rats after infusion with a ganaxolone-CAPTISOL solution (example 7), and the effect of these ganaxolone

formulations on rats in a pilocarpine-induced status epilepticus model (example 8). *Id.*, ¶¶ [0104]-[0136].

In example 8, rats with lithium-pilocarpine-induced SE were dosed with vehicle (30% CAPTISOL), allopregnanolone (15 mg/kg), or a CAPTISOL-ganaxolone formulation administered intravenously (12 or 15 mg/kg) either 15 or 60 minutes post SE-onset. *Id.*, ¶¶ [0117], [0127]. The rats used in the study weighed between 269 and 351 grams; therefore, the most ganaxolone administered to a rat in this study was 5.265 mg (15 mg/kg x .351 kg). *Id.*, ¶ [0120].

"Regardless of frequency range, the vehicle groups showed little reduction in EEG power from the time of dosing to approximately 2 h post dosing, then EEG power declined towards baseline from 2-5 h post dosing." *Id.*, ¶ [0132]. "Allopregnanolone at 15 mg/kg, 15 minutes post-seizure onset, produced a strong reduction in SE up to 1 h post dosing that gradually abated" and, "[a]t 2 h post dosing, SE in this group was nearly back to the vehicle level. *Id.*, ¶ [0133]. "After a 60 [minute] dosing delay, there was strong reduction in SE for the first 15 [minutes] after dosing in the 0-5 and 5-10 Hz frequency range," after which "SE returned back to the vehicle by 2 h post dosing and remained there." *Id.*

"Ganaxolone at 12 and 15 mg/kg produced qualitatively similar results." *Id.*, [0134]. When dosed 15 minutes after SE-onset, ganaxolone "reduced EEG power across all frequency ranges to levels at or below baseline for at up to 5 h." *Id.*,

¶ [0135]. "When dosed at 60 [minutes] post SE-onset, EEG power was also strongly reduced but not below the baseline for frequencies up to 70 Hz." *Id.*, ¶ [0136]. Zhang reports no EEG data beyond 5 hours post administration of ganaxolone.

B. Saporito P1 (Ex. 1013)

Petitioner's Exhibit 1013 ("Saporito P1") is an undated document titled "Ganaxolone Administered Intravenously Prevents Behavioral Seizures and Promotes Survival in the Rat Lithium-Pilocarpine Model of Status Epilepticus." Ex. 1013, 1.

Saporito P1 reports the percentage of rats protected from seizure after administration of a vehicle, 6, 9, and 12 mg/kg ganaxolone, or 15 mg/kg allopregnanolone. *See* Ex. 1013, Fig. 2. Saporito P1 also provides the survival rate in rats 24 hours after administration of a vehicle, 6, 9, and 12 mg/kg ganaxolone, or 15 mg/kg allopregnanolone. *See id.*, Fig. 3.

C. Saporito P2 (Ex. 1014)

Petitioner's Exhibit 1014 ("Saporito P2") is an undated document titled "Intravenous Administration of Ganaxolone Attenuates Electroencephalographic Seizures in a Diazepam Resistant Model of Status Epilepticus." Ex. 1014, 1.

Saporito P2 reports the EEG seizure response in rats measured just over 5 hours after administration of a vehicle, 12 and 15 mg/kg ganaxolone, and 15 mg/kg allopregnanolone. *Id.*, Figs. 3-4.

D. Marinus's Orphan Drug Press Release (Ex. 1011)

Petitioner's Exhibit 1011 is a press release dated April 15, 2016, titled "Marinus Pharmaceuticals Receives FDA Orphan Drug Designation for Ganaxolone IV to Treat Status Epilepticus." Ex. 1011, 1. Marinus's Orphan Drug Press Release states that "the U.S. Food and Drug Administration (FDA) has granted Orphan Drug Designation to the intravenous (IV) formulation of [Marinus's] CNS-selective $GABA_A$ modulator, ganaxolone, for the treatment of status epilepticus." *Id.*, 1. The Orphan Drug Press Release also notes that "[a] Phase 1 clinical trial evaluating the safety, tolerability and pharmacokinetics of ganaxolone IV is expected to initiate in the first half of 2016." *Id.* In the press release, Marinus's CEO also states that SE is a "difficult to treat seizure disorder with limited treatment options." *Id.*

E. Marinus's Phase I Press Release (Ex. 1022)

Petitioner's Exhibit 1022 is a press release dated June 22, 2016, titled "Marinus Pharmaceuticals Doses First Subject in Phase 1 Clinical Trial for Ganaxolone IV." Ex. 1022, 1. Marinus's Phase I Press Release states that on June 22, 2016, Marinus "has dosed the first subject in its Phase 1 clinical trial of ganaxolone IV, an intravenous (IV) formulation of Marinus' CNS-selective GABAA modulator, for the treatment of status epilepticus (SE)." *Id.* The press release also notes that the "study is designed to evaluate the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of ganaxolone IV in healthy volunteers, with

data anticipated in the second half of 2016." *Id.* Specifically, the press release states that the Phase 1 study "will include a dose escalation of a bolus dosage of ganaxolone IV and a bolus dose of ganaxolone IV, followed by continuous infusion." *Id.*

VI. Person of Ordinary Skill in the Art

Solely for the purposes of this Preliminary Response, Patent Owner does not dispute Petitioner's definition of a skilled artisan.

VII. Dr. Rogawski's Declaration

The Board should not credit Dr. Rogawski's declaration for two independent reasons: bias and failure to render an independent opinion.

First, Petitioner failed to disclose the full extent of its relationship with Dr. Michael A. Rogawski in the Petition and accompanying exhibits. Dr. Rogawski has served on Marinus's Scientific Advisory Board since at least April 30, 2020. *See* Ex. 2011, 2; *see also* Marinus Pharmaceuticals Announces Formation of Scientific Advisory Board, https://ir.marinuspharma.com/news/news-details/2020/Marinus-Pharmaceuticals-Announces-Formation-of-Scientific-Advisory-Board/default.aspx (last accessed June 11, 2023); Ex. 2012. Dr. Rogawski's work and papers are also repeatedly cited in an article reporting the results of Petitioner's phase 2 clinical study regarding the administration of ganaxolone to treat RSE. *See* Ex. 2003, 2390 (reference numbers 25, 37, and 40). Neither the Petition nor Dr. Rogawski's expert declaration and *curriculum vitae* discloses this relationship. *See, e.g.*, Pet., 3; Ex.

1003. In such instances of a failure to disclose the full extent of the relationship of a party's declarant, the Board has afforded little weight to the declarant's testimony, especially when it is not sufficiently corroborated. *Blasters, Inc. v. Waterblasting, LLC*, IPR2018-00504, Paper 26 at 23 (PTAB July 16, 2019) (attributing little to no weight to Petitioner's declarant's testimony that was not sufficiently corroborated where declarant held position and had equity stake in Petitioner); *see also Polaris Wireless, Inc. v. Trueposition, Inc.*, IPR2013-00323, Paper 62 at 39 (PTAB Nov. 3, 2014) (appropriately weighing Petitioner's declarant's testimony in light of declarant's position as Vice President of Petitioner with significant financial interests).

Second, and independently, Dr. Rogawski is nothing but a mouthpiece for Petitioner's attorneys. As shown in the table below, Dr. Rogawski's declaration is simply a word-for-word copy of the Petition. Indeed, there are several instances relating to the challenged claims where Dr. Rogawski's declaration merely repeats the conclusory attorney argument in the Petition verbatim or near-verbatim, without providing any supporting evidence or technical reasoning to support those assertions.

Petition	Rogawski Declaration (Ex. 1003)
Pet., 19: Seeing these results in the rat pilocarpine model, persons skilled in the art would have reasonably believed that ganaxolone would show efficacy	¶ 40: Seeing these results in the rat pilocarpine model, persons skilled in the art would have reasonably believed that ganaxolone would show efficacy

Petition	Rogawski Declaration (Ex. 1003)
in treating human SE as well, for the reasons discussed above.	in treating human SE as well, for the reasons discussed above.
Pet., 45: While Zhang does not expressly disclose that its ganaxolone formulations provide "improvement to the patient after administration for more than 8 hours," this would be the natural result of administering them to a patient with SE, as taught by Zhang. As such, Zhang inherently teaches the limitation of claim 22.	¶ 93: Zhang does not expressly state the composition provides improvement for more than 8 hours after administration. In Zhang's Example 8, the rats experiencing SE were sacrificed after 5 hours and, so, even though some effects of ganaxolone were sustained for the entire 5 hours, because the experiment was stopped at 5 hours, there is no data demonstrating a response "for more than 8 hours." To the extent that improvement to the patient were to occur after that time period, however, it would be the natural result of administering the ganaxolone formulations in the manner taught in Zhang.
Pet. 45: Moreover, Zhang states: "Methods of treatment also include administering multiple injections of the β-cyclodextrin-ganaxolone injectable formulation over a period of 1 to 10 days. The injections may be given at intervals of 1 to 24 hours." A skilled artisan would immediately recognize that if a single bolus treatment for SE suppresses seizures for up to 2 hours as ganaxolone is clearly shown to do in Tables 6 and 7, then the treatment could be repeated at intervals of 2 hours to provide sustained treatment for more than 8 hours.	¶ 94: Moreover, Zhang states: "[m]ethods of treatment also include administering multiple injections of the β-cyclodextrin-ganaxolone injectable formulation over a period of 1 to 10 days. The injections may be given at intervals of 1 to 24 hours." (Zhang, Ex. 1009, ¶ [0074].) A skilled artisan would immediately recognize that if a single bolus treatment for SE suppresses seizures for up to 2 hours as ganaxolone is clearly shown to do in Tables 6 and 7, then the treatment could be repeated at intervals of 2 hours to provide sustained treatment for more than 8 hours.
Pet. 48: To the extent that Zhang does not anticipate claims 1–3, 10–17, and 19–31, however, they are obvious over	¶ 107: If the Zhang Publication does not anticipate all the limitations of claims 1–3, 10–17, and 19–31, it at

Petition	Rogawski Declaration (Ex. 1003)
Zhang, at least because Zhang suggests the subject matter of claims 1–3, 10–17, and 19–31, as described below.	least suggests them by the same teachings I laid out above in Section VI. C.
Pet., 48-49: A POSA would have, based on common knowledge, supplied any limitations that Zhang does not teach directly, and a POSA would have arrived at the recited claims with a reasonable expectation of success. For example, as Dr. Rogawski explains, the rat lithium-pilocarpine model was, and is, considered to be a widely accepted model to identify potential treatments for SE. Example 8 of Zhang teaches that the IV-administered ganaxolone formulations terminates SE in the model.	¶ 108: Based on the teachings in Zhang, those of skill in the art would have had a reasonable expectation of success in achieving the claimed methods. As discussed above in Section IV, the rat lithium-pilocarpine model was, and is, a widely accepted model to identify potential treatments for SE. Example 8 of Zhang teaches that IV-administered ganaxolone terminates SE, i.e., ganaxolone gave a positive result in the model.
Pet., 49: And, based on Zhang's teachings, including, for example, the results described in Example 8, a POSA would have had a reasonable expectation of success at arriving at the claimed methods of treating SE with ganaxolone—whether in a rat patient or a human patient.	¶ 109: Thus, a person of skill in the art reading Zhang would at least have had a reasonable expectation of success in achieving the claimed methods of treating SE with ganaxolone, whether in a rat patient or a human patient.
Pet., 53: And, as noted above, a POSA would have arrived at the concentrations, dosing amounts and/or patient outcomes based on Marinus's publications. If not, however, a person of skill in the art would certainly not have arrived at them based on the only dose (20 mg/kg) for which data is presented the '817 patent (Example 3) that could possibly suggest efficacy for treating SE in a rat. Therefore, to the extent that Marinus's publications do not render claims 21–31 anticipated or	¶ 159: A person of skill in the art would have arrived at these dosing amounts and administration schedules based on Marinus's publications. If not, however, a person of skill in the art would certainly not have arrived at them based on the only dose (20 mg/kg) for which data presented in the '817 patent (Example 3) could possibly suggest efficacy for treating SE in a rat. Therefore, to the extent that Marinus's publications do not render these concentrations, doses, and

Petition	Rogawski Declaration (Ex. 1003)
obvious, the '817 patent does not enable them.	administration schedules anticipated or obvious, the '817 patent does not enable them.

Accordingly, the Board should afford this testimony little to no weight. *See Xerox Corp. v. Bytemark, Inc.*, IPR2022-00624, Paper 12 at 5 (PTAB Feb. 10, 2023) (*sua sponte* Director Review) (finding that "the cited declaration testimony is conclusory and unsupported, adds little to the conclusory assertion for which it is offered to support, and is entitled to little weight under 37 C.F.R.§ 42.65(a)" (internal quotation marks omitted)); *Xerox Corp. v. Bytemark, Inc.*, IPR2022-00624, Paper 9 at 15 (PTAB Aug. 24, 2022) (finding expert declaration that "merely repeats, *verbatim*, the conclusory assertion for which it is offered to support" and that "does not cite to any additional supporting evidence or provide any technical reasoning to support his statement" is "entitled to little weight"); *see also Motorola Mobility, LLC v. Int'l Trade Comm'n*, 737 F.3d 1345, 1349-50 (Fed. Cir. 2013) (expert's single sentence opinion, without explanation, failed to show that a prior-art device inherently performed the claimed functionality).

VIII. Claim Construction

A. "Treating status epilepticus comprising administering to a patient in need thereof" (Claims 22 and 25-31)

"Treating status epilepticus comprising administering to a patient in need thereof" in claims 22 and 25-31 means "treating a human patient suffering from SE."

This construction is supported by the intrinsic record. *See Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005) (en banc).

The claim language itself demands this construction. The challenged claims require that the method be performed on "a patient in need thereof" and that the method be used for "treating status epilepticus." The claim preamble thus "sets forth the objective method, and the body of the claim directs that the method be performed on someone 'in need.'" *See Jansen v. Rexall Sundown, Inc.*, 342 F.3d 1329, 1332 (Fed. Cir. 2003); *see also Grünenthal GmbH v. Antecip Bioventures II LLC*, PGR2019-00028, Paper 6 at 8 (PTAB Aug. 20, 2019) ("In particular, for method-of-treatment claims, when the preamble provides antecedent basis for a phrase such as 'a patient in need thereof' in the body of the claim, the preamble is limiting, but, when the preamble is merely a statement of purpose and intended result, it is non-limiting." (internal quotation marks omitted)). A skilled artisan would thus understand that the "someone 'in need'" would be a human patient suffering from SE, and is not a rat or other animal receiving ganaxolone for research purposes.

The specification further supports this construction. Specifically, the specification refers to "treating" in the context of addressing *clinical* and *subclinical* symptoms of a disease or a condition, and not in the context of preclinical, research uses. Ex. 1001, 29:29-51. The specification notes that "The benefit to a subject to be treated [i.e., a human patient suffering from SE] may be statistically significant,

mathematically significant, or at least perceptible to the subject and/or the *physician*." *Id*., 29:46-48 (emphasis added). The specification does not correlate "treating" and "treatment" to using rats for research purposes. Similarly, the specification refers to "effective amount" and "therapeutically effective amount" in terms of a "disorder, disease, or condition *being treated.*" Ex. 1001, 29:52-56 (emphasis added).

The Examples further confirm this construction. Specifically, Examples 1 and 2 refer throughout to "treatment" in the context of giving an active agent to human patients. Contrast this with Examples 3 and 4 where several active agents, including ganaxolone, are "administered" to rats. These examples do not refer to treating the rats but rather state that "[t]he dose of each of the investigational compounds will be administered to rats." *E.g.*, Ex. 1001, 38:22-24.

Moreover, for claims 25-31, a skilled artisan would understand that the doses recited in these claims (ranging from 500 mg to 1050 mg) are at least 130 times larger than the doses administered to rats in the '817 patent's examples and would likely kill a rat. A skilled artisan would thus understand that in the context of claims 22 and 25-31 and the specification, the claim term refers to administering doses of ganaxolone to a *human* patient, not a rat.

For instance, Example 3 of the '817 patent reports that the highest dose of ganaxolone administered to a rat was 2.5 mg (20 mg/kg x 0.125 kg). *See* Ex. 1001,

35:44-48 ("male Sprague Dawley rats (n = 10 time or treatment/group, 100-125 g; Charles Rivers Laboratories)"); *id.*, 36:22-24 ("The doses administered for allopregnanolone, ganaxolone, or gaboxadol are 0.5 mg/kg, 2 mg/kg, 5 mg/kg, 10 mg/kg, or 20 mg/kg."). The lowest dose recited in claims 25-31 (500 mg/day) is 200 times higher than the highest amount of ganaxolone given to a rat in example 3. Similarly, in Example 4 of the '817 patent, the highest dose of ganaxolone administered to a rat was 3.75 mg (30 mg/kg x 0.125 kg). *See* Ex. 1001, 37:62-66 ("male Sprague Dawley rats (n = 13 time or treatment group; 100-125 g at arrival from Charles Rivers Laboratories)"); *id.*, 37:45-60 (Table 2 providing highest dose of ganaxolone (GNX) as 30 mg/kg). Thus, the lowest dose recited in claims 25-31 is 133 times higher than the highest amount of ganaxolone given to a rat in Example 4. Based on the doses of ganaxolone administered in the asserted claims being so much higher than the doses administered to rats in Examples 3 and 4 of the '817 patent, a skilled artisan would understand that administering the claimed high doses of ganaxolone to a rat would be lethal to the rat and that the patients in the claims must be human.

Patent Owner's construction is also consistent with the '817 patent's prosecution history. Nothing in the prosecution history correlates "treating" to using rats for research purposes. And, as Petitioner admits, neither the Applicant nor Examiner provided such a construction during prosecution. Pet., 85.

Petitioner improperly construes the term "patient" in a vacuum, divorced from the context of the claims and written description. Pet., 34-35; *see Eon Corp. IP Holdings v. Silver Spring Networks*, 815 F.3d 1314, 1320 (Fed. Cir. 2016) ("A party is . . . not entitled to a claim construction divorced from the context of the written description and prosecution history." (internal quotation marks omitted)); *Medrad, Inc. v. MRI Devices Corp.*, 401 F.3d 1313, 1319 (Fed. Cir. 2005) (finding that a claim term's "ordinary meaning" is not something that is determined "in a vacuum."). That is, Marinus fails to consider that the "patient" at issue must be "in need thereof," *i.e.*, in need of treatment for SE. Rather, Petitioner focuses on a single passage in the '817 patent that simply states that "[p]atient . . . *include[s]*" multiple species. Ex. 1001, 32:65-67. "Include" does not mean "require," and, as shown above, "patient" must be read in the context of its use. In the challenged claims, "patient" refers to a "human" patient in need of treatment. And in the context of claims 22 and 25-31, the recited doses for human treatment further highlight Petitioner's selective and unsupported construction. Only Patent Owner's proposed construction for "treating status epilepticus comprising administering to a patient in need thereof" considers the full context of the claim term and meets *Phillips*' requirement that the claim language be viewed in the context of the specification from the skilled artisan's perspective.

IX. Petitioner Has Not Established That It Is More Likely Than Not That Any Challenged Claim Is Unpatentable.

A. Ground 1: Petitioner has not demonstrated that Zhang anticipates claims 22 and 25-31.

1. Zhang does not disclose "treating status epilepticus comprising administering to a patient in need thereof" from claims 22 and 25-31.

Claims 22 and 25-31 depend from claim 21, which recites "administering to a patient in need thereof a pharmaceutical composition comprising ganaxolone or a pharmaceutically acceptable salt thereof wherein the pharmaceutical composition is administered intravenously." Under the correct construction, "treating status epilepticus comprising administering to a patient in need thereof" requires treating a *human* patient suffering from SE. *See supra* § VIII.A. Petitioner, however, points to nothing in Zhang that describes treating a human patient, let alone one suffering from SE. Pet., 35-38. Petitioner cites only to ¶¶ [0005] and [0031], both of which relate to a formulation of ganaxolone, and ¶¶ [0104]-[0136], which are directed to the Examples, none of which describe treating a human patient suffering from SE. Nor can Petitioner point to any relevant disclosure in Zhang that describes intravenously administering ganaxolone to a human patient suffering from SE. Thus, for this reason alone, Petitioner has not established that Zhang anticipates any of the challenged claims, all of which depend from claim 21.

Petitioner attempts to gloss over the absence of any express or inherent disclosure and instead asserts that, upon seeing the rat data disclosed in Zhang, "a person skilled in the art would have *reasonably believed* that ganaxolone would show efficacy in treatment of SE in human patient as well." Pet., 38 (emphasis added). But it is inappropriate to rely on the knowledge of a skilled artisan to supply missing claim limitations when evaluating anticipation. *See, e.g.*, *Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1548 (Fed. Cir. 1983); *Sandoz Inc. v. Pharmacyclics LLC*, IPR2019-00865, Paper 8 at 20-21 (PTAB Sept. 26, 2019) (finding petitioner "improperly relies on the knowledge of the POSA to supply the limitations recited in these claims"). Moreover, as discussed above in Section VII, Petitioner's alleged evidence on this point should be afforded little weight because it is based on attorney argument and supported by conclusory expert testimony that merely repeats the attorney argument near verbatim. *Compare* Pet., 37-38 *with* Ex. 1003, ¶¶ 40, 68. For this additional reason, Petitioner has not established that Zhang describes "treating status epilepticus comprising administering to a patient in need thereof" under the correct construction.

2. Zhang does not describe "improvement to the patient after administration for more than 8 hours" from claim 22.

Claim 22 further recites that the claimed pharmaceutical composition administered intravenously provides "improvement to the patient after

administration for more than 8 hours." Petitioner and Dr. Rogawski concede that "Zhang does not expressly disclose that its ganaxolone formulation" provides this therapeutic effect. Pet., 45; *see also* Ex. 1003, ¶ 93. Dr. Rogawski explains that, "[i]n Zhang's Example 8, the rats experiencing SE were sacrificed after 5 hours and, so, even though some effects of ganaxolone were sustained for the entire 5 hours, because the experiment was stopped at 5 hours, there is no data demonstrating a response 'for more than 8 hours.'" Ex. 1003, ¶ 93. Petitioner must thus resort to inherency, asserting that "to the extent that improvement to the patient were to occur after [5 hours], however, it would be the natural result of administering the ganaxolone formations in the manner taught in Zhang." Pet., 44-45; Ex. 1003, ¶ 93. Neither Petitioner nor Dr. Rogawski, however, cites to any evidence in support. For this reason alone, Petitioner's argument regarding anticipation of claim 22 is without merit. *See Eve Energy Co. v. Varta Microbattery GmbH*, IPR2022-01486, Paper 17 at 14-15 (PTAB Mar. 14, 2023) ("Attorney argument is not evidence." (citation omitted)); *Xerox*, IPR2022-00624, Paper 12 at 5.

Petitioner's inherency argument that the 8-hour limitation "would be the natural result of administering [Zhang's ganaxolone formulations] to a patient with SE" also fails to meet the legal standard. Pet., 45. A showing of inherent anticipation requires that the limitation inevitably occur, not just might occur. *Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 960-61 (Fed. Cir. 2014) (affirming judgment that claims

were not inherently anticipated where the prior art only showed that the limitation might occur, not that it inevitably occurred); *Galderma Labs., L.P. v. Teva Pharms. USA, Inc.*, 799 F. App'x 838, 845-46 (Fed. Cir. 2020) (reversing judgment of inherent anticipation where achieving claimed efficacy limitations was not inevitable). As mentioned, Petitioner points to no evidence as to why "improvement to the patient after administration for more than 8 hours" would inevitably happen based on Zhang's disclosure. *See* Pet., 44-45. Moreover, Zhang discloses that any effect of ganaxolone in reducing EEG power diminishes by 5 hours:

> However, between 2 to 5 h, EEG power above 30 Hz was not different from the vehicle group, indicating it was also not significantly different from the baseline EEG power level. Note also that at the higher frequency ranges, EEG power in the vehicle groups returned towards baseline after 2 h, so that differences between the GNX and vehicle groups were not significant.
>
> . . .
>
> Again, the EEG power levels were maintained at baseline for up to 5 h post dosing, however, the EEG levels of the vehicle group also returned to baseline for the frequency ranges above 30 Hz so the drug showed no effect.

Ex. 1009, ¶¶ [0135]-[0136]. Indeed, ganaxolone showed a significant reduction in seizures 3-5 hours after administration for only one low frequency group, 0-5 Hz. *See id.*, 25-26 (Tables 6 and 7). And Zhang provides no data regarding seizure reduction beyond 5 hours. Zhang therefore cannot inherently anticipate claim 22

because it does not show that the claim limitation inevitably would occur. In fact, it shows the contrary.

Moreover, as discussed above in Section VII, Dr. Rogawski's declaration on this point should be afforded little weight because it is based on attorney argument and supported by conclusory testimony that merely repeats the attorney argument near verbatim. *Compare* Pet., 44-45 *with* Ex. 1003, ¶ 93.

Petitioner's argument that the 8-hour limitation in claim 22 can be satisfied by repeated treatments of ganaxolone "at intervals of 2 hours" is also without merit for at least three reasons. Pet., 45 (citing Ex. 1009, ¶ [0074]).

First, here again, Petitioner improperly relies on what a skilled artisan allegedly would have known to fill the gaps in Zhang. Pet., 45 ("A skilled artisan would immediately recognize . . . ."). The knowledge of a skilled artisan, however, has no place in an anticipation analysis. *See*, *Connell*, 722 F.2d at 1548; *Sandoz*, IPR2019-00865, Paper No. 8 at 20-21.

Second, to draw the conclusion it does from a single general paragraph in Zhang, Petitioner necessarily resorts to improper picking and choosing from different portions of Zhang to allegedly meet this limitation. *See* Pet., 45 (citing only Ex. 1009, ¶ [0074]). To anticipate, a reference must describe every element of the claimed invention, "arranged as in the claim," and "without *any* need for picking, choosing, and combining various disclosures not directly related to each other." *Net*

MoneyIN, Inc. v. VeriSign, Inc., 545 F.3d 1359, 1369, 1371 (Fed. Cir. 2008). The Board has previously declined to institute where petitioners cobbled together various, distinct embodiments from a prior-art reference. *See, e.g.*, *Panasonic Corp. v. Optical Devices, LLC*, IPR2014-00302, Paper 9 at 13-14 (PTAB July 11, 2014) (it is not enough that the prior-art reference discloses "multiple, distinct teachings that the artisan might somehow combine to achieve the claimed invention").

After admitting that Zhang "does not expressly disclose that its ganaxolone formulations provide 'improvement to the patient after administration for more than 8 hours,'" Petitioner appears to cobble together disparate portions of Zhang's disclosure to allegedly show anticipation of claim 22. Pet., 44-45. In particular, Petitioner cites to paragraph 74 in Zhang's general disclosure, which refers to giving an injectable ganaxolone formulation at intervals of 1 to 24 hours, and states that a skilled artisan would "immediately recognize that if a single bolus treatment for SE suppresses seizures for up to 2 hours" from Tables 6 and 7 in Example 8, "then the treatment could be repeated at intervals of 2 hours to provide sustained treatment for more than 8 hours." *Id.*, 45. But the Petition cites to no support for its statement about what a skilled artisan would "immediately recognize" based on Zhang's disclosure. *Id.* Nor can Petitioner cite to any support because Zhang never ties its general disclosure of giving an injectable ganaxolone formulation "at intervals of 1 to 24 hours" to Zhang's Example 8. Ex. 1009, ¶ [0074].

The dosing schedules of paragraph 74 of Zhang are not identified as being relevant to any method of treatment, let alone treating a human patient suffering from SE. Instead, Zhang generally discusses a wide variety of treatment options, including the disease or disorder treated (e.g., "seizures, traumatic brain injury, stroke" in paragraph 74 specifically, and at least 31 diseases or disorders in Zhang generally, *see id.*, ¶¶ [0069]-[0073]), the type of administration (e.g., "intramuscularly or intravenously"), and dose amount. *id.*, ¶ [0074]. Indeed, paragraph 74 of Zhang does not even refer to treating SE, which means Petitioner improperly assumes that Zhang's reference to giving an injectable ganaxolone formulation at intervals of 1 to 24 hours refers to treating SE. Petitioner's apparent reliance on discrete portions of Zhang directed to distinct teachings precludes a finding of anticipation. *See Net MoneyIN*, 545 F.3d at 1369, 1371.

Third, Zhang's paragraph 74 states only that the β-cyclodextrin ganaxolone "injections may be given at intervals of 1 to 24 hours." Ex. 1009, ¶ [0074]. It does not say anything about treating SE or administering multiple doses of ganaxolone to treat any of the at least 31 diseases or disorders identified in Zhang, let alone SE. It also does not state that multiple treatments can prolong an anti-seizure effect from a single treatment such that there is "improvement to the patient after administration for more than 8 hours." And, notably, Petitioner provides no evidence as to why "improvement to the patient after administration for more than 8 hours" would

inevitably happen after repeated treatment or as to why a skilled artisan would "immediately recognize" that if a single treatment for SE suppresses seizures for up to 2 hours, then repeated treatments would provide sustained improvement for more than 8 hours. *See* Pet., 45; Ex. 1003, ¶ 94. Moreover, as discussed above in Section VII, Dr. Rogawski's declaration on this point should be afforded little weight because it is based on attorney argument and supported by conclusory testimony that merely repeats the attorney argument near verbatim. *Compare* Pet., 45 *with* Ex. 1003, ¶ 94.

Petitioner has thus failed to demonstrate that Zhang describes "improvement to the patient after administration for more than 8 hours" and anticipates claim 22.

3. Zhang does not describe the dose ranges in claims 25-31.

Claims 25-31 further recite administering specific dose ranges of ganaxolone to treat SE: 500 mg to 1000 mg/day (claim 25); 625 mg to 650 mg/day (claim 26); 650 mg to 675 mg/day (claim 27); 675 to 700 mg/day (claim 28); 625 to 700 mg/day (claim 29); 700 mg to 725 mg/day (claim 30); 1025 mg to 1050 mg (claim 31)). Petitioner's calculations assume that 500-1000 mg relates to 7.14-14.29 mg, 625-650 mg relates to 8.93-9.29 mg, 650-675 mg relates to 9.29-9.64 mg, 675-700 mg relates to 9.64-10 mg, 625-700 mg relates to 8.93-10 mg, 700-725 mg relates to 10-10.36 mg, and 1025-1050 mg relates to 14.64-15 mg. Zhang does not describe any of the ranges recited in claims 25-31. Specifically, there are no single embodiments

described in Zhang that fall within the scope of claims 25-31. For this reason alone, Zhang does not anticipate challenged claims 25-31.

To overcome that deficiency, Petitioner instead points to a single range of doses in paragraph 85, where Zhang states that "[i]n certain embodiments each bolus dose comprises about 1 mg/kg to about 20 mg/kg ganaxolone." Pet., 46-47 (quoting Ex. 1009, ¶ [0085]). But in doing so, Petitioner again relies on improper picking and choosing from various portions of Zhang, undermining any finding of anticipation. *Net MoneyIN*, 545 F.3d at 1369, 1371.

Nothing in Zhang ties its disclosure of bolus doses of "about 1 mg/kg to about 20 mg/kg" to any one disease state, let alone treating SE. As discussed above in Section V.A, Zhang's general disclosure is not specific to any one disease state, dosage strength, or dosing regimen. Indeed, Zhang includes numerous options beyond dose amount—it also postulates that the ganaxolone formulations could be used to treat at least 31 different diseases or disorders. *See* Ex. 1009, ¶¶ [0069]-[0073]. It also indicates that the methods of treatment "also include administering multiple injections . . . over a period of 1 to 10 days." Ex. 1009, ¶ [0074]. It also states that "The injections may be given at intervals of 1 to 24 hours" and that the injectable formulation is injected every 1 hr, for example. *Id*. Thus, in essence, Zhang's range of "from about 1 mg/kg to about 20 mg/kg" dosed every hour for one day leads to a potential dose range of about 24 mg/kg/day to about 480 mg/kg/day

(1,680 mg/day for a 70 kg adult to 33,600 mg/day for a 70 kg adult). Petitioner's narrow focus on only a single aspect of Zhang highlights its improper picking and choosing.

Moreover, paragraph 85 of Zhang generically refers to various dosing regimens of ganaxolone formulations, without tying those dosing regimens to treating any disease, let alone SE. Ex. 1009, ¶ [0085]. Petitioner again improperly assumes that Zhang's broad disclosure of a bolus dose of "about 1 mg/kg to about 20 mg/kg," which itself required improperly picking and choosing among Zhang's broader disclosure, relates to SE, despite Zhang never saying as much. Nor does paragraph 85 of Zhang describe administering any of the specific dose ranges recited in claims 25-31. *Id.* It instead provides several broad dose ranges for administering a ganaxolone formulation in the abstract, and not for any specific disease. *Id.* This level of picking and choosing from disparate paragraphs in Zhang cannot support Petitioner's anticipation challenge. *See, e.g.*, *Luye Pharma Grp. Ltd. v. Alkermes Pharma Ire. Ltd.*, IPR2016-01095, Paper 13 at 11 (PTAB Nov. 30, 2016).

B. Grounds 2-4: Petitioner has not demonstrated that claims 22 and 25-31 would have been obvious over any of the asserted references.

1. Objective indicia support the nonobviousness of claims 22 and 25-31.

The Petition is devoid of any mention of objective evidence of non-obviousness. Pet., 49 ("Ovid did not point to any objective evidence otherwise.").

As the Board has repeatedly held, "known evidence of secondary considerations should be addressed in the petition." *Robert Bosch Tool Corp. v. SD3, LLC*, IPR2016-01751, Paper 15 at 22-25, 32 (PTAB Mar. 22, 2017). Indeed, objective evidence of nonobviousness must be considered in an obviousness analysis. *See In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1075-80 (Fed. Cir. 2012); *see also Graham v. John Deere Co.*, 383 U.S. 1, 36 (1966). Petitioner's failure to address the significant objective evidence showing unexpected results, long-felt but unmet need, and failure of others dooms the Petition and supports the nonobviousness of claims 22 and 25-31 of the '817 patent. Here, the objective evidence was not only publicly available, but much of the objective evidence comes from Petitioner's own statements. Petitioner's failure to address this objective evidence supports denial. *See Robert Bosch*, IPR2016-01751, Paper 15 at 22-25, 32 (denying institution where petitioner failed to address known evidence of objective indicia).

There is a clear nexus between the objective evidence described below and the methods of treating SE by administering ganaxolone that are recited in claims 22 and 25-31, as the claimed methods have been found to be critical in treating SE through seizure cessation and reduction in seizure burden. *See* Ex. 2003, 2386, 2388; *see also WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1329 (Fed. Cir. 2016).

a. The methods of treating SE by administering ganaxolone recited in claims 22 and 25-31 demonstrate unexpected results.

The methods of treating SE by administering ganaxolone recited in claims 22 and 25-31 were found to be unexpected and critical to the claimed invention. "To be particularly probative, evidence of unexpected results must establish that there is a difference between the results obtained and those of the closest prior art, and that the difference would not have been expected by one of ordinary skill in the art at the time of the invention." *Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.*, 752 F.3d 967, 977 (Fed. Cir. 2014). While "differences in degree" of a known and expected property are not as persuasive in rebutting obviousness as differences in "kind," differences in degree may be probative, however, when they represent "a marked superiority in an expected property." *Id.* (internal quotation marks omitted); *In re Hoch*, 428 F.2d 1341, 1344 n.5 (CCPA 1970) (explaining that unexpected "differences in properties" can mean "significant difference in degree of the same property amounting to marked superiority" for purposes of evaluating unexpected results).

Statements by Petitioner and Petitioner's own work after the filing date of the '817 patent confirm that the treatment methods recited in claims 22 and 25-31 provided unexpected results over what a skilled artisan would have expected in view of Zhang. *See Knoll Pharm. Co. v. Teva Pharms. USA, Inc.*, 367 F.3d 1381, 1385

(Fed. Cir. 2004) ("Evidence [of unexpected results] developed after the patent grant is not excluded from consideration, for understanding of the full range of an invention is not always achieved at the time of filing the patent application."); *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1307 (Fed. Cir. 2011) ("We have held that evidence of unexpected results may be used to rebut a case of *prima facie* obviousness even if that evidence was obtained after the patent's filing or issue date.").

During prosecution of Petitioner's U.S. App. Nos. 17/186,569 and 17/729,427, filed three years after the effective filing date of the '817 patent, Petitioner traversed obviousness rejections over the U.S. national stage entry of Zhang (US2016/0228454) by submitting identical declarations from a Marinus scientist.[6] Ex. 2007, 29-32; Ex. 2008, 25-28. The claims pending at the time the declarations were submitted related to treating SE by administering an effective amount of ganaxolone "to produce and maintain a ganaxolone plasma concentration

[6] Petitioner's declaration was submitted by Joseph Hulihan, M.D on July 7, 2021. *See* Ex. 2007, 29; Ex. 2008, 25. Dr. Hulihan would have qualified as a skilled artisan under Petitioner's definition as of the '817 patent's filing date. *See* Ex. 2007, 29 at ¶ 1; Ex. 2008, 25 at ¶ 1 (describing Dr. Hulihan's years of experience as a neurologist and work in "clinical care, research, drug development, and medical affairs in connection with numerous neurological and psychiatric conditions, including epilepsy").

of about 500 ng/ml to about 1000 ng/ml for about 8 to about 12 hours." Ex. 2008, 15; *see also* Ex. 2007, 18. In the declarations, the scientist stated that:

> Marinus Pharmaceuticals Inc. is investigating the use of ganaxolone for treating SE. Given the complexities of SE and difficulties in treating SE, we initially believed that a *high ganaxolone exposure for a long treatment period of at least 4 days duration, would be required to break SE*, *i.e.*, stop seizures and prevent seizures from rapidly returning when ganaxolone was discontinued.

Ex. 2007, 30 at ¶ 7 (emphasis added); Ex. 2008, 26 at ¶ 7. It was thus Petitioner's expectation—and specifically a scientist who meets Petitioner's definition of a skilled artisan—that high ganaxolone exposure for at least four days would be required to "break SE" in view of Zhang being asserted against its claims. *Id.*

In an article describing a phase 2 clinical trial that examined the use of intravenous ganaxolone for the treatment of refractory SE that was "sponsored and supported by [Petitioner]," however, it was discovered that "[r]eductions in seizure burden occurred rapidly in all three ganaxolone dose cohorts" tested. Ex. 2003, 2381, 2388. During the study, the three ganaxolone dose cohorts studied included 500 mg/day (low), 650 mg/day (medium), and 713 mg/day (high). *Id.*, 2383. For each dose cohort, "ganaxolone infusion was initiated as an IV bolus (over 3 min) with continuous infusion of decreasing infusion rates for 48-96 h followed by an 18-h taper." *Id.* The primary endpoint of the study was "the number of patients who did not require escalation to a third-line IV anesthetic for RSE control within the first 24

h of ganaxolone initiation" and the study's secondary endpoints included "the number of patients who maintained SE cessation 24 h after ganaxolone taper and at week 4, time to cessation of SE, and ganaxolone safety/tolerability and pharmacokinetics." *Id.*, 2383-84.

All three dose cohorts met the primary endpoint: "No patient who received ganaxolone added to the standard-of-care ASMs required treatment with IV anesthetics within 24 h of ganaxolone initiation (Table 2)." *Id.*, 2385; *see also id.*, 2386 (Table 2). Moreover, 94% of patients (16 of 17 patients) "achieved and maintained SE cessation for 24 h following ganaxolone initiation as determined by trial-site investigator assessment (Table 2)" and 82% (14 of 17 patients) "did not require treatment for SE with additional second-line IV ASMs or IV anesthetics through 24 h following competition of the ganaxolone infusion (Table 2)." *Id.*, 2386. And in the follow-up period after ganaxolone discontinuations, "85% of evaluable patients did not have SE relapse." *Id.*

The authors concluded that "IV ganaxolone treatment resulted in rapid seizure cessation in RSE" and that "[r]eductions in seizure burden occurred rapidly in all three ganaxolone dose cohorts." *Id.*, 2388. The authors also stated that it was "important to note that SE did not recur in the majority of patients, even after discontinuation of ganaxolone infusion." *Id.* Overall, the authors reported that the

data "suggest that ganaxolone has the potential to provide significant clinical benefit to patients with RSE." *Id.*

The "rapid" seizure cessation and reduction in seizure burden and lack of recurrence of SE after discontinuation of the ganaxolone infusion resulting from IV administration of 500 mg/day, 650 mg/day, and 713 mg/day were unexpected over Petitioner's and its scientist's (a person of ordinary skill) expectation that "high ganaxolone exposure for a long treatment period of at least 4 days duration, would be required to break SE." Ex. 2007, 30 at ¶ 7; Ex. 2008, 26 at ¶ 7. Upon seeing these unexpected clinical study results, a skilled artisan would have also understood that higher doses of ganaxolone (i.e., from 713 mg/day to 1050 mg/day) would have this same "rapid" effect on seizure cessation and reduction in seizure burden. These unexpected results therefore support the nonobviousness of claims 25-31.

Moreover, it was unexpected that 94% of patients in the clinical study "achieved and maintained SE cessation for 24 h following ganaxolone initiation" (Ex. 2003, 2386) based on Petitioner's and its scientist's expectation "that a high ganaxolone exposure for a long treatment period of at least 4 days duration, would be required to break SE." Ex. 2007, 30 at ¶ 7; Ex. 2008, 26 at ¶ 7. This unexpected result supports the nonobviousness of claim 22.

The phase 2 clinical study results were particularly unexpected for the dose range recited in claim 30 (i.e., 700 mg to 725 mg/day ganaxolone). In the

declarations submitted to distinguish the pending claims of Petitioner's U.S. App. Nos. 17/186,569 and 17/729,427 over the U.S. national stage entry of Zhang, the Marinus scientist stated that it was "surprisingly revealed" that maintaining a plasma concentration of about 500 ng/mL to about 1000 ng/mL ganaxolone for about 8 to about 12 hours was "completely unexpected" for achieving "persistent suppression of SE" and "completely contrary to [the scientist's] expectations." Ex. 2007, 31 at ¶¶ 9-10; Ex. 2008, 27 at ¶¶ 9-10. The scientist also stated that "this surprising and unexpected discovery and the claimed treatment method provide significant clinical advantages for patients." Ex. 2007, 31 at ¶ 11; Ex. 2008, 27 at ¶ 11. Namely, it now provides "a method that can effectively break SE using ganaxolone" and "provides enhanced safety for patients by limiting the duration of exposure to high drug levels to only about 8 to about 12 hours," which "lessens the risk of unwanted adverse events." *Id.*

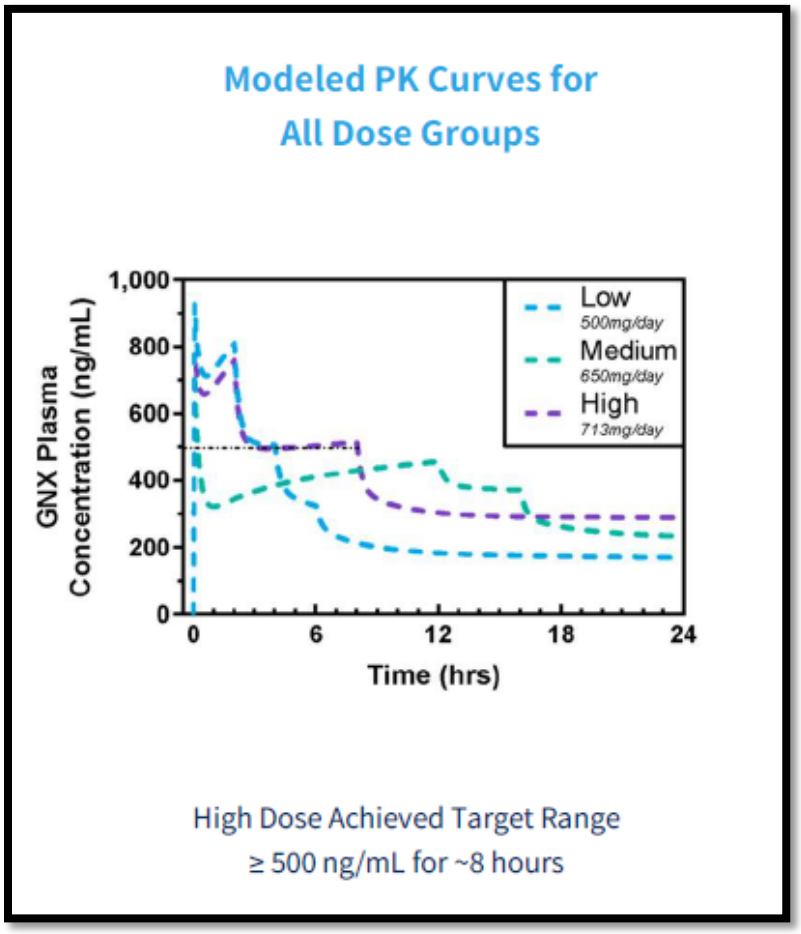
The article describing Petitioner's phase 2 trial specifically ties the 713 mg/day dose to maintaining plasma levels above the critical 500 ng/mL threshold for at least 8 hours. In particular, the article states that:

> Sustained clinical response was associated with maintaining ganaxolone plasma concentrations ≥500 ng/ml. Ganaxolone plasma levels ≥500 ng/ml were achieved only briefly during the initial bolus for patients in the medium-dose cohort, whereas those in low- and high-dose cohorts maintained such levels for 4 and 8 h, respectively. The greatest decrease in seizure burden was

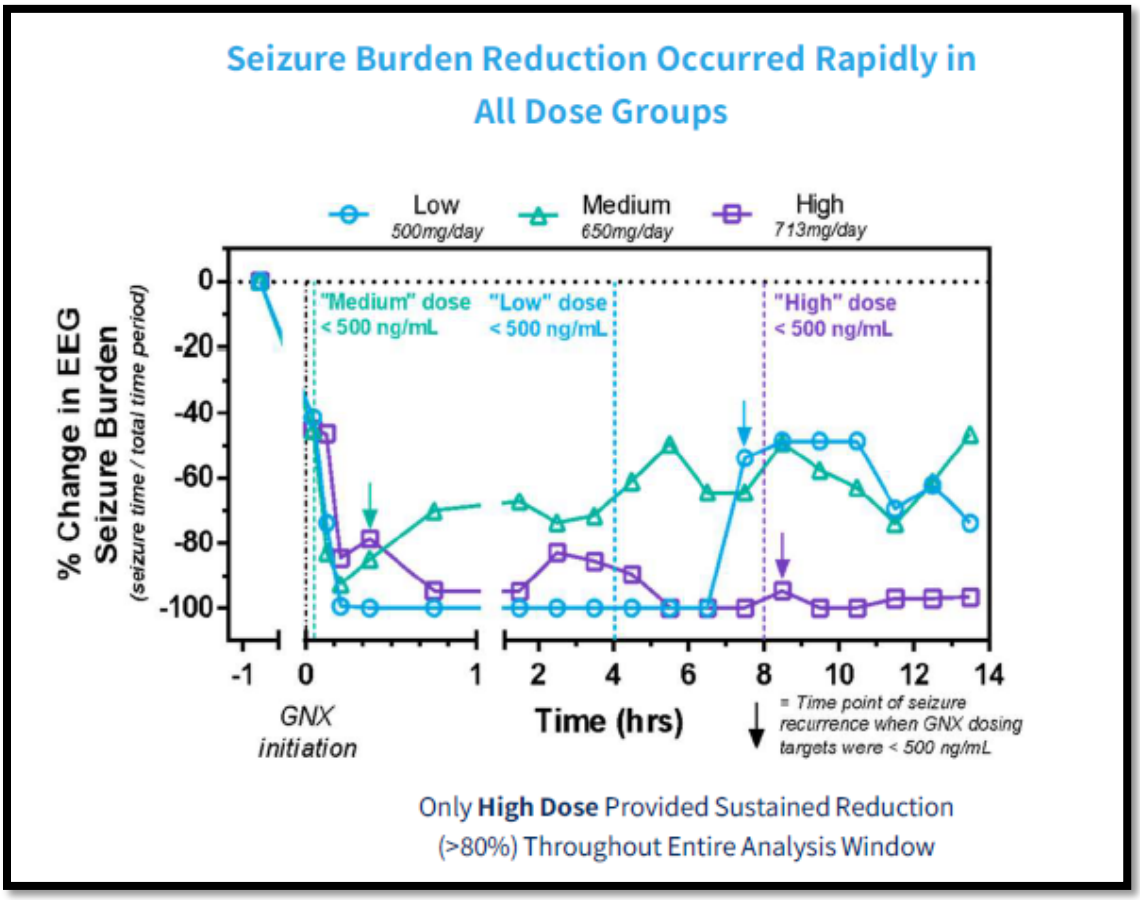
> seen when ganaxolone concentrations were maintained at ≥500 ng/m for at least 8 h.

Ex. 2003, 2386; *see also id.*, 2384 (Figure 2 stating that "[h]igh dose GNX achieves and maintains target plasma levels (≥500 ng/ml) for ~8 h, designed to sustain SE cessation"). In other words, only the 713 mg/day dose of ganaxolone (high dose cohort) sustained ganaxolone plasma concentrations for at least 8 hours.

In a June 2023 corporate presentation, Petitioner again reported the results of the same phase 2 clinical trial. Ex. 2002, 25-27. Petitioner provided the below chart, stating that "High Dose [713 mg/day ganaxolone] Achieved Target Range ≥ 500 ng/mL for ~8 hours":



Id., 27. Petitioner also provided another chart, stating that "Only High Dose [713 mg/day ganaxolone] Provided Sustained Reduction (>80%) Throughout Entire Analysis Window":



Id. Taking these two statements together, Petitioner provided that only a dose of 713 mg/day allows for a plasma concentration ≥500 ng/mL for greater than 8 hours and sustained seizure reduction throughout the entire time period tested. As a dose of 713 mg/day falls squarely within the claimed range of 700 mg to 725 mg/day, these statements further confirm that the effects of the 713 mg/day dose on seizure burden reduction and cessation were unexpected over Petitioner's and its skilled artisan scientist's expectations and were markedly superior over the other doses encompassed by Zhang's extremely broad disclosure. *See Bristol-Myers Squibb*, 752 F.3d at 977.

Based on Petitioner's above admissions, the improvement recited in claim 22 and the dose ranges recited in claims 25-31 provided unexpected results over the closest prior art, Zhang. These unexpected results thus support the nonobviousness of claims 22 and 25-31, and Petitioner has made no attempt to show otherwise.

b. There was a long-felt but unmet need for the claimed methods of treatment.

Before August 2016, SE was known to be "a life-threatening condition, associated with high mortality and if not treated immediately, c[ould] result in brain damage, cognitive impairment and death." Ex. 1011, 1. SE is also known to be "the second most common neurologic emergency in the U.S." with "150,000 cases per year." Ex. 2002, 22. Moreover, according to Petitioner, SE "[b]ecomes more treatment refractory with progression." *Id.* As Petitioner admits, "[b]ecause of the serious risks associated with treatment failures, the development of new treatments that can address SE is critical." Pet., 12; *see also* Ex. 1001, 2:5-9.

The prior art is replete with statements recognizing the long-felt need for a drug that could treat SE. Reddy acknowledged that one of the "key areas of unmet clinical needs in epilepsy" included "new AEDs for drug-resistant seizures and SE." Ex. 1004, 18306. Petitioner's Phase I Press Release from June 2016 states that SE has "limited treatments" available and that despite "single or combination IV antiepileptic drugs [being] used in an attempt to break the seizures . . . there are

approximately 45,000 patients in the U.S. who do not respond to treatment and progress to established SE." Ex. 1022, 1. Similarly, Petitioner's Orphan Drug Press Release from April 2016 states that SE is a "difficult to treat seizure disorder with limited treatment options." Ex. 1011, 1.

Ganaxolone administered according to the methods in claims 22 and 25-31 filled this unmet need. *See supra* § III.A. As shown in Petitioner's phase 2 clinical trial, the claimed improvement and dose ranges of ganaxolone resulted in rapid seizure cessation and reduction in seizure burden. Ex. 2003, 2386, 2388. The dose ranges of ganaxolone recited in claims 25-31 also have "the potential to provide significant clinical benefit to patients with RSE." *Id.*, 2388. Moreover, Petitioner's ongoing phase 3 clinical trial for the use of intravenous ganaxolone to treat RSE uses the same dose paradigm as its phase 2 clinical trial. Ex. 2002, 28.

c. Failure of others in treating SE.

Patent Owner's claimed methods stand against a stark backdrop of repeated failures for treating SE. Intravenous benzodiazepines, such as lorazepam and diazepam, are among the "first-line therapies" for treating SE, but as Petitioner admits, "[a] significant drawback to these therapies is that their efficacy decreases dramatically as the duration of SE increases, and there can be a complete loss of efficacy after a certain amount of time." Pet., 11 (citing Ex. 1004, 18287). When there is a complete loss of efficacy, "more drastic second-line (phenytoin and

fosphenytoin) and third-line therapies (propofol or phenobarbital) must be employed, but are not always successful." Ex. 1004, 18287; *see also* Ex. 1009, ¶ [0001]; Pet., 11-12. These failures support the nonobviousness of claims 22 and 25-31. *See Cyclobenzaprine*, 676 F.3d at 1081-82.

2. Ground 2: Petitioner has not demonstrated that claims 22 and 25-31 would have been obvious over Zhang.

a. Claim 22

i. No motivation

Petitioner fails to demonstrate that a skilled artisan would have been motivated by Zhang's disclosure to meet the limitation of claim 22, which requires using an intravenous administration of ganaxolone to achieve an "improvement to the patient after administration for more than 8 hours." As discussed above in Section IX.A.2, nowhere does Zhang disclose "improvement to the patient after administration for more than 8 hours." Neither the Petition nor Dr. Rogawski's declaration makes any attempt to demonstrate why a skilled artisan would have been motivated by Zhang to arrive at this limitation. *See* Pet., 48-49; Ex. 1003, ¶¶ 106-109. Indeed, the word "motivation" appears nowhere in Petitioner's discussion of claim 22. *Id.* Petitioner instead merely asserts that Zhang "suggests" the subject matter of claim 22 and that "a POSA would have, based on common knowledge, supplied any limitations that Zhang does not teach directly." Pet., 48-49 (citing Ex. 1003, ¶¶ 106-109).

To the extent Petitioner asserts that Zhang suggests the limitation of claim 22 through its disclosure in paragraph 74 that a β-cyclodextrin-ganaxolone injection "may be given at intervals of 1 to 24 hours," and would combine this disclosure with Example 8, Petitioner's argument is legally insufficient. *See* Pet., 49 n.193 (citing Pet., VIII.A.6). The fact that an element is disclosed or that a skilled artisan is capable of doing something alone is insufficient to demonstrate obviousness—the petitioner must still provide a showing of a "suggestion or motivation to modify the teachings of that reference," even when combining disclosures within a single reference. *See SIBIA Neurosciences, Inc. v. Cadus Pharm. Corp.*, 225 F.3d 1349, 1356 (Fed. Cir. 2000) ("In appropriate circumstances, a single prior art reference can render a claim obvious. However, there must be a showing of a suggestion or motivation to modify the teachings of that reference to the claimed invention in order to support the obviousness conclusion." (internal citations omitted)). This is especially true where, as here, Zhang never ties its disclosure in paragraph 74 that a β-cyclodextrin-ganaxolone injection "may be given at intervals of 1 to 24 hours" to treating SE or Zhang's Example 8. And Petitioner makes no attempt to supply this connection.

Moreover, Petitioner's attempt to supply a motivation or fill in a limitation missing from Zhang through the "common knowledge" of a skilled artisan without any reasoned basis or evidentiary support is improper. *Arendi S.A.R.L. v. Apple Inc.*,

832 F.3d 1355, 1362 (Fed. Cir. 2016) ("'common sense' [or common knowledge]—whether to supply a motivation to combine or a missing limitation—cannot be used as a wholesale substitute for reasoned analysis and evidentiary support, especially when dealing with a limitation missing from the prior art references specified").

Because Petitioner has set forward no motivation, its obviousness challenge based on Zhang alone is facially deficient and fails.

ii. No reasonable expectation of success

Petitioner fails to show that a skilled artisan would have had a reasonable expectation of success in using intravenous administration of ganaxolone to achieve an "improvement to the patient after administration for more than 8 hours." Pet. 48-49. Petitioner baldly asserts that Zhang "suggests" the subject matter of claim 22 and that "a POSA would have arrived at the recited claims with a reasonable expectation of success." Pet., 48-49. But as discussed above in Section IX.A.2, a skilled artisan would not have had a reasonable expectation of success based on Zhang's disclosure.

Zhang's Example 8 discloses that the effect of ganaxolone on reducing EEG power is largely diminished by 5 hours and that ganaxolone showed a significant reduction at 3-5 hours in only one low frequency group (0-5 Hz):

> However, between 2 to 5 h, EEG power above 30 Hz was not different from the vehicle group, indicating it was also not significantly different from the baseline EEG power level. Note also that at the higher frequency ranges, EEG power in the vehicle groups returned towards baseline

> after 2 h, so that differences between the GNX and vehicle groups were not significant.
>
> . . .
>
> Again, the EEG power levels were maintained at baseline for up to 5 h post dosing, however, the EEG levels of the vehicle group also returned to baseline for the frequency ranges above 30 Hz so the drug showed no effect.

Ex. 1009, ¶¶ [0135]-[0136]. Zhang provides no data regarding seizure reduction beyond 5 hours.

Petitioner points to no evidence as to why a skilled artisan would have had a reasonable expectation of success that intravenous administration of ganaxolone would result in "improvement to the patient after administration for more than 8 hours" when Zhang itself shows an absence of any effect by 5 hours. Petitioner instead relies on conclusory attorney argument (and Dr. Rogawski's near-verbatim repetition of that attorney argument) that, "based on Zhang's teachings, including, for example, the results described in Example 8, a POSA would have had a reasonable expectation of success at arriving at the claimed methods of treating SE with ganaxolone—whether in a rat patient or a human patient." Pet., 49 (citing Ex. 1003, ¶¶ 106-109; Pet., 35-48 (Petitioner's arguments for Ground 1)); *compare* Pet., 44-45, 48-49 *with* Ex. 1003, ¶¶ 106-109. As discussed above in Section VII, this argument and support should be entitled to little weight.

Moreover, Petitioner fails to show that a skilled artisan would have had a reasonable expectation of success that ganaxolone treatment "repeated at intervals of 2 hours" would result in "improvement to the patient after administration for more than 8 hours." Pet., 45, 48-49. Petitioner relies only on paragraph 74 of Zhang, which states that ganaxolone can be administered "at intervals of 1 to 24 hours." Ex. 1009, ¶ [0074]. Paragraph 74 of Zhang does not state, however, that multiple treatments can prolong an effect from a single treatment, let alone a prolonged effect on SE. And Petitioner relies on no evidence demonstrating why a skilled artisan would have had a reasonable expectation of success that multiple, repeated treatments would result in "improvement to the patient after administration for more than 8 hours" if a single treatment for SE suppresses seizures for up to 2 hours. As discussed above in Section VII, Dr. Rogawski's declaration on this point should also be afforded little weight because it is based on attorney argument and supported by conclusory testimony that merely repeats the attorney argument near verbatim. *Compare* Pet., 45, 48-49 *with* Ex. 1003, ¶¶ 94, 106-109.

Because Petitioner has failed to put forward any evidence demonstrating that a skilled artisan would have had a reasonable expectation of achieving "improvement to the patient after administration for more than 8 hours" based on Zhang's disclosure, Petitioner's obviousness challenge is facially deficient and fails. *See Eli Lilly & Co. v. Teva Pharms. Int'l GmbH*, 8 F.4th 1331, 1343-1345 (Fed. Cir.

2021) (holding that petitioner must "prove . . . that the skilled artisan would have reasonably expected success" in achieving the claimed method of treatment).

b. Claims 25-31

i. No motivation

Petitioner has failed to demonstrate that a skilled artisan would have been motivated to choose the narrow dose ranges for treating SE recited in claims 25-31 from the broad dose range relied upon by Petitioner in paragraph 85 of Zhang (i.e., "about 1 mg/kg to about 20 mg/kg ganaxolone"). *See* Pet., 46-49; Ex. 1003, ¶¶ 99-109. Indeed, the word "motivation" appears nowhere in Petitioner's discussion of claims 25-31. *Id.*

Petitioner instead merely asserts that "a person of skill in the art would *readily be able* to calculate the total daily dose in mg" and that "Zhang's bolus doses of 1 mg/kg to 20 mg/kg, for a 70 kg patient, encompass each of the amounts recited in claims 24-31." Pet., 47, 48 (emphasis added). As discussed above, the fact that an element is disclosed or that a skilled artisan is capable of doing something alone is insufficient to demonstrate obviousness, even when combining disclosures within a single reference. The petitioner must still provide a showing of a "suggestion or motivation to modify the teachings of that reference." *See SIBIA*, 225 F.3d at 1356. This is especially true where, as here, paragraph 85 of Zhang refers to administering

various dose ranges and numerous dosing regimens of ganaxolone to a patient without identifying any disease or disorder to be treated. *See* Ex. 1009, ¶ [0085].

Because Petitioner has set forward no motivation, its obviousness challenge is facially deficient and fails.

ii. No reasonable expectation of success

Petitioner fails to show that a skilled artisan would have had a reasonable expectation of success in treating SE with the dose ranges recited in claims 25-31 based on the disclosure of Zhang. Pet. 48-49. Petitioner merely asserts that to the extent Zhang "do[es] not teach the limitations" of claims 25-31, it "suggests" them and that "a POSA would have arrived at the recited claims with a reasonable expectation of success." Pet., 48-49. Petitioner does not, however, substantiate this contention for claims 25-31 with any evidence. Rather, both Petitioner and Dr. Rogawski merely state that Example 8 is "a widely accepted model to identify potential treatments for SE," and that it "teaches that IV-administered ganaxolone terminates SE, i.e., ganaxolone gave a positive result in the model." *E.g.*, Ex. 1003, ¶¶ 108-109; *see also* Pet., 48-49. Petitioner provides no explanation as to how this alleged positive result would have provided a reasonable expectation of success for the specifically-recited doses of claims 25-31 in a *human* patient.

Moreover, Zhang does not include any examples in humans of ganaxolone's efficacy in treating a human patient suffering from SE, let alone in the specifically

recited dose ranges in claims 25-31. *See supra* § IX.A.1. The lack of efficacy data in humans is significant because of the noted difficulties in treating SE. *See supra* § IX.B.1.b-c; *see also* Ex. 1011, 1 (recognizing that SE is a "difficult to treat seizure disorder with limited treatment options"); *OSI Pharms., LLC v. Apotex Inc.*, 939 F.3d 1375, 1386 (Fed. Cir. 2019) ("The lack of erlotinib-NSCLC efficacy data or other indication of success here is significant because of the highly unpredictable nature of treating NSCLC."); *Novartis Pharms. Corp. v. West-Ward Pharms. Int'l Ltd.*, 923 F.3d 1051, 1060-62 (Fed. Cir. 2019).

Stated differently, it is not enough for a petitioner "to have shown that a skilled artisan would have pursued the claimed method as a treatment option," i.e., that Zhang provides a positive result; rather, a petitioner must also "show that the skilled artisan would have reasonably expected to achieve success in the treatment." *Eli Lilly & Co. v. Teva Pharms. Int'l GmbH*, 8 F.4th 1331, 1344 (Fed. Cir. 2021); *see also Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) (finding that a skilled artisan must have been motivated to do more than "pursue a 'general approach that seemed to be a promising field of experimentation.'"); *Sanofi v. Watson Labs. Inc.*, 875 F.3d 636, 642, 647-48 (Fed. Cir. 2017) (prior-art statement that treatment was "expected" to reduce rehospitalization was a "hypothesis," not a "'concrete' factual assertion" that would give a reasonable expectation of success). Petitioner relies on no evidence demonstrating that a skilled artisan would have

"reasonably expected to achieve success in the treatment" based on Zhang's disclosure. *Eli Lilly*, 8 F.4th at 1344. Petitioner has thus failed to show that a skilled artisan, based on Zhang's disclosure, would have had a reasonable expectation of success in treating a human patient suffering from SE with the doses recited in claims 25-31.

3. Ground 3: Petitioner has not demonstrated that claims 22 and 25-31 would have been obvious over Zhang in combination with Saporito P1 and/or Saporito P2.

a. Petitioner has not demonstrated that Saporito P1 and Saporito P2 were sufficiently accessible to qualify as prior art.

"[P]ublic accessibility" is the touchstone in determining whether a reference is a "printed publication." *In re Hall*, 781 F.2d 897, 898-99 (Fed. Cir. 1986). "Indeed, the key inquiry is whether or not a reference has been made 'publicly accessible.'" *In re Klopfenstein*, 380 F.3d 1345, 1348 (Fed. Cir. 2004). "[T]he reference must have been sufficiently accessible to the public interested in the art; dissemination and public accessibility are the keys to the legal determination whether a prior art reference was 'published.'" *In re Cronyn*, 890 F.2d 1158, 1160 (Fed. Cir. 1989).

"The determination of whether a reference is a 'printed publication' under 35 U.S.C. §102[] involves a case-by-case inquiry into the facts and circumstances surrounding the reference's disclosure to members of the public." *Klopfenstein*, 380 F.3d at 1350 (citing *Cronyn*, 890 F.2d at 1161; *Hall*, 781 F.2d at 899); *see also Blue*

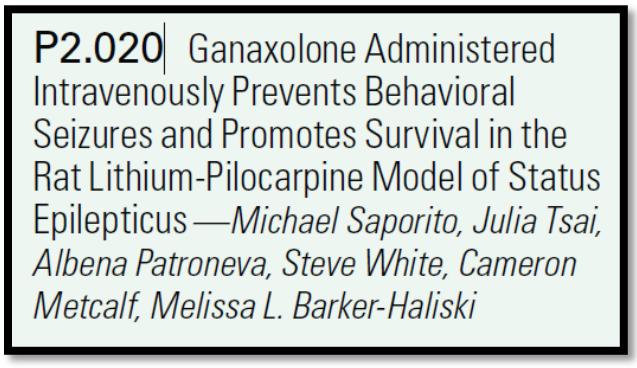
Calypso, LLC v. Groupon, Inc., 815 F.3d 1331, 1348 (Fed. Cir. 2016). Limited distribution, even to those skilled in the art, may not amount to "publication" under the statute unless the material is otherwise so situated that "any one who chooses may avail himself of the information it contains." *In re Bayer*, 568 F.2d 1357, 1360, 1362 (CCPA 1978) (internal citation omitted).

Petitioner has failed to establish that Saporito P1 and Saporito P2 were sufficiently publicly accessible before the priority date of the '817 patent. Saporito P1 and Saportio P2 are not dated, and there is no indication on their face that they were presented at the 2016 AAN meeting. *See* Ex. 1013; Ex. 1014. The Saporito Declaration does not indicate how many people attended the poster sessions other than the sessions being "well attended" (Ex. 1015, ¶¶ 10, 21) or that the declarant "interacted with a number of meeting attendees" at Poster Session IV (*id.*, ¶ 15).

The Petition and the Saporito Declaration also provide no explanation of whether Exhibits 1013 and 1014 are the same posters that were presented at the April 2016 AAN meeting apart from merely stating that they are. *See* Pet., 5-7; Ex. 1015. The Saporito declaration is silent as to whether these exhibits are the same files that contained the original Saporito P1 and Saporito P2 posters. Ex. 1015. The Saporito declaration also does not provide any chain of custody for the files that Petitioner alleges are the posters that were presented and does not indicate whether the declarant possessed these files or if someone else did. Moreover, the produced

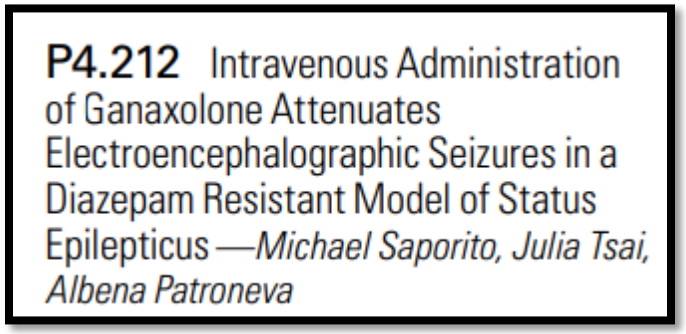
versions of Saporito P1 and Saporito P2 are provided as one page and followed by four "broken up" pages that are clearly not the posters as they would have been hung at the 2016 AAN meeting. *See* Ex. 1013; Ex. 1014.

The authorship of Saporito P1 and Saporito P2 further call into question their public availability, which Petitioner fails to address. Specifically, Saporito P1 identifies an extra author (Donna Henry) that is not included in the AAN Meeting Brochure. *See* Ex. 1012 at 46 (P2.020). The Saporito Declaration does not address this discrepancy in authorship of Saporito P1. *See* Ex. 1015. That Saporito P1 contains a different set of authors than the meeting brochure that purportedly discusses the underlying poster begs the question—unanswered by Petitioner—as to whether Saporito P1 is the poster that was presented at the 2016 AAN meeting.


P2.020 Ganaxolone Administered Intravenously Prevents Behavioral Seizures and Promotes Survival in the Rat Lithium-Pilocarpine Model of Status Epilepticus —*Michael Saporito, Julia Tsai, Albena Patroneva, Steve White, Cameron Metcalf, Melissa L. Barker-Haliski*

Saporito P2, on the other hand, does not provide the names of any authors on the poster itself, despite the AAN Meeting Brochure listing three authors (Michael Saporito, Julia Tsai, and Albena Patroneva). *See* Ex. 1012 at 97 (P4.212). The Saporito Declaration does not address this discrepancy in authorship of Saporito P2.

See Ex. 1015. That Saporito P2 lists none of the authors listed in the AAN Meeting Brochure again demonstrates that Petitioner failed to show Saporito P2 is the poster that was presented at the 2016 AAN meeting.


P4.212 Intravenous Administration of Ganaxolone Attenuates Electroencephalographic Seizures in a Diazepam Resistant Model of Status Epilepticus —*Michael Saporito, Julia Tsai, Albena Patroneva*

Based on at least the above, Petitioner has not demonstrated that Saporito P1 and Saporito P2 were sufficiently "publicly accessible" to qualify as prior art.

b. Neither Zhang nor Saporito P1 and/or Saporito P2 discloses "treating status epilepticus comprising administering to a patient in need thereof" from claims 22 and 25-31.

As discussed above in Section IX.A.1, Zhang does not disclose intravenously administering to a human patient suffering from SE a pharmaceutical composition comprising ganaxolone or a pharmaceutically acceptable salt thereof, as claims 22 and 25-31 require.

Saporito P1 and Saportio P2 also do not disclose intravenously administering to a human patient a pharmaceutical composition comprising ganaxolone or a pharmaceutically acceptable salt thereof. As Petitioner admits, Saporito P1 "reports on a study conducted by Marinus to investigate the effects of IV-administered

ganaxolone in the *rat* lithium-pilocarpine model." Pet., 50 (emphasis added); *see also* Ex. 1013, 1. Similarly, Petitioner admits that Saporito P2 shows "that *rats* were administered lithium chloride followed by pilocarpine to induce SE" and that "[g]anaxolone was administered via IV bolus injection 15 or 60 minutes after the detection of SE onset." Pet., 52 (emphasis added); *see also* Ex. 1014, 1. Thus, neither Saporito P1 nor Saporito P2 discloses intravenously administering ganaxolone to a human patient suffering from SE.

Petitioner has thus failed to show that Zhang combined with Saporito P1 and/or Saporito P2 discloses "treating status epilepticus comprising administering to a patient in need thereof" under the correct construction.

c. Claim 22

i. No motivation

As discussed above in Section IX.B.2.a.i., Petitioner has provided no motivation to combine different aspects of Zhang to arrive at the limitations recited in claim 22 (i.e., "improvement to the patient after administration for more than 8 hours"). Petitioner also does not argue that Saporito P1 and/or Saporito P2 cures this deficiency in Zhang. *See* Pet., 50-54, 56. Additionally, Petitioner's assertion that a skilled artisan "would have readily combined these references—as they both describe the same drug, the same disease, and the same animal model"—is legally insufficient. Pet., 54. Neither "[m]ere compatibility of the references" nor a showing

"that the prior art references are analogous art or in the same field of endeavor as the challenged patent" is sufficient "to establish that one of ordinary skill would have had reason to combine it teachings with other prior art in the manner set forth in the claim." *Johns Manville Corp. v. Knauf Insulation, Inc.*, IPR2018-00827, Paper 9 at 10 (PTAB Oct. 16, 2018). Therefore, Petitioner's combination of Zhang and Saporito P1 and/or Saporito P2 fails for the same reasons discussed above.

ii. No reasonable expectation of success

As discussed above in Section IX.A.2, Zhang does not disclose "improvement to the patient after administration for more than 8 hours," as claim 22 requires. Petitioner further fails to show that a skilled artisan would have had a reasonable expectation of success in combining Zhang with Saporito P1 and/or Saporito P2 to arrive at the intravenous administration of ganaxolone resulting in "improvement to the patient after administration for more than 8 hours."

Petitioner relies on its reasonable expectation of success argument from Ground 2 of the Petition (Pet., 56), but as discussed in Section IX.B.2.a.ii above, Petitioner failed to put forward any evidence demonstrating that a skilled artisan would have had a reasonable expectation of achieving "improvement to the patient after administration for more than 8 hours" based on Zhang's disclosure alone.

Saporito P1 and Saporito P2 do not cure Zhang's deficiency as neither shows that a ganaxolone SE treatment would provide "improvement to the patient after

administration for more than 8 hours." *See* Ex. 1013; Ex. 1014. Like Zhang's Example 8, Figures 3 and 4 in Saporito P2 demonstrate that the effect of ganaxolone on reducing EEG power is largely diminished by 6 hours, after which there is no additional data. Ex. 1014, 1. Similarly, for Figure 2 in Saporito P1, the rats "were observed for the presence or absence of convulsive seizures (stage 3 or greater) for an additional 2 hours" after ganaxolone administration and rats that "did not exhibit a convulsive seizure during that time period were considered protected." Ex. 1013, 1. Thus, Saporito P1 does not contain any data beyond 2 hours after administration. Given that Saporito P1 and Saporito P2, like Zhang, do not provide any data beyond at most 6 hours, they do not provide a skilled artisan with a reasonable expectation of success in achieving "improvement to the patient after administration for more than 8 hours."

Petitioner's argument that "Saporito P1 shows that ganaxolone promoted survival in the rats, measured 24 hours after the onset of CSE, suggesting improvement after 8 hours" has no support in Dr. Rogawski's declaration or in Saporito P1 itself. Pet., 56. Dr. Rogawski does not opine, and Saporito P1 does not disclose, that increased survival measured 24 hours after the onset of CSE represents an improvement in treating SE after 8 hours. *See* Ex. 1003, ¶ 114; Ex. 1013, 1. Figure 3 in Saporito P1 instead simply counted "the number of surviving animals" 24 hours after CSE onset. Ex. 1013, 1. Thus, Petitioner relies on mere attorney argument to

show this limitation. Additionally, Saporito P1's disclosures about 24-hour survival rate show no statistical significance of the data, unlike the data disclosed in Saporito P2. *Compare* Ex. 1014 (Saporito P2 reporting statistical analysis "by two-ANOVA followed by post-hoc Dunnett's test") *with* Ex. 1013, 1 (Saporito P1 providing no statistical analysis).

d. Claims 25-31

i. No motivation

As discussed above in Section IX.B.2.b.i, Petitioner has failed to establish that a skilled artisan would have been motivated to choose the narrower dose ranges recited in claims 25-31 from the broader dose range disclosed in Zhang (1 mg/kg to 20 mg/kg). Neither the Petition nor Dr. Rogawski's declaration contends that either of Saporito P1 or Saporito P2 would cure the deficiency in Zhang by providing a motivation for choosing the dose ranges recited in claims 25-31. *See* Pet., 57.

Additionally, Saporito P1's disclosure that 6 mg/kg, 9 mg/kg, and 12 mg/kg ganaxolone "blocks Convulsive Status Epilepticus (CSE)" in Figure 2 shows no statistical significance of the data, unlike the data disclosed in Saporito P2. *Compare* Ex. 1014, 1 (Saporito P2 reporting statistical analysis "by two-ANOVA followed by post-hoc Dunnett's test") *with* Ex. 1013, 1 (Saporito P1 providing no statistical analysis).

ii. No reasonable expectation of success

As discussed above in Section IX.B.2.b.ii, Petitioner has not shown that a skilled artisan would have had a reasonable expectation of success in treating a human patient suffering from SE with the doses recited in claims 25-31 based on Zhang's disclosure. Petitioner does not contend that Saporito P1 or Saporito P2 cure this deficiency in Zhang. Pet., 57. Therefore, Petitioner's combination of Zhang and Saporito P1 and/or Saporito P2 fails for the same reasons discussed above.

4. Ground 4: Petitioner has not demonstrated that claims 22 and 25-31 would have been obvious over Zhang in combination with Marinus's Orphan Drug Press Release, and/or Marinus's Phase I Press Release.

a. No motivation for claims 22 and 25-31

Petitioner makes no effort to establish that a skilled artisan would have been motivated to combine Zhang with Marinus's Orphan Drug Press Release and/or Marinus's Phase I Press Releases to arrive at the limitations recited in claims 22 and 25-31. *See* Pet., 57-65. Petitioner instead asserts that a skilled artisan "would have readily combined" these references (Pet., 60 (citing Ex. 1003, ¶ 124)), while Dr. Rogawski states that a skilled artisan "reading Zhang would have had reason to look for additional publications related to the treatment of SE by administering ganaxolone to a patient in need" (Ex. 1003, ¶ 124). Such vague and general motivations offered without any supporting evidence are legally insufficient to demonstrate obviousness. *See Innogenetics, N.V. v. Abbott Labs.*, 512 F.3d 1363,

1373-74 (Fed. Cir. 2008) (determining that striking "vague and conclusory obviousness testimony" was not an abuse of discretion); *see also KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (requiring that there "must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness"). Petitioner's proposed combination therefore fails.

b. No reasonable expectation of success for claims 22 and 25-31

Petitioner fails to show that a skilled artisan would have had a reasonable expectation of success that intravenous administration of ganaxolone would result in "improvement to the patient after administration for more than 8 hours" or that administration of ganaxolone at the doses recited in claims 25-31 would treat SE in human patients based on Zhang in combination with Marinus's Orphan Drug Press Release and/or Marinus's Phase I Press Release.

For the reasons discussed above in Section IX.B.2, Zhang does not provide a reasonable expectation of success for claims 22 and 25-31. Moreover, Marinus's Orphan Drug Press Release and Marinus's Phase I Press Releases do not cure the deficiencies of Zhang by providing a reasonable expectation that ganaxolone would either (1) successfully provide "improvement to the patient after administration for more than 8 hours," as recited in claim 22, or (2) successfully treat SE when administered at the doses recited in claims 25-31.

Neither Press Release discloses any information about ganaxolone's efficacy in treating SE in a human or otherwise. *See* Ex. 1011, 1; Ex. 1022, 1. Here, both Press Releases predate phase 1 clinical trials for testing the safety, tolerability, and pharmacokinetics of ganaxolone IV—notably, not its efficacy in treating SE—from completing, let alone receiving any reportable data. *See* Ex. 1011, 1 ("A Phase 1 clinical trial evaluating the safety, tolerability and pharmacokinetics of ganaxolone IV is expected to initiate in the first half of 2016."); Ex. 1022, 1 ("We look forward to reporting the results on this Phase 1 study later this year."). The lack of efficacy data in humans is significant because of the noted difficulties in treating SE. *See supra* § IX.B.1.b-c; *see also* Ex. 1011, 1 (recognizing that SE is a "difficult to treat seizure disorder with limited treatment options"); *OSI Pharms.*, 939 F.3d at 1386 ("The lack of erlotinib-NSCLC efficacy data or other indication of success here is significant because of the highly unpredictable nature of treating NSCLC."); *Novartis*, 923 F.3d at 1060-62.

Moreover, it is not enough for a petitioner "to have shown that a skilled artisan would have pursued the claimed method as a treatment option"; rather, a petitioner must also "show that the skilled artisan would have reasonably expected to achieve success in the treatment." *Eli Lilly*, 8 F.4th at 1344; *see also Medichem*, 437 F.3d at 1165 (finding that a skilled artisan must have been motivated to do more than "pursue a 'general approach that seemed to be a promising field of

experimentation.'"); *Sanofi*, 875 F.3d at 642, 647-48 (prior-art statement that treatment was "expected" to reduce rehospitalization was a "hypothesis," not a "'concrete' factual assertion" that would give a reasonable expectation of success). Petitioner has not done so here.

The Press Releases are therefore insufficient to cure Zhang's failure to provide a reasonable expectation of success. *See supra* IX.B.2.

C. Ground 7: Petitioner has not demonstrated that claims 22 and 25-31 are unpatentable for lack of enablement.

Petitioner asserts that "to the extent that Marinus's publications do not render claims [22 and 25]-31 anticipated or obvious, the '817 patent does not enable them." Pet., 77-78. Petitioner's enablement challenge, however, is facially deficient as it does not address or analyze any of the factors set forth in *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988). *See Merck Sharp & Dohme Corp. v. Wyeth LLC*, PGR2017-00016, Paper 9 at 8 (PTAB Oct. 20, 2017) ("Petitioner's failure to adequately address the *Wands* factors supports denial of the Petitions in both [PGRs]."). Petitioner's enablement ground should be denied for this reason alone.

Instead of providing a cogent analysis grounded in the *Wands* factors, Petitioner makes the conclusory assertion that "a person of skill in the art would certainly not have arrived at [the claimed concentrations, dosing amounts and/or patient outcomes] based on the only dose (20 mg/kg) for which data is presented [in]

the ’817 patent (Example 3) that could possibly suggest efficacy for treating SE in a rat.” Pet., 78 (citing Ex. 1003, ¶¶ 158-160). Dr. Rogawski’s declaration fares no better as it merely repeats verbatim the attorney argument in the Petition. *Compare* Pet., 78 *with* Ex. 1003, ¶ 159. Even so, as discussed in Section IX.B.1.a, Petitioner’s own post-filing date clinical testing, which is grounded in the original disclosure of the ’817 patent, shows that the claimed methods of treatment were found to be effective for treating SE, which demonstrates the extent of the ’817 patent’s enabling disclosure. For this additional reason, Petitioner has not demonstrated that the challenged claims are not enabled.

X. The Board Should Deny the Petition Based on Its Discretion Under § 325(d).

The Board should deny the Petition under § 325(d). Discretionary denial under § 325(d) is appropriate when “the same or substantially the same prior art or arguments previously were presented to the Office.” 35 U.S.C. § 325(d).

Thus, § 325(d) identifies “two separate issues” for the Board to consider in exercising its discretion to deny institution of review: (1) “whether the petition presents to the Office the same or substantially the same art previously presented to the Office”; and (2) “whether the petition presents to the Office the same or substantially the same arguments previously presented to the Office.” *Solvay USA Inc. v. WorldSource Enters., LLC*, IPR2020-00768, Paper 12 at 7 (PTAB Sept. 25,

2020) (citing *Advanced Bionics LLC v. MED-EL Elektromedizinische Gerate GmbH*, IPR2019-01469, Paper 6 at 7 (PTAB Feb. 13, 2020)). The Board may also consider the following factors when determining whether to exercise discretion under § 325(d):

> (a) the similarities and material differences between the asserted art and the prior art involved during examination; (b) the cumulative nature of the asserted art and the prior art evaluated during examination; (c) the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection; (d) the extent of the overlap between the arguments made during examination and the manner in which Petitioner relies on the prior art or Patent Owner distinguishes the prior art; (e) whether Petitioner has pointed out sufficiently how the Examiner erred in its evaluation of the asserted prior art; and (f) the extent to which additional evidence and facts presented in the Petition warrant reconsideration of the prior art or arguments.

Becton, Dickinson & Co. v. B. Braun Melsungen AG, IPR2017-01586, Paper 8 at 17-18 (PTAB Dec. 15, 2017). The Board applies "a two-part framework, first considering *Becton, Dickinson* factors (a), (b), and (d) to determine whether the same or substantially the same art or arguments were previously presented to the Office, and if so, evaluating *Becton, Dickinson* factors (c), (e), and (f) to determine whether the Petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims." *Solvay*, IPR2020-00768, Paper 12 at 7 (citing *Advanced Bionics*, IPR2019-01469, Paper 6 at 7-11).

A. The art and arguments presented are the same or substantially the same as those previously presented to the Office.

Discretionary denial under § 325(d) is appropriate because Zhang, the primary reference Petitioner relies on, was undoubtedly presented to and considered by the Office during examination of the '817 patent.

As an initial matter, Zhang is listed on the face of the '817 patent under References Cited as having been cited by a third party. Ex. 1001, 2 (WO 2016127170 A1). Zhang was first disclosed to the Office in a January 6, 2021 IDS submitted by the applicant. *See* Ex. 1002, 19 (WO 2016127170).

Zhang was again submitted to the Office in a February 8, 2021 Third-Party Submission filed by Robert H. Underwood of Hogan Lovells US LLP. *See id.*, 38 (Reference 2). The submission discusses Zhang in great detail, including many of the same passages that Petitioner relies on in its Petition. *Id.*, 40-41. Specifically, the submission states that Zhang "includes *in vivo* data demonstrating that ***ganaxolone*** has a ***therapeutic effect*** in a well-known and predictive ***rodent model of SE*** (*see, e.g.*, Example 8 at ¶¶ [0117]-[0136]." *Id.*, 40. Based on this disclosure, the submission concludes that Zhang "demonstrates a positive therapeutic effect for ***treating SE*** using ***ganaxolone*** in a well-known and predictive model (emphasis added)." *Id.* The submission also included a claim chart that relied on, inter alia, Zhang's Example 8. *See id.*, 46, 47, 52. The third-party submission was "determined

to be compliant . . . and [was] entered in the application." Ex. 2013, 2. And, on February 18, 2022, the Examiner signed the Third-Party Submission indicating that the Examiner had considered all references included with the submission, including Zhang. Ex. 1002, 95-96.

The June 24, 2022 Notice of Allowance states that "Claims 1-31 are neither anticipated nor rendered obvious over the record," including Zhang, "and therefore are allowable." Ex. 1002, 201. Zhang therefore was presented to and considered by the Office during prosecution of claims 22 and 25-31, and the claims were found to be allowable in view of Zhang.

Petitioner's arguments regarding the consideration of the remaining documents it asserts are irrelevant. *See* Pet., 82-85. None of those additional references addresses the substance of any of the limitations in claims 22 and 25-31. *E.g.*, Pet., 57. Thus, it is completely irrelevant whether the Office considered them or not because Petitioner itself offers no evidence from them related to the claims at issue that goes beyond its reliance on Zhang, which was considered multiple times.

For example, with respect to claim 22, and as discussed above in Section IX.B.3, Petitioner states, without support, that "Saporito P1 shows that ganaxolone promoted survival in the rats, measured 24 hours after the onset of CSE, suggesting improvement after 8 hours." Pet., 56. Saporito P1, however, does not cure the deficiency of Zhang, which fails to disclose improvement after administration for

more than 8 hours. *See* Ex. 1013. Petitioner is simply trying to confuse the Board by attempting to equate rat survival with improvement. Moreover, Saporito P1's 24-hour survival rate data does not demonstrate that the ganaxolone administration "provides improvement to the patient after administration for more than 8 hours," as claim 22 requires. Dr. Rogawski also does not state Saportio P1's disclosure of survival rate suggest "improvement to the patient after administration for more than 8 hours."

Petitioner does not rely on Saporito P1 to prove the additional limitation recited in claims 25-31. Saporito P1 is therefore irrelevant to the obviousness analysis for claims 25-31.

Petitioner also does not rely on Saporito P2, Marinus's Orphan Drug Press Release, or Marinus's Phase I Press Release for its obviousness grounds related to the additional limitations in claims 22 and 25-31. *See* Pet., 56 (Ground 3, claim 22), 57 (Ground 3, claim 25-31), 63-64 (Ground 4, claim 22), 64-65 (Ground 4, claim 25-31). Thus, these four references are irrelevant to the obviousness analysis for claims 22 and 25-31.

Because Zhang was considered during prosecution and the remaining references are irrelevant to the at-issue limitations in claims 22 and 25-31, the Office considered the same or substantially the same art that was presented during prosecution of the '817 patent. *See, e.g.*, *Live Nation Entm't, Inc. v. Complete Entm't*

Res. B.V., PGR2017-00038, Paper 11 at 9-10, 17 (PTAB Jan. 16, 2018) (denying institution where third-party submission in a related application with "very similar" claims included the "same or substantially the same prior art and arguments" as the petition; and petition appeared to copy portions of the third-party submission); *see also Cultec, Inc. v. StormTech LLC*, IPR2017-00777, Paper 7 at 7-13 (PTAB Aug. 22, 2017).

B. Petitioner has not established that the Office erred in a manner material to the patentability of claims 22 and 25-31.

Petitioner's arguments that the Examiner purportedly did not recognize that the claims encompass treating a rat with chemically induced SE and that Zhang demonstrated an actual reduction to practice of claim 1 say nothing about the patentability of claims 22 and 25-31. Pet., 85-86. Indeed, none of Petitioner's arguments attempting to establish Officer error refer to claims 22 and 25-31.

In any event, as discussed in detail above, none of the asserted references discloses or suggests an improvement of SE treatment for 8 hours after ganaxolone administration, as required by claim 22. And the dose ranges in the prior art do not disclose or suggest the doses recited in claims 25-31 with sufficient specificity, as the claimed doses represent a "marked superiority" over other doses in the range disclosed in the prior art. *See supra* § IX.

Petitioner is also incorrect to state that the Examiner "failed to properly consider evidence highly probative to the (un)patentability of the challenged claims." Pet., 85. As discussed above in Section IV.B, the same Examiner who examined the application that led to the '817 patent, Examiner Shiao, examined Patent Owner's priority applications claiming the use of ganaxolone for the treatment of other epileptic disorders. The Examiner also considered the same prior-art references that were presented and considered during prosecution of the '817 patent, including Zhang (Ex. 2009, 4; Ex. 2010, 4), and issued multiple office actions with obviousness, enablement, and double patenting rejections (*see* Exs. 1026, 1027). This demonstrates that the Examiner had acquired familiarity with the use of ganaxolone for epilepsy treatment and with the relevant prior art in that field.

Dr. Rogawski's declaration also does not establish Examiner error. *See Boragen, Inc. v. Syngenta Participations AG*, IPR2020-00124, Paper 18 at 4-5 (PTAB Aug. 10, 2020) (expert declaration is not "a super-factor that overrides others" in exercising discretion under § 325(d)); *see also Regeneron Pharms., Inc. v. Kymab Ltd.*, IPR2019-01579, Paper 9 at 18 (PTAB Mar. 20, 2020) ("[T]he fact that the Declaration of Petitioner's expert was not before the Examiner during prosecution does not itself demonstrate that the Examiner erred."). Moreover, as repeatedly discussed above and in Section VII, Dr. Rogawski's declaration merely

repeats the conclusory and unsupported attorney argument in the Petition and thus should be entitled to little weight.

XI. Conclusion

Petitioner has not established that it is more likely than not that claims 22 and 25-31 are unpatentable. Accordingly, the Board should deny institution of a post-grant review.

Respectfully submitted,

Dated: June 20, 2023

/Anthony C. Tridico/
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CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(d), I, Anthony C. Tridico, certify that **Patent Owner's Preliminary Response** contains 18,581 words, excluding those portions identified in 37 C.F.R. § 42.24(a), as measured by the word-processing system used to prepare this paper.

Dated: June 20, 2023

/Anthony C. Tridico/
Anthony C. Tridico
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CERTIFICATE OF SERVICE

The undersigned certifies that a copy of the foregoing **Patent Owner's Preliminary Response** and **Exhibits 2001-2013** were served electronically via email on June 20, 2023, in their entirety on the following:

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Petitioner has consented to electronic service by email.

Dated: June 20, 2023

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