

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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MARINUS PHARMACEUTICALS, INC.,  
Petitioner,

v.

OVID THERAPEUTICS INC.,  
Patent Owner.

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Case PGR2023-00020  
Patent 11,395,817 B2

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**PATENT OWNER'S RESPONSE**

## TABLE OF CONTENTS

|                                                                                                                                                     | <b>Page</b> |
|-----------------------------------------------------------------------------------------------------------------------------------------------------|-------------|
| I. Introduction .....                                                                                                                               | 1           |
| II. Background and State of the Art .....                                                                                                           | 3           |
| A. Status epilepticus .....                                                                                                                         | 3           |
| B. Patent Owner’s endeavors in epilepsy and seizure disorder<br>treatment .....                                                                     | 5           |
| C. Marinus touts the unexpected benefits of Ovid’s inventions .....                                                                                 | 8           |
| III. The ’817 Patent .....                                                                                                                          | 10          |
| A. The specification and claims .....                                                                                                               | 10          |
| B. Patent Owner’s statutory disclaimer under 37 C.F.R. § 1.321(a)<br>of challenged claims 1-21 and 23-24 .....                                      | 12          |
| IV. Dr. Rogawski’s Declaration .....                                                                                                                | 13          |
| V. Claim Construction .....                                                                                                                         | 17          |
| A. “Treating status epilepticus comprising administering to a patient<br>in need thereof” (claims 22 and 25-31) .....                               | 17          |
| B. “Improvement to the patient after administration for more than 8<br>hours” (claim 22) .....                                                      | 24          |
| VI. Ground 1: Zhang Does Not Anticipate Claims 22 and 25-31 .....                                                                                   | 25          |
| A. Zhang does not describe “treating status epilepticus comprising<br>administering to a patient in need thereof” from claims 22 and<br>25-31 ..... | 25          |
| B. Zhang does not describe “improvement to the patient after<br>administration for more than 8 hours” from claim 22 .....                           | 28          |
| C. Zhang does not describe the dose ranges in claims 25-31 .....                                                                                    | 36          |
| VII. Grounds 2-4: Petitioner Has Not Demonstrated that Claims 22 and 25-31<br>Would Have Been Obvious Over Any of the Asserted References .....     | 39          |

|    |                                                                                                                                                                              |    |
|----|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|
| A. | Objective indicia support the nonobviousness of claims 22 and 25-31 .....                                                                                                    | 39 |
| 1. | The methods of treating SE by administering ganaxolone recited in claims 22 and 25-31 demonstrate unexpected results .....                                                   | 40 |
| 2. | There was a long-felt but unmet need for the claimed methods of treatment.....                                                                                               | 49 |
| 3. | Failure of others in treating SE .....                                                                                                                                       | 51 |
| B. | Ground 2: Claims 22 and 25-31 would not have been obvious over Zhang.....                                                                                                    | 52 |
| 1. | Claim 22 .....                                                                                                                                                               | 52 |
| a. | No motivation .....                                                                                                                                                          | 52 |
| b. | No reasonable expectation of success .....                                                                                                                                   | 54 |
| 2. | Claims 25-31 .....                                                                                                                                                           | 57 |
| a. | No motivation .....                                                                                                                                                          | 57 |
| b. | No reasonable expectation of success .....                                                                                                                                   | 58 |
| C. | Ground 3: Claims 22 and 25-31 would not have been obvious over Zhang in combination with Saporito P1 and/or Saporito P2. ....                                                | 61 |
| 1. | Petitioner has not demonstrated that Saporito P1 and Saporito P2 were sufficiently accessible to qualify as prior art. ....                                                  | 61 |
| 2. | 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..... | 65 |
| 3. | Claim 22 .....                                                                                                                                                               | 67 |
| a. | No motivation .....                                                                                                                                                          | 67 |

|       |                                                                                                                                                                                  |    |
|-------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|
| b.    | No reasonable expectation of success .....                                                                                                                                       | 68 |
| 4.    | Claims 25-31 .....                                                                                                                                                               | 71 |
| a.    | No motivation .....                                                                                                                                                              | 71 |
| b.    | No reasonable expectation of success .....                                                                                                                                       | 72 |
| D.    | Ground 4: Claims 22 and 25-31 would not have been obvious<br>over Zhang in combination with Marinus’s Orphan Drug Press<br>Release, and/or Marinus’s Phase I Press Release. .... | 72 |
| 1.    | No motivation for claims 22 and 25-31 .....                                                                                                                                      | 72 |
| 2.    | No reasonable expectation of success for claims 22 and<br>25-31 .....                                                                                                            | 74 |
| VIII. | Ground 7: Claims 22 and 25-31 Are Not Unpatentable for<br>Lack of Enablement .....                                                                                               | 76 |
| IX.   | Conclusion .....                                                                                                                                                                 | 78 |

## TABLE OF AUTHORITIES

|                                                                                                                            | Page(s)    |
|----------------------------------------------------------------------------------------------------------------------------|------------|
| <b>Cases</b>                                                                                                               |            |
| <i>Allergan, Inc. v. Apotex Inc.</i> ,<br>754 F.3d 952 (Fed. Cir. 2014).....                                               | 29         |
| <i>Arendi S.A.R.L. v. Apple Inc.</i> ,<br>832 F.3d 1355 (Fed. Cir. 2016).....                                              | 53         |
| <i>Aventis Pharms. Inc. v. Amino Chems. Ltd.</i> ,<br>715 F.3d 1363 (Fed. Cir. 2013).....                                  | 22         |
| <i>In re Bayer</i> ,<br>568 F.2d 1357 (CCPA 1978) .....                                                                    | 62         |
| <i>Bettcher Indus., Inc. v. Bunzl USA, Inc.</i> ,<br>661 F.3d 629 (Fed. Cir. 2011).....                                    | 30         |
| <i>Blasters, Inc. v. Waterblasting, LLC</i> ,<br>IPR2018-00504, Paper 26 (PTAB July 16, 2019).....                         | 14         |
| <i>Blue Calypso, LLC v. Groupon, Inc.</i> ,<br>815 F.3d 1331 (Fed. Cir. 2016).....                                         | 61         |
| <i>Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.</i> ,<br>752 F.3d 967 (Fed. Cir. 2014).....                          | 41, 48     |
| <i>Connell v. Sears, Roebuck &amp; Co.</i> ,<br>722 F.2d 1542 (Fed. Cir. 1983).....                                        | 26, 33     |
| <i>In re Cronyn</i> ,<br>890 F.2d 1158 (Fed. Cir. 1989).....                                                               | 61         |
| <i>In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.</i> ,<br>676 F.3d 1063 (Fed. Cir. 2012)..... | 39, 51     |
| <i>Eli Lilly &amp; Co. v. Teva Pharms. Int’l GmbH</i> ,<br>8 F.4th 1331 (Fed. Cir. 2021).....                              | 56, 60, 76 |

|                                                                                                                   |    |
|-------------------------------------------------------------------------------------------------------------------|----|
| <i>Eon Corp. IP Holdings v. Silver Spring Networks</i> ,<br>815 F.3d 1314 (Fed. Cir. 2016) .....                  | 23 |
| <i>Eve Energy Co. v. Varta Microbattery GmbH</i> ,<br>IPR2022-01486, Paper 17 (PTAB Mar. 14, 2023) .....          | 29 |
| <i>Galderma Labs., L.P. v. Teva Pharms. USA, Inc.</i> ,<br>799 F. App'x 838 (Fed. Cir. 2020) .....                | 29 |
| <i>Genetics Inst., LLC v. Novartis Vaccines &amp; Diagnostics, Inc.</i> ,<br>655 F.3d 1291 (Fed. Cir. 2011) ..... | 41 |
| <i>Graham v. John Deere Co.</i> ,<br>383 U.S. 1 (1966) .....                                                      | 40 |
| <i>Grünenthal GmbH v. Antecip Bioventures II LLC</i> ,<br>PGR2019-00028, Paper 6 (PTAB Aug. 20, 2019) .....       | 18 |
| <i>In re Hall</i> ,<br>781 F.2d 897 (Fed. Cir. 1986) .....                                                        | 61 |
| <i>Innogenetics, N.V. v. Abbott Labs.</i> ,<br>512 F.3d 1363 (Fed. Cir. 2008) .....                               | 73 |
| <i>Intelligent Bio-Systems, Inc. v. Illumina Cambridge Ltd.</i> ,<br>821 F.3d 1359 (Fed. Cir. 2016) .....         | 77 |
| <i>Jansen v. Rexall Sundown, Inc.</i> ,<br>342 F.3d 1329 (Fed. Cir. 2003) .....                                   | 18 |
| <i>Johns Manville Corp. v. Knauf Insulation, Inc.</i> ,<br>IPR2018-00827, Paper 9 (PTAB Oct. 16, 2018) .....      | 68 |
| <i>In re Klopfenstein</i> ,<br>380 F.3d 1345 (Fed. Cir. 2004) .....                                               | 61 |
| <i>Knoll Pharm. Co. v. Teva Pharms. USA, Inc.</i> ,<br>367 F.3d 1381 (Fed. Cir. 2004) .....                       | 41 |
| <i>KSR Int'l Co. v. Teleflex Inc.</i> ,<br>550 U.S. 398 (2007) .....                                              | 73 |

|                                                                                                                   |            |
|-------------------------------------------------------------------------------------------------------------------|------------|
| <i>Luye Pharma Grp. Ltd. v. Alkermes Pharma Ire. Ltd.</i> ,<br>IPR2016-01095, Paper 13 (PTAB Nov. 30, 2016) ..... | 38         |
| <i>Medichem, S.A. v. Rolabo, S.L.</i> ,<br>437 F.3d 1157 (Fed. Cir. 2006) .....                                   | 60, 76     |
| <i>Medrad, Inc. v. MRI Devices Corp.</i> ,<br>401 F.3d 1313 (Fed. Cir. 2005) .....                                | 23         |
| <i>Merck Sharp &amp; Dohme Corp. v. Wyeth LLC</i> ,<br>PGR2017-00016, Paper 9 (PTAB Oct. 20, 2017) .....          | 76, 77     |
| <i>Microprocessor Enhancement Corp. v. Texas Instruments Inc.</i> ,<br>520 F.3d 1367 (Fed. Cir. 2008) .....       | 22         |
| <i>Net MoneyIN, Inc. v. VeriSign, Inc.</i> ,<br>545 F.3d 1359 (Fed. Cir. 2008) .....                              | 33, 34, 37 |
| <i>Novartis Pharms. Corp. v. West-Ward Pharms. Int’l Ltd.</i> ,<br>923 F.3d 1051 (Fed. Cir. 2019) .....           | 60, 75     |
| <i>OSI Pharms., LLC v. Apotex Inc.</i> ,<br>939 F.3d 1375 (Fed. Cir. 2019) .....                                  | 60, 75     |
| <i>Panasonic Corp. v. Optical Devices, LLC</i> ,<br>IPR2014-00302, Paper 9 (PTAB July 11, 2014) .....             | 33         |
| <i>Phillips v. AWH Corp.</i> ,<br>415 F.3d 1303 (Fed. Cir. 2005) (en banc) .....                                  | 17, 23     |
| <i>Polaris Wireless, Inc. v. Trueposition, Inc.</i> ,<br>IPR2013-00323, Paper 62 (PTAB Nov. 3, 2014) .....        | 14         |
| <i>Raytheon Techs. Corp. v. General Electric Co.</i> ,<br>993 F.3d 1374 (Fed. Cir. 2021) .....                    | 13         |
| <i>Robert Bosch Tool Corp. v. SD3, LLC</i> ,<br>IPR2016-01751, Paper 15 (PTAB Mar. 22, 2017) .....                | 39         |
| <i>Sandoz Inc. v. Pharmacyclics LLC</i> ,<br>IPR2019-00865, Paper 8 (PTAB Sept. 26, 2019) .....                   | 26, 33     |

|                                                                                                  |        |
|--------------------------------------------------------------------------------------------------|--------|
| <i>Sanofi v. Watson Labs. Inc.</i> ,<br>875 F.3d 636 (Fed. Cir. 2017) .....                      | 60, 76 |
| <i>SIBIA Neurosciences, Inc. v. Cadus Pharm. Corp.</i> ,<br>225 F.3d 1349 (Fed. Cir. 2000) ..... | 53, 57 |
| <i>In re Wands</i> ,<br>858 F.2d 731 (Fed. Cir. 1988) .....                                      | 3, 76  |
| <i>WBIP, LLC v. Kohler Co.</i> ,<br>829 F.3d 1317 (Fed. Cir. 2016) .....                         | 40     |
| <i>Xerox Corp. v. Bytemark, Inc.</i> ,<br>IPR2022-00624, Paper 12 (PTAB Feb. 10, 2023) .....     | 17, 29 |
| <i>Xerox Corp. v. Bytemark, Inc.</i> ,<br>IPR2022-00624, Paper 9 (PTAB Aug. 24, 2022) .....      | 17     |

## **Federal Statutes**

|                             |    |
|-----------------------------|----|
| 35 U.S.C. § 102 .....       | 61 |
| 35 U.S.C. § 253(a) .....    | 12 |
| 35 U.S.C. § 312(a)(3) ..... | 77 |
| 35 U.S.C. § 322(a)(3) ..... | 77 |

## **Regulations**

|                            |    |
|----------------------------|----|
| 37 C.F.R. § 1.321(a) ..... | 12 |
| 37 C.F.R. § 42.65(a) ..... | 17 |
| 37 C.F.R. § 42.73(b) ..... | 13 |

## **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 and life-threatening seizure disorder characterized by continuous seizure activity or multiple seizures that last longer than 30 minutes without regaining consciousness. Ex. 1004, 18287; Ex. 1011, 1; Ex. 2014, ¶¶ 14, 16. Before the claimed inventions, several drugs were used to treat SE but often 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 are unpatentable for anticipation, obviousness, or lack of enablement. None have any merit. Zhang, Petitioner’s lead reference for its anticipation and obviousness challenges, does not disclose or suggest that ganaxolone would have been successful to treat SE in humans in the manner claimed. Ex. 1009. Indeed, 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 various 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 has failed to prove by a preponderance of the evidence that any of claims 22 and 25-31 of the '817 patent are unpatentable.

## **II. Background and State of the Art**

### **A. Status epilepticus**

Epilepsies and seizure disorders fall under the field of neurology and include various neurological disorders characterized by abnormal electrical activity in the brain that causes seizures. Ex. 2014, ¶ 13. A seizure is an atypical electrical discharge in the brain that results in changes in consciousness, sensation, and behavior. Ex. 1004, 18285; Ex. 2014, ¶ 13. Epilepsy is a chronic condition characterized by recurring unprovoked seizures. *Id.*

SE is one 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; Ex. 2014, ¶ 14. SE is “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; Ex. 2014, ¶ 14. As acknowledged by Petitioner, SE is “the second most common neurologic emergency in the U.S.” with “150,000 cases per year.” Ex. 2002, 22; Ex. 2014, ¶ 14.

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 any category of seizure disorders—it is a neurologic emergency with limited and drastic treatment options. Ex. 2003, 2382; Ex. 2014, ¶ 15. For example, antiseizure medicines are the first line of defense against SE, but 30-57% of patients fail to respond to these first-line therapies. *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).

Mortality rates are as high as 35% in treatment-resistant SE patients and “nearly half of the surviving patients have subsequent neurologic deficits.” Ex. 2003,

2382; Ex. 2014, ¶ 16. Indeed, Petitioner’s own CEO has described SE as a “difficult to treat seizure disorder with limited treatment options.” Ex. 1011, 1; Ex. 2014, ¶ 16. Thus, one of the “key areas of unmet clinical needs in epilepsy” included “new [antiepileptic drugs] for drug-resistant seizures and SE.” Ex. 1004, 18306; Ex. 2014, ¶ 16.

**B. Patent Owner’s endeavors in epilepsy and seizure disorder treatment**

Patent Owner Ovid is a pioneer of developing therapies for challenging neurological disorders. Ex. 2004, 3; Ex. 2014, ¶ 17. 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. Ovid has four drug 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  $K^+Cl^-$  cotransporter 2 (“KCC2”) activators (in preclinical development for treating resistant epilepsies and other neuropathologies).

Ex. 2004, 5; Ex. 2014, ¶ 17. Ovid's research in this field extends beyond these clinical candidates. Besides the '817 patent directed to treating SE, Ovid has 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. Ex. 2014, ¶ 18. 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 of ganaxolone for treating SE. Ex. 2014, ¶ 18. The results generated in Marinus's clinical trials align seamlessly with the treatment methods outlined in the '817 patent. *Id.* 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. *Id.*

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; Ex. 2014, ¶ 19. During the study, the three ganaxolone dose cohorts studied included 500 mg/day (low), 650 mg/day (medium), and 713 mg/day (high). Ex. 2003, 2383; Ex. 2014, ¶ 19. These three ganaxolone doses are each encompassed by one or more of the ’817 patent’s claims. Ex. 2014, ¶ 19. 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.” Ex. 2003, 2383; Ex. 2014, ¶ 19. All three dose cohorts met the primary endpoint: “No patient who received ganaxolone added to the standard-of-care [antiseizure medicines (“ASMs”)] required treatment with IV anesthetics within 24 h of ganaxolone initiation (Table 2).” Ex. 2003, 2385; Ex. 2014, ¶ 19. 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 the ganaxolone infusion.” Ex. 2003, 2386; Ex. 2014, ¶ 19. 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.” Ex. 2003, 2388; Ex. 2014, ¶ 19.

**C. Marinus touts the unexpected benefits of Ovid’s inventions**

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; Ex. 2014, ¶ 20. In that provisional application, Petitioner stated that “[t]here is an unmet medical need for therapeutics effective against treatment-resistant forms of SE,” and that “[i]t is an object of the invention to provide a treatment for status epilepticus.” Ex. 2006, 21. Marinus filed several applications claiming the benefit of this provisional application, including U.S. Application Nos. 17/186,569<sup>1</sup> and 17/729,427.<sup>2</sup> During prosecution of these applications, the Office

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<sup>1</sup> U.S. App. No. 17/186,659 later issued as U.S. Patent No. 11,110,100.

<sup>2</sup> U.S. App. No. 17,729,427 later issued as U.S. Patent No. 11,679,117.

repeatedly rejected pending claims<sup>3</sup> 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, Marinus 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 when ganaxolone was discontinued.” Ex. 2007, 30 at ¶ 7; Ex. 2008, 26 at ¶ 7; Ex. 2014, ¶ 21.

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; Ex. 2014, ¶ 22. This result was “completely contrary” to Marinus’s and its scientist’s expectations. Ex. 2007, 31 at ¶ 10; Ex. 2008, 27 at ¶ 10; Ex. 2014, ¶ 22.

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<sup>3</sup> 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 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.

### **III. The '817 Patent**

#### **A. The specification and claims**

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.

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; Ex. 2014, ¶ 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; Ex. 2014, ¶ 24.

The specification contains four examples. Example 3 provides a detailed description of the “evaluation of the ability of allopregnanolone, ganaxolone, and gaboxadol to block benzodiazepine-resistant status epilepticus.” Ex. 1001, 35:31-37:15. As depicted in the timeline 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 minutes after the onset of pilocarpine-induced

convulsive SE. *Id.*, Fig. 2, 35:59-61, 36:22-24; Ex. 2014, ¶ 25. 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. Ex. 1001, 35:61-67; Ex. 2014, ¶ 25. Table 2 and Figures 3 and 4 show that administration of 20 mg/kg ganaxolone, but not allopregnanolone and gaboxadol, was effective to induce significant protection against SE, characterized by no observation of further convulsive seizures after 10 minutes of drug administration. Ex. 1001, Table 2, Figs. 3 and 4; Ex. 2014, ¶ 25. At a lower dose (10 mg/kg), ganaxolone also afforded protection against SE despite not reaching a statistically significant threshold. Ex. 1001, Table 2, Figs. 3 and 4; Ex. 2014, ¶ 26. Both 10 and 20 mg/kg of ganaxolone treatment also promoted 24-hour survival of the experimental animals, although the effects were not statistically significant. *Id.* And, Figure 5 shows that all doses of ganaxolone examined, except the lowest dose (0.5 mg/kg), reduced the number of observed seizures after treatment. Ex. 1001, 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; Ex. 2014, ¶ 27. 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. Ex. 1001, 37:28-32; Ex. 2014, ¶ 27.

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 salt 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. 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. *See* Ex. 2001. 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).

#### **IV. 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, 1-2; Ex. 2012; Ex. 2015, 33:2-12. In his role as a member of the Scientific Advisory Board, Dr. Rogawski provides comments to Marinus on its various clinical and preclinical programs, including ganaxolone for treating SE. Ex. 2015, 33:13-34:5. Marinus also compensates Dr. Rogawski for his role on the Scientific Advisory Board. *Id.*, 34:6-15. 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. *See 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.

| <b>Petition</b>                                                                                                                                                                                                           | <b>Rogawski Declaration (Ex. 1003)</b>                                                                                                                                                                                |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Pet., 19: Seeing these results in the rat pilocarpine model, persons skilled in the art would have reasonably believed that ganaxolone would show efficacy in treating human SE as well, for the reasons discussed above. | ¶ 40: Seeing these results in the rat pilocarpine model, persons skilled in the art would have reasonably believed that ganaxolone would show efficacy in treating human SE as well, for the reasons discussed above. |

| Petition                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Rogawski Declaration (Ex. 1003)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>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.</p>                                                                                                                                                                                                                                               | <p>¶ 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.</p> |
| <p>Pet. 45: Moreover, Zhang states: “Methods of treatment also include administering multiple injections of the <math>\beta</math>-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.</p> | <p>¶ 94: Moreover, Zhang states: “[m]ethods of treatment also include administering multiple injections of the <math>\beta</math>-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.</p>        |
| <p>Pet. 48: To the extent that Zhang does not anticipate claims 1–3, 10–17, and 19–31, however, they are obvious over Zhang, at least because Zhang suggests</p>                                                                                                                                                                                                                                                                                                                                                                                                                        | <p>¶ 107: If the Zhang Publication does not anticipate all the limitations of claims 1–3, 10–17, and 19–31, it at least suggests them by the same</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |

| Petition                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Rogawski Declaration (Ex. 1003)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| the subject matter of claims 1–3, 10–17, and 19–31, as described below.                                                                                                                                                                                                                                                                                                                                                                                                                                | 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., 78: 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 administration schedules anticipated or |

| Petition                                       | Rogawski Declaration (Ex. 1003)                |
|------------------------------------------------|------------------------------------------------|
| obvious, the '817 patent does not enable them. | 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”).

## V. 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.” Ex. 2014, ¶ 58. 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) (“[F]or 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 POSA thus would have understood that the “someone ‘in need’” would be a human patient suffering from SE, and is not a rat or other non-human animal receiving ganaxolone for research purposes. Ex. 2014, ¶ 58.

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; Ex. 2014, ¶ 59. The specification notes that “[t]he 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. Ex. 2014, ¶ 59. 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 simply “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. As Patent Owner’s expert, Dr. Sankar, explains, a POSA thus would have understood that, in light of the specification, the term “treating” refers to treating clinical and subclinical symptoms of a disease or a condition in a human patient, not preclinical or research uses with a rat or other non-human animals. Ex. 2014, ¶¶ 59-60.

Moreover, for claims 25-31, a POSA would have understood that the doses recited in these claims (ranging from 500 mg to 1050 mg) are 130 to 200 times larger than the doses administered to rats in the ’817 patent’s examples. *See, e.g.*, Ex. 2014, ¶ 61. A POSA thus would have understood that, in the context of claims 25-31 and the specification, the claim term refers to administering doses of ganaxolone to a *human* patient, not a rat. *Id.*

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 rat). *See* Ex.

1001, 35:44-48 (rats used weighed 100-125 g); *id.*, 36:22-24 (highest dose of ganaxolone administered was 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 rat). *See* Ex. 1001, 37:62-66 (rats used weighed 100-125 g); *id.*, 37:45-60 (Table 3 providing highest dose of ganaxolone (GNX) as 30 mg/kg). Thus, the lowest dose recited in claims 25-31 is 133 times larger than the largest amount of ganaxolone given to a rat in Example 4. Ex. 2014, ¶ 61.

Additionally, the specification describes administering weight-based doses of ganaxolone as high as 40 mg/kg. Ex. 1001, 8:11-22 (“Ganaxolone or a pharmaceutically acceptable salt thereof can be administered in doses ranging from 10 mg/kg to 40 mg/kg.”). Using the highest weight of a rat from Examples 3 and 4 (.125 g), the doses of ganaxolone recited in claims 25-31 relate to weight-based dosing in a rat spanning 4000 mg/kg (for 500 mg dose) to 8400 mg/kg (for 1050 mg dose). Such weight-based doses are 100 to over 200 times higher than those described in the '817 patent specification for treating a patient. Thus, administering a 500 mg dose of ganaxolone to a rat would not fall within the range disclosed in the specification. A POSA thus would have understood that the “patient” being

administered the dosage amounts recited in claims 25-31 would not have been a rat. *See* Ex. 2014, ¶ 63.

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.

Extrinsic evidence also supports the understanding that the doses recited in claims 25-31 would not be administered to a rat. For example, in Zhang, the rats in Example 8 weighed between 269 and 351 grams. Ex. 1009, ¶ [0120]. Therefore, the highest amount of ganaxolone administered to a rat in Zhang was 5.265 mg (15 mg/kg x .351 kg). *Id.*, ¶¶ [0117], [0120]. This is nearly 100 times smaller than the lowest dose amount of ganaxolone recited in claims 25-31. A POSA would have understood that the dose amounts recited in claims 25-31 are directed to treating a *human patient* suffering from SE, not a rat. Ex. 2014, ¶ 62.

Further, studies performed in 1997 found that ganaxolone is "a potent anticonvulsant against fully kindled stage 5 seizures induced by corneal kindling in rats" with an effective dose (ED<sub>50</sub>) of 4.5 mg/kg administered intraperitoneally. Ex. 1028, 1284; Ex. 2014, ¶ 64. The doses recited in claims 25-31 are about 1000 to 2000 times more than the effective dose in a rat (assuming 0.125 g as the weight of a rat, the highest weight used in the '817 patent examples) and a POSA would have

understood that the dose amounts in claims 25-31 would not have been used in a method to *treat* SE in a rat.

A POSA also would have understood that administering several thousand mg/kg ganaxolone to a rat would not result in treating SE and would instead be toxic to the rat. Ex. 2014, ¶ 64. Studies evaluating the safety of administering ganaxolone to rats and its effects on a rat's central nervous system report that motor function is impaired starting at 5 mg/kg, sedation occurs at 15 mg/kg, loss of righting reflex occurs at 20 mg/kg, ataxia occurs at more than 20 mg/kg, and cognitive function is “significantly impaired” and considered “adverse” at 30 mg/kg. Ex. 2017, 25; Ex. 2014, ¶ 64; *see also* Ex. 2018, 3 (reporting lowest published toxic dose of ganaxolone administered subcutaneously to a rat is 3.46 mg/kg). A POSA would have understood that administering doses of ganaxolone at 100 times greater than those doses studied would result in extreme impairment to the rat's central nervous system and would not consider such high doses to be treating SE, as required by claims 25-31. Ex. 2014, ¶ 64. Therefore, interpreting “patient” in claims 25-31 to include a rat would lead to a “nonsensical reading” of claims 25-31. *See Microprocessor Enhancement Corp. v. Texas Instruments Inc.*, 520 F.3d 1367, 1376-77 (Fed. Cir. 2008) (holding that same claim term can have different meanings based on the context when uniform construction would lead to a “nonsensical reading”); *see also Aventis Pharms. Inc. v. Amino Chems. Ltd.*, 715 F.3d 1363, 1374 (Fed. Cir.

2013) (holding that “the same claim term can have different constructions depending upon the context of how the term is used within the claims and specification”).

Petitioner and the Board in its Institution Decision improperly construe the term “patient” in a vacuum, divorced from the context of the claims and written description. Pet., 34-35; Decision, 7-9; *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 did not address that the claimed “patient” 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 (emphasis added). “Include” does not mean “require.” And, as shown above, “patient” must be read in the context of its use, which in the challenged claims refers to treating a human patient in need of treatment for SE. In the context of claims 22 and 25-31, the recited doses clearly meant for administration to humans further highlight Petitioner’s selective and unsupported construction contrary to *Phillips*. 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*'s requirement that the claim language be viewed in the context of the specification from the POSA's perspective.

**B. “Improvement to the patient after administration for more than 8 hours” (claim 22)**

“Improvement to the patient after administration for more than 8 hours” in claim 22 means that there is improvement to the human patient more than 8 hours after the full dose of ganaxolone is given, regardless of whether the full amount of ganaxolone is given in a single administration or multiple administrations. Ex. 2014, ¶ 65.

The plain and ordinary language of claim 22 requires there to be improvement to the patient for more than 8 hours *after administration* of the amount of ganaxolone required to treat SE. While the claim language allows for that total amount of ganaxolone to be divided into multiple doses, the claim requires measuring improvement *after* that total amount has been administered.

As Dr. Sankar explains, a POSA would have understood that whether the administration of a particular drug results in sustained improvement to a patient with SE would be assessed after the full dose of the drug is administered to the patient. Ex. 2014, ¶ 66. A POSA would not have started considering whether a dose demonstrates improvement to the patient after administration of only the first portion

of the total dose because the total dose of a drug is typically required to provide the expected effect. *Id.*

Therefore, a POSA would have understood that “improvement to the patient after administration for more than 8 hours” in claim 22 means that there is improvement to the human patient more than 8 hours after the full dose of ganaxolone is given, regardless of whether the full amount of ganaxolone is given in a single administration or multiple administrations.<sup>4</sup>

## **VI. Ground 1: Zhang Does Not Anticipate Claims 22 and 25-31**

### **A. Zhang does not describe “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 proper construction, “treating status epilepticus comprising administering to a patient in need thereof” requires treating a *human* patient suffering from SE. *See supra* § V.A. Petitioner, however, points to nothing in Zhang that describes treating a human patient, let alone one suffering from SE. Pet., 35-38; Ex. 2014, ¶ 70. Petitioner cites only to paragraphs [0005] and

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<sup>4</sup> When asked whether “Claim 22 requires improvement to the patient for more than eight hours after the total amount required to treat SE is administered,” Dr. Rogawski responded that he “d[id] not have an opinion on that.” Ex. 2015, 46:9-13.

[0031], both of which relate to a formulation of ganaxolone used for administration to rats, and paragraphs [0104]-[0136], which are directed to the Examples, none of which describe treating a human patient suffering from SE. Ex. 2014, ¶ 70. Nor can Petitioner point to any relevant disclosure in Zhang that describes intravenously administering ganaxolone to a human patient suffering from SE. *Id.* 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 patients as well.” Pet., 38 (emphasis added). But it is inappropriate to rely on the knowledge of a POSA 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”).

Further, as Dr. Sankar explains, animal models do not translate directly to human treatment. Ex. 2014, ¶ 71. For example, in the rat lithium-pilocarpine model, SE is chemically induced using pilocarpine, which differs from its onset in most

humans, which is typically due to various clinical circumstances (e.g., infection, inadvertently missing doses of anti-seizure medicines, trauma, stroke, carcinomatous meningitis, etc.). *Id.* Because SE is chemically induced in rats using pilocarpine, researchers have found that this has resulted in “variations in SE induction and pilocarpine sensitivity between different batches of the same strain of rats” and “most likely result[s] in the wide-ranging experimental data reported from different laboratories.” Ex. 1006, 3; Ex. 2014, ¶ 71. Moreover, one would understand that doses administered to rats cannot be directly compared to doses administered to humans on a mg/kg basis. Ex. 2014, ¶ 71. This is due, at least in part, to rats metabolizing compounds at a much faster rate than humans by the hepatic microsomal system. *Id.* As a result, higher doses (in mg/kg) of a compound are typically administered to rats than humans. *Id.* Therefore, data from the rat pilocarpine model provides information only as to what compounds could potentially be used to treat SE in humans and does not provide specific information regarding effective doses of those compounds in humans. *Id.*

Petitioner’s expert, Dr. Rogawski, also explained that he had studied “a variety of neuroactive steroids” other than ganaxolone that demonstrated “some degree of activity in ... status epilepticus” in an animal model. Ex. 2015, 24:14-25:7. Yet only one of these other compounds, allopregnanolone, advanced to clinical trials in humans for treating SE, where it eventually failed to receive FDA approval

because it did not meet the primary efficacy endpoints in a Phase 3 clinical trial. Ex. 2015, 23:9-24:1. This further demonstrates that data in animal models identifies at best potential agents that could be effective for treating SE in humans.

Moreover, as discussed above in Section IV, 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 proper construction.

**B. 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 formulations provide 'improvement to the patient after administration for more than 8 hours.'" 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 thus must resort to inherency, asserting that “[t]o the extent that improvement to the patient were to occur after [5 hours], however, it would be the natural result of administering the ganaxolone formulations in the manner taught in Zhang.” Pet., 44-45; Ex. 1003, ¶ 93. But Zhang cannot demonstrate that ganaxolone has any effect on SE in a human patient, through inherency or otherwise, because ganaxolone was not administered to a human patient. *See generally* Ex. 1009; Ex. 1004, ¶ 76. Further, neither Petitioner nor Dr. Rogawski 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 15 (PTAB Mar. 14, 2023) (“[A]ttorney 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 discussed above in Section V.B, the proper construction of “improvement to the patient after administration for more than 8 hours” in claim 22 requires that there is improvement to the human patient more than 8 hours starting after the full dose of ganaxolone is given, regardless of whether the full amount of ganaxolone is given in a single administration or multiple administrations. 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; Ex. 2014, ¶ 75. In fact, Dr. Rogawski admitted that after the 5-hour mark in Zhang’s Example 8 that “it’s possible that there could be improvement, there might not be improvement. When one is treating a medical condition, there’s always a degree of variability and one doesn’t expect a certain outcome.” Ex. 2015, 155:7-16; *see also* Ex. 2014, ¶¶ 76-78. This is insufficient to demonstrate anticipation by inherency. *Bettcher Indus., Inc. v. Bunzl USA, Inc.*, 661 F.3d 629, 639 (Fed. Cir. 2011) (holding that inherency “may not be established by probabilities or possibilities”).

Petitioner also led the Board to erroneously conclude that “Zhang demonstrates that ganaxolone continues to improve status epilepticus in rats for 5+ hours.” Decision, 27. Earlier in its Institution Decision the Board states that Zhang

“suggests that ganaxolone continued providing improvement up to the 5 hour point,” *id.*, 26, and that “the experiment was stopped at 5 hours,” Ex. 1003, ¶ 93, which means that there is no data in Zhang beyond that point, Ex. 2014, ¶¶ 76-77; Ex. 1003, ¶ 93 (Dr. Rogawski stating that “because the experiment stopped at 5 hours, there is no data demonstrating a response ‘for more than 8 hours’”). Therefore, it cannot be that Zhang “demonstrates that ganaxolone continues to improve status epilepticus in rats for 5+ *hours*.” Decision, 27 (emphasis added).

Zhang instead discloses the opposite—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]; Ex. 2014, ¶ 76. 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); Ex. 2014, ¶ 76. And Zhang

provides no data regarding seizure reduction beyond 5 hours post administration. Ex. 2014, ¶ 77; Ex. 1003, ¶ 93. Zhang therefore cannot inherently anticipate claim 22 because it does not show that the claim limitation inevitably would occur; and, if anything, it shows the contrary.

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 four reasons. Pet., 45 (citing Ex. 1009, ¶ [0074]).

*First*, Petitioner's argument that "the treatment could be repeated at intervals of 2 hours to provide sustained treatment for more than 8 hours" (Petition, 45) contradicts the ordinary and customary reading of the claim language, which requires improvement to the patient for more than 8 hours after the *total dose* of ganaxolone required to treat SE has been administered. *See supra* § V.B. While the plain claim language allows for the total dose to be divided into multiple administrations, improvement must be shown for more than 8 hours after the total dose has been administered to the patient. That is, the claim cannot be met by showing that there is improvement to the patient more than 8 hours after only the first portion of the total dose required to treat SE has been administered, as Petitioner asserts.

*Second*, here again, Petitioner improperly relies on what a POSA allegedly would have known to fill the gaps in Zhang. Pet., 45 ("A skilled artisan would

immediately recognize . . . .”). The knowledge of a POSA, however, has no place in an anticipation analysis. *See, Connell*, 722 F.2d at 1548; *Sandoz*, IPR2019-00865, Paper No. 8 at 20-21.

*Third*, 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); *see also 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

POSA 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 POSA 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]; Ex. 2014, ¶ 79.

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. Ex. 2014, ¶ 80; Ex. 2015, 71:2-8. Instead, Zhang generally discusses various treatment options, including the disease or disorder treated (e.g., at least 31 diseases or disorders in Zhang generally, *see* Ex. 1009, ¶¶ [0069]-[0074]), the type of administration (e.g., “intramuscularly or intravenously”), and dose amount. *id.*, ¶ [0074]. Ex. 2014, ¶ 80. Indeed, paragraph 74 of Zhang does not even refer to treating SE (*see* Ex. 2015, 71:2-8), 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. Ex. 2014, ¶ 80. 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.

*Fourth*, Zhang’s paragraph 74 states only that the  $\beta$ -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 that after the total dose of ganaxolone is administered (whether through single or multiple injections) there is “improvement to the patient after administration for more than 8 hours.”

Notably, Petitioner provides no evidence as to why improvement to the patient for more than 8 hours after the total dose of ganaxolone is administered would inevitably happen once the total dose is divided into multiple injections at 2-hour intervals or that if a single injection for SE suppresses seizures for up to 2 hours, then dividing the total dose into injections repeated every two hours would necessarily and inevitably provide sustained improvement to the patient for more than 8 hours after the total dose required to treat SE has been administered, as claim 22 requires. *See* Pet., 45; Ex. 1003, ¶ 94; Ex. 2014, ¶ 80. This is because paragraph 74 only mentions the duration between doses of ganaxolone (*see* Ex. 2015, 74:16-75:5), it does not mention for how long after the total dose of ganaxolone is administered that ganaxolone provides sustained improvement in SE. In fact, Zhang shows the opposite—at best, Zhang’s Example 8 discloses that ganaxolone shows improvement in rats for up to 2 hours, after which the effects of ganaxolone *diminish*. *See* Ex. 1009, 26-27 (Tables 6 and 7), ¶¶ [0135]-[0136]; Ex. 2014, ¶ 76.

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

**C. 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 these claimed ranges relate to the following weight-based dose amounts in a 70-kg human patient: 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, however, does not describe any of the ranges recited in claims 25-31. Ex. 2014, ¶ 81. Specifically, there is no single embodiment described in Zhang that falls within the scope of claims 25-31. For this reason alone, Zhang does not anticipate claims 25-31.

To overcome that deficiency, Petitioner points to a single range of doses 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. Zhang’s general disclosure is not specific to any one disease state, dosage strength, or dosing regimen. Ex. 2014, ¶ 82. 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]; that the methods of treatment “also include administering multiple injections ... over a period of 1 to 10 days,” *id.*, ¶ [0074]; and that “[t]he 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 (or 1,680 mg/day to 33,600 mg/day for a 70 kg adult). Ex. 2014, ¶¶ 82-83. 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]; Ex. 2015, 75:6-76:1. 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. Ex. 1009, ¶ [0085]; Ex. 2014, ¶ 81. It instead provides several broad dose ranges for administering a ganaxolone formulation in the abstract, and not for any specific disease. Ex. 1009, ¶ [0085]; Ex. 2014, ¶ 82. 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).

Zhang’s range of “from about 1 mg/kg to about 20 mg/kg” dosed from every 1 to 24 hours allows for potential daily doses ranging from about 1 mg/kg/day to about 480 mg/kg/day or, as a weight-based dose range for a 70 kg adult human, about 70 mg/day to 33,600 mg/day. Ex. 2014, ¶ 83. Therefore, Zhang provides an extremely broad range of potential doses of ganaxolone. But it is not true that “any dose of ganaxolone would function to treat status epilepticus patients and result in improvement to the patient as required by claims 25-31.” Decision, 30; *see* Ex. 2014, ¶ 84. Zhang’s disclosure of 70 mg/day to 33,600 mg/day for a 70 kg adult human encompasses several broad dose ranges that would be ineffective to treat SE patients and not result in improvement to the patient as claims 25-31 require. Ex. 2014, ¶ 85. Therefore, Zhang’s extremely broad disclosure, which is untethered to a particular

disease state and any effective dose ranges, does not describe any of the ranges recited in claims 25-31. *Id.*

Further, Zhang’s Example 8 provides data in only the rat-lithium pilocarpine model and only at ganaxolone doses of 12 mg/kg and 15 mg/kg. Ex. 1009, ¶ [0117]. As discussed above in Section VI.A, doses administered to rats cannot be directly compared to doses administered to humans on a mg/kg basis. Ex. 2014, ¶ 87. This is due, at least in part, to rats metabolizing compounds at a much faster rate than humans. Ex. 2014, ¶ 87; *supra* § VI.A. To account for this difference, higher doses (in mg/kg) of a compound are typically administered to rats than humans by the hepatic microsomal system. Ex. 2014, ¶ 87. Therefore, the data in Example 8 of Zhang does not describe treating SE using any of the doses described in claims 25-31. *Id.*, ¶ 88.

## **VII. Grounds 2-4: Petitioner Has Not Demonstrated that Claims 22 and 25-31 Would Have Been Obvious Over Any of the Asserted References**

### **A. 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 its obviousness position. Here, the objective evidence was not only publicly available, but much of the objective evidence comes from Petitioner's own statements.

There is also 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).

**1. 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. Ex. 2014, ¶ 107. "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).

Statements by Petitioner and its own work after the ’817 patent’s filing date confirm that the treatment methods recited in claims 22 and 25-31 provided unexpected results over what a POSA would have expected in view of Zhang. Ex. 2014, ¶ 107; *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) (same).

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.<sup>5</sup> 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 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 POSA—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.*; Ex. 2014, ¶ 108.

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

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<sup>5</sup> 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”).

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.*, 2381. 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 completion of the ganaxolone infusion (Table 2).” *Id.*, 2386.

And in the follow-up period four weeks 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 POSA 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. Ex. 2014, ¶¶ 109-112.

Moreover, it was unexpected that 82% of patients “did not require treatment for SE with additional second-line IV ASMs or IV anesthetics through 24 h following completion of the ganaxolone infusion (Table 2)” and that in the follow-up period four weeks after ganaxolone discontinuations, “85% of evaluable patients did not have SE relapse,” *id.*, 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. Ex. 2014, ¶ 113.

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

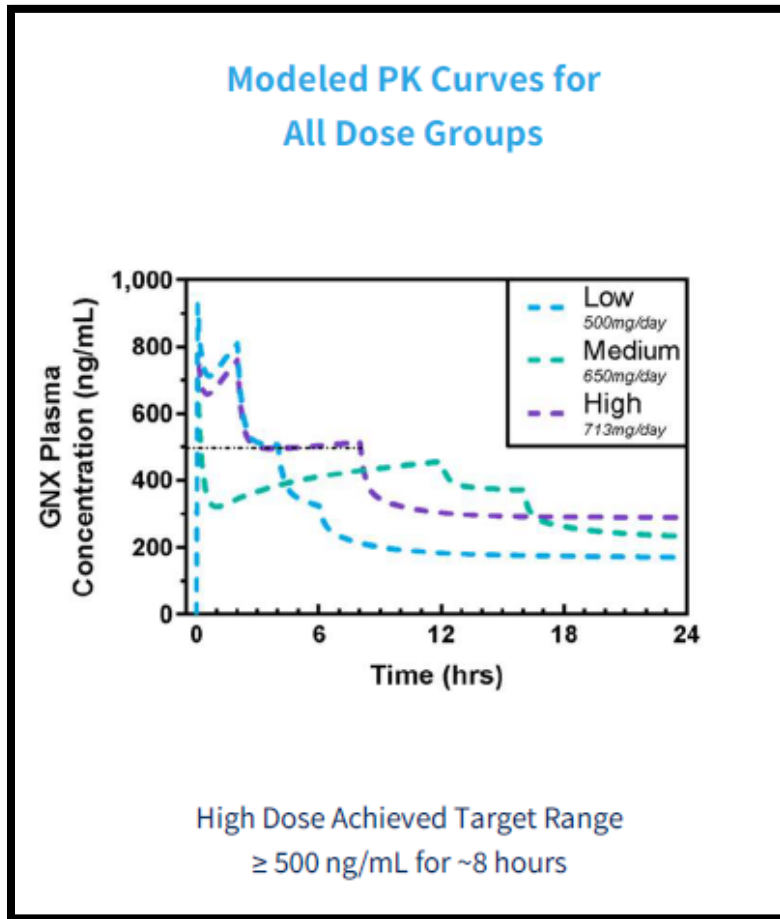
provides “a method that can effectively break SE using ganaxolone” and “provides enhanced safety for patients by limiting the duration of exposure to high drug levels to only about 8 to about 12 hours,” which “lessens the risk of unwanted adverse events.” *Id.*

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:

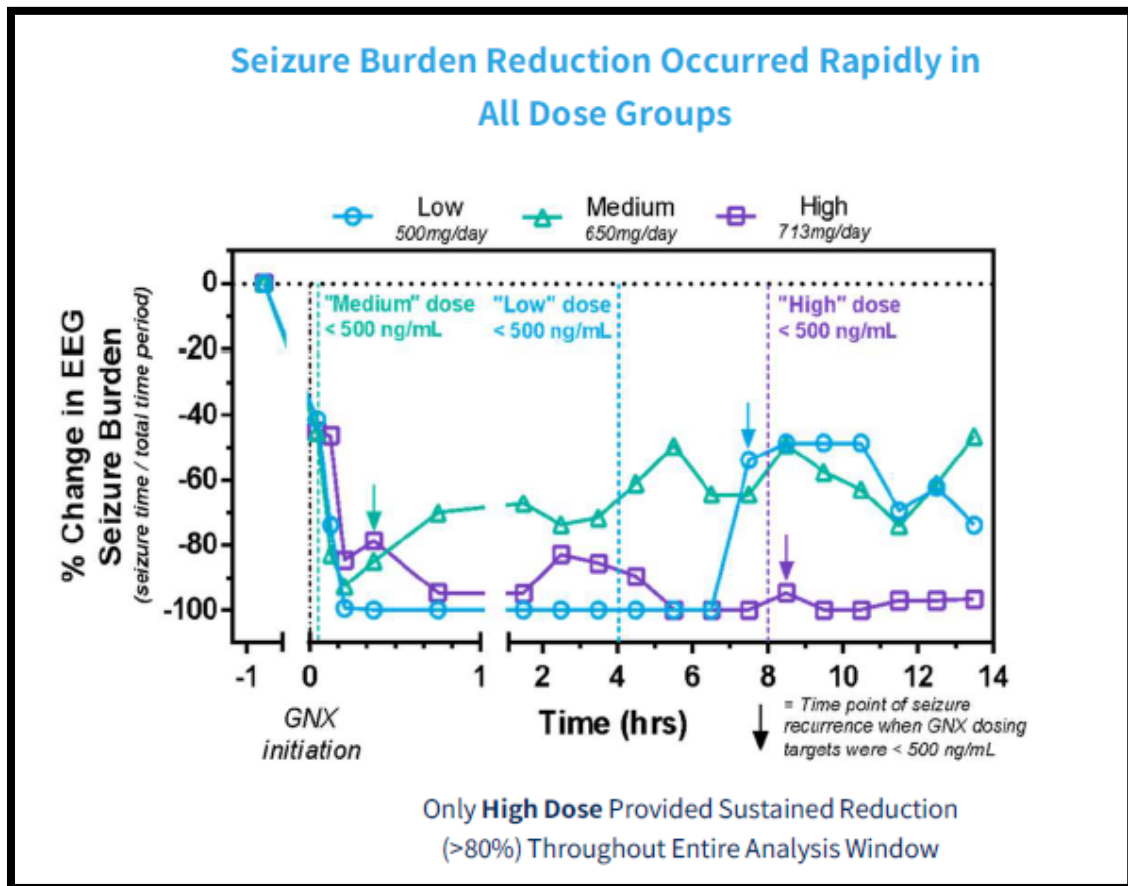
Sustained clinical response was associated with maintaining ganaxolone plasma concentrations  $\geq 500$  ng/ml. Ganaxolone plasma levels  $\geq 500$  ng/ml were achieved only briefly during the initial bolus for patients in the medium-dose cohort, whereas those in low- and high-dose cohorts maintained such levels for 4 and 8 h, respectively. The greatest decrease in seizure burden was seen when ganaxolone concentrations were maintained at  $\geq 500$  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 ( $\geq 500$  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  $\geq 500$  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  $\geq 500$  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 POSA scientist's expectations and were markedly superior over the other doses encompassed by Zhang's extremely broad disclosure. Ex. 2014, ¶¶ 113-116; see *Bristol-Myers Squibb*, 752 F.3d at 977.

Moreover, these results surprisingly revealed that ganaxolone could result in “improvement to the patient after administration for more than 8 hours,” particularly in view of Zhang’s Example 8, which showed that any effect of ganaxolone in reducing EEG power diminishes by 5 hours, *see* Ex. 1009, ¶¶ [0135]-[0136], and that ganaxolone showed a significant reduction in seizures 3-5 hours after administration for only one low frequency group, 0-5 Hz. *See id.*, 26-27 (Tables 6 and 7).

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. Ex. 2014, ¶¶ 117-118. These unexpected results thus support the nonobviousness of claims 22 and 25-31. Ex. 2014, ¶¶ 118, 141, 162.

**2. 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. Ex. 2014, ¶¶ 119-121; *see supra* § II. 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.

### 3. Failure of others in treating SE

Patent Owner's claimed methods stand against a stark backdrop of repeated failures for treating SE. Ex. 2014, ¶ 122. 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.

Moreover, allopregnanolone was seen as a promising candidate for treating SE in humans, however, it did not receive FDA approval because it failed to meet its primary efficacy endpoints in a Phase 3 clinical trial. Ex. 2015, 23:6-24:1. This failure is particularly telling because allopregnanolone, like ganaxolone, is a neuroactive steroid and allosteric modulator of the GABA<sub>A</sub> receptor. Ex. 2015, 24:2-13.

All of these failures support the nonobviousness of claims 22 and 25-31. Ex. 2014, ¶ 122; *see Cyclobenzaprine*, 676 F.3d at 1081-82.

**B. Ground 2: Claims 22 and 25-31 would not have been obvious over Zhang.**

**1. Claim 22**

**a. No motivation**

A POSA would not 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.” Ex. 2014, ¶ 89-92. As discussed above in Section VI.B, nowhere does Zhang describe “improvement to the patient after administration for more than 8 hours” under the proper construction *See also* Ex. 2014, ¶ 91. Neither the Petition nor Dr. Rogawski’s declaration makes any attempt to demonstrate why a POSA 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  $\beta$ -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 POSA 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  $\beta$ -cyclodextrin-ganaxolone injection “may be given at intervals of 1 to 24 hours” to treating SE or Zhang’s Example 8. Ex. 2014, ¶ 92; Ex. 2015, 71:2-8. And Petitioner makes no attempt to supply this connection.

Moreover, Petitioner’s attempt to supply a motivation to fill in a limitation missing from Zhang through the “common knowledge” of a POSA 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 there is no motivation, Petitioner's obviousness challenge based on Zhang alone fails.

**b. No reasonable expectation of success**

A POSA would not 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." Ex. 2014, ¶ 93-98. 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 VI.B, a POSA would not have had a reasonable expectation of success based on Zhang's disclosure. Ex. 2014, ¶ 93.

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). *See* Ex. 1009, ¶¶ [0135]-[0136]. Zhang provides no data regarding seizure reduction beyond 5 hours. Ex. 2014, ¶ 94; Ex. 1003, ¶ 93. Dr. Rogawski also admitted that after the 5-hour mark in Zhang's Example 8, "it's possible that there could be improvement, there might not be improvement. When one is treating a medical condition, there's always a degree of variability and one doesn't expect a certain outcome." Ex. 2015, 155:7-16.

Petitioner points to no evidence as to why a POSA 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 IV, this argument and support should be entitled to little weight.

Moreover, a POSA would not 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.” Ex. 2014, ¶¶ 95, 98. As described above in Section V.B, the correct interpretation of claim 22 requires improvement to the human patient 8 hours starting after the full dose of ganaxolone is given, regardless of whether the dose of ganaxolone is given in a single administration or multiple administrations. Ex. 2014, ¶¶ 65-66, 96. Under this construction, Zhang provides no indication to a POSA that there would have been a

reasonable expectation of success in treating SE as required by claim 22. Ex. 2014, ¶ 97; *see also supra* § VI.B.

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 that multiple treatments can prolong an effect from a single treatment, let alone a prolonged effect on SE. Ex. 2014, ¶¶ 95, 98. Indeed, Zhang’s Example 8 at best shows that any effect ganaxolone has on improving SE diminishes by 5 hours. Ex. 1009, ¶¶ [0135]-[0136]; Ex. 2014, ¶ 75.

Petitioner relies on no evidence demonstrating why a POSA 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 IV, 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 a POSA would not 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 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 claimed method of treatment).

## **2. Claims 25-31**

### **a. No motivation**

A POSA would not have been motivated to choose the specific 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”). Ex. 2014, ¶¶ 99-102. In fact, the word “motivation” appears nowhere in Petitioner’s discussion of claims 25-31. *See* Pet., 46-49; Ex. 1003, ¶¶ 99-109.

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 POSA 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]; Ex. 2014, ¶ 102; Ex. 2015, 75:6-76:2.

Zhang provides no suggestion or motivation to choose the dose ranges recited in claims 25-31 from among the broad range of doses and treatment options described in Zhang. Ex. 2014, ¶¶ 101-102. Because Petitioner has set forward no motivation, its obviousness challenge fails.

**b. No reasonable expectation of success**

Petitioner fails to show that a POSA 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; Ex. 2014, ¶¶ 103-106. 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.

As discussed in Section VI.A, this alleged positive result in the rat pilocarpine model would not have provided a POSA with a reasonable expectation of success

for treating *human* patients with the specific doses of ganaxolone recited in claims 25-31. Ex. 2014, ¶¶ 71, 105. A POSA would have understood that the effectiveness of a particular dose in the rat pilocarpine model does not directly translate to human treatment due to at least the differences in the onset of SE in rats (chemically induced) and humans (occurring by various clinical circumstances) and a rat's faster metabolism by the hepatic microsomal system. Ex. 2014, ¶ 71. As Dr. Rogawski recognizes, the rat pilocarpine model at most can predict that a compound potentially could be useful in the treatment of SE in humans. *See, e.g.*, Ex. 1003, ¶¶ 25 (stating that animal models are used to identify treatments that “*may* be effective in terminating SE in humans” (emphasis added)), 27 (stating that the rat pilocarpine model “evaluate[s] *potential* treatments for SE” (emphasis added)), 33 (acknowledging that the rat pilocarpine “predicts” whether a therapy “*could be useful* in the treatment of SE in humans” (emphasis added)); Ex. 2014, ¶ 71. This prediction often does not translate into demonstrated efficacy in humans, particularly in the neuroactive steroid class of compounds that ganaxolone belongs to. *See, e.g.*, Ex. 2015, 23:6-25:7.

Zhang does not include any examples in humans of ganaxolone's efficacy in treating a human patient suffering from SE, let alone with the specific doses recited in claims 25-31. Ex. 2014, ¶ 105; *see supra* § VI.A. The lack of efficacy data in humans is significant because of the noted difficulties in treating SE. *See supra*

§ VII.A.2-3; *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, 1384 (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).

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 identifies ganaxolone as a potential therapy that could be useful to treat SE in humans; 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, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) (finding that a POSA 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 POSA would have “reasonably expected to achieve success in the treatment” of SE in humans based on Zhang’s disclosure. *Eli Lilly*, 8 F.4th at 1344. At most, Zhang’s results in the rat

pilocarpine model demonstrate only that ganaxolone “*could be useful* in the treatment of SE in humans.” *See, e.g.*, Ex. 1003, ¶ 33 (emphasis added). Petitioner has thus failed to show that a POSA, 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. Ex. 2014, ¶ 106.

**C. Ground 3: Claims 22 and 25-31 would not have been obvious over Zhang in combination with Saporito P1 and/or Saporito P2.**

**1. 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 (internal citations omitted); *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 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. Ex. 2016, 48:8-22, 71:16-23; *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). And Dr. Saporito admitted that he could not remember or provide a more specific number of attendees. Ex. 2016, 64:23-65:20 (“Q. ... [D]id you pin down more of a specific number? ... A. I didn’t count them.”), 66:17-67:23 (“Q. ... [H]ow many would you estimate you interacted with? ... A. Any -- it’s a very rough estimate, right. ... I really don’t remember.”), 79:15-80:21 (“Q. ... How many people stopped to ask questions? A. It’s hard. I can’t put a specific number on the number of people who asked questions. ... Q. Would you say the number of people that viewed the poster -- Poster 2 was comparable to the number of people that viewed Poster 1? A. It’s hard to say. It was a long time ago.”).

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. While the Supplemental Saporito declaration states without support that these exhibits are the same as the original Saporito P1 and Saporito P2 posters, Dr. Saporito was unable to provide additional support for his conclusion other than that he labeled the version attached to his declaration as “the final version” of each poster. Ex. 1033 at ¶¶ 4, 7; Ex. 2016, 48:16-52:12 (admitting that there may be changes made to the final PDF version after it is sent for printing), 71:13-73:8.

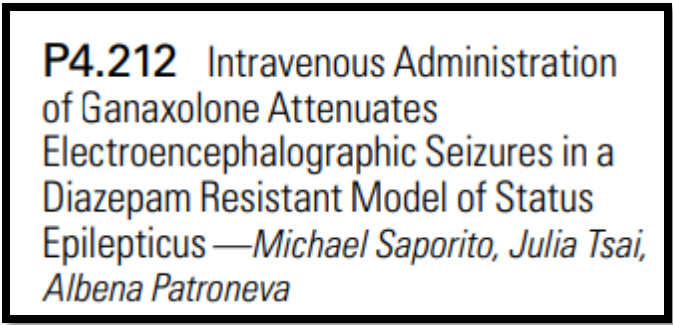
Neither the Saporito declaration nor the Supplemental Saporito declaration provides any chain of custody for the files that Petitioner alleges are the posters that were presented or indicates whether the declarant possessed these files or if someone else did. And while Dr. Saporito clarified that these exhibits came from his files, as described above, he admitted that the only evidence connecting the exhibits to the presented versions is that the exhibits came from files labeled “final” in his files. Ex. 2016, 14:4-7, 48:16-52:12, 71:13-73:8. 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; Ex. 2016, 90:2-91:7 (admitting that he did not split the posters into four pieces and he does not know who did).

The authorship of Saporito P1 and Saporito P2 further calls into question their public availability. Specifically, Saporito P1 identifies an extra author (Donna Henry) who is not included in the AAN Meeting Brochure. *See* Ex. 1012 at 48 (P2.020) (shown below); Ex. 2016, 54:3-8. The Saporito Declaration does not address this discrepancy in authorship of Saporito P1, and Dr. Saporito had no reason, other than a “guess,” as to why there was this discrepancy. *See* Ex. 1015; Ex. 2016, 54:3-20 (“I don’t remember specifically why Donna wasn’t included ... But my best guess ... is that after we wrote and submitted it, we probably decided that Donna should be one of the authors.”). 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 99 (P4.212) (shown

below); Ex. 2016, 73:9-12 (“It should have had authors on it.”). The Saporito Declaration does not address this discrepancy in authorship of Saporito P2 and Dr. Saporito explained that Saporito P2 *should have* listed the authors on its face. *See* Ex. 1015; Ex. 2016, 73:9-22. That Saporito P2 lists none of the authors listed in the AAN Meeting Brochure again begs the question as to whether 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,  
Albenia Patroneva*

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

**2. 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 VI, Zhang does not describe 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. Ex. 2014, ¶¶ 125-28.

Saporito P1 and Saporito P2 also do not describe intravenously administering to a human patient a pharmaceutical composition comprising ganaxolone or a

pharmaceutically acceptable salt thereof. Ex. 2014, ¶ 126. 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 describes intravenously administering ganaxolone to a human patient suffering from SE.

Additionally, as discussed in Section VI.A, it is common knowledge to a POSA that animal models do not translate directly to human treatment. Ex. 2014, ¶ 127. For instance, in the rat lithium pilocarpine model used in the references relied upon by Petitioner, SE is chemically induced using pilocarpine. This results in “variations in SE induction and pilocarpine sensitivity between different batches of the same strain of rats” and “most likely result[s] in the wide-ranging experimental data reported from different laboratories.” Ex. 1006, 3. In contrast, in humans, SE typically comes about because of various clinical circumstances (e.g., infection, inadvertently missing doses of anti-seizure medicines, trauma, stroke, carcinomatous meningitis, etc.). Ex. 2014, ¶ 127.

Moreover, doses of ganaxolone administered to rats cannot be directly compared with doses administered to humans because rats metabolize compounds at a much faster rate than humans by the hepatic microsomal system. Ex. 2014, ¶ 127; *supra* § VI.A. As a result, higher doses by weight of a compound are typically administered to rats than humans. Ex. 2014, ¶ 127. Additionally, Dr. Rogawski’s own experience dictates that neuroactive steroids showing “some degree of activity in ... status epilepticus” in animal models often fail to advance to clinical trials in humans and/or receive FDA approval for treating SE. Ex. 2015, 23:6-25:7.

A POSA thus would have understood that the rat data disclosed in Saporito P1 and Saporito P2 neither discloses intravenously administering to a human patient a pharmaceutical composition comprising ganaxolone or a pharmaceutically acceptable salt thereof nor provides the information necessary for a POSA to reach those limitations. Ex. 2014, ¶¶ 127-128.

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. Ex. 2014, ¶ 128.

### **3. Claim 22**

#### **a. No motivation**

As discussed above in Section VII.B.1.a., there is 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”). Ex. 2014, ¶¶ 123-24, 129. Petitioner does not argue that Saporito P1 and/or Saporito P2 cures this deficiency in Zhang. *See* Pet., 50-54, 56. Indeed, neither reference provides the additional details necessary to arrive at the claimed limitations, as both references provide only data from rats, which a POSA would have understood does not translate directly to human treatment. Ex. 2014, ¶ 130; *supra* § VI.A.

Petitioner’s assertion that a POSA “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 relevant to the field of endeavor of the challenged patent” is sufficient “to establish that one of ordinary skill would have had reason to combine its 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. Ex. 2014, ¶ 131.

**b. No reasonable expectation of success**

As discussed in Section VI.B, Zhang does not disclose “improvement to the patient after administration for more than 8 hours,” as claim 22 requires. Ex. 2014, ¶ 132. A POSA would not 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.” Ex. 2014, ¶¶ 132-36.

Petitioner relies on its reasonable expectation of success argument from Ground 2 of the Petition (Pet., 56), but as discussed in § VII.B.1.b, a POSA would not have had a reasonable expectation of achieving “improvement to the patient after administration for more than 8 hours” based on Zhang’s disclosure alone, and Petitioner has failed to put forward any evidence to the contrary. Ex. 2014, ¶ 133.

Moreover, 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; Ex. 2014, ¶ 133. 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; Ex. 2014, ¶ 134; Ex. 2015, 110:121-112:8. 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; Ex. 2014, ¶ 134. Thus, Saporito P1 does not contain any data beyond 2 hours after administration. Ex. 2014, ¶ 134. Given that Saporito P1 and Saporito P2, like Zhang,

do not provide any data beyond at most 6 hours, they do not provide a POSA with a reasonable expectation of success in achieving “improvement to the patient after administration for more than 8 hours.” *Id.*, ¶ 135.

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; Ex. 2014, ¶ 136. 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). A POSA would have understood that 24-hour survival in rats as reported in Saporito P1 does not necessarily suggest improvement in treating SE in humans after 8 hours. Ex. 2014, ¶ 136.

Therefore, a POSA would not have had a reasonable expectation of success in combining Zhang with Saporito P1 and/or Saporito P2 to arrive at the claimed limitations. Ex. 2014, ¶¶ 132-36.

#### **4. Claims 25-31**

##### **a. No motivation**

As discussed above in Section VII.B.2.a, a POSA would not have been motivated to choose the specific dose ranges recited in claims 25-31 from the broader dose range disclosed in Zhang (1 mg/kg to 20 mg/kg). Ex. 2014, ¶¶ 137-38. And 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. Neither reference would provide such a motivation. Ex. 2014, ¶¶ 137-38.

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).

**b. No reasonable expectation of success**

As discussed above in Section VII.B.2.b, Petitioner has not shown that a POSA 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. Nor would a POSA have had a reasonable expectation of success in doing so with the addition of Saporito P1 or Saporito P2. Ex. 2014, ¶¶ 139-40. 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.

**D. Ground 4: Claims 22 and 25-31 would not have been obvious over Zhang in combination with Marinus's Orphan Drug Press Release, and/or Marinus's Phase I Press Release.**

**1. No motivation for claims 22 and 25-31**

A POSA would not 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. Ex. 2014, ¶¶ 142-161. Petitioner instead asserts that a POSA "would have readily combined" these references (Pet., 60 (citing Ex. 1003, ¶ 124)), while Dr. Rogawski states that a POSA "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”).

Indeed, a POSA would not have been motivated by Zhang’s disclosure 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. Ex. 2014, ¶¶ 144, 153. As discussed in Section VII.B, nothing in Zhang’s disclosure would have motivated a POSA to meet the limitation of claim 22, as Zhang does not disclose “improvement to the patient after administration for more than 8 hours.” Ex. 2014, ¶ 145. Nor would Zhang have motivated a POSA to choose the specific dose ranges disclosed in claims 25-31. Ex. 2014, ¶ 154. And a POSA would not have been motivated by Zhang to seek out additional publications related to the treatment of SE by administering ganaxolone to a patient in need because Zhang’s disclosure is limited to data in rats. Ex. 2014, ¶¶ 146, 155. Petitioner’s proffered motivation therefore fails. *Id.*

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

Petitioner fails to show that a POSA 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. Ex. 2014, ¶¶ 147, 156.

For the reasons discussed above in Section VII.B, Zhang does not provide a reasonable expectation of success for claims 22 and 25-31. Ex. 2014, ¶¶ 148, 157. 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. Ex. 2014, ¶¶ 148, 157.

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; Ex. 2015, 18-22, 143:22-145:3. 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.”); Ex. 2014, ¶¶ 149, 158. Even so, the Phase 1 study could not have established efficacy because the study’s subjects were healthy human volunteers. Ex. 1022, 1. The lack of efficacy data in humans is significant because of the noted difficulties in treating SE. *See supra* § VII.A.2-3; *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; *Novartis*, 923 F.3d at 1060-62.

Moreover, the fact that the FDA granted orphan drug status to Marinus for the use of ganaxolone to treat SE, and the fact that Marinus was allowed to proceed to Phase I clinical trials for this use, say nothing about the efficacy of the drug. Ex. 2014, ¶¶ 150-51, 159-60. Less than 14% of drugs granted orphan drug designation ultimately receive FDA approval and the success rate for *phase III* clinical studies for anti-epileptic drugs is only around 10%. Ex. 2014, ¶¶ 150-51, 159-60; Ex. 2019, 3; Ex. 2020, 2. Thus, a POSA would not have found the Press Releases indicative of the efficacy of ganaxolone for the treatment of SE. Ex. 2014, ¶¶ 151, 160.

Furthermore, 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; *Sanofi*, 875 F.3d at 642, 647-48. Petitioner has not done so here.

The Press Releases are therefore insufficient to cure Zhang’s failure to provide a reasonable expectation of success. Ex. 2014, ¶¶ 152, 161; *see supra* VII.B.2.

#### **VIII. Ground 7: Claims 22 and 25-31 Are Not 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.

Instead of providing a cogent analysis grounded in the factors from *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988), 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). And 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. This is facially deficient. *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 ...”).

As the Board recognized in its Institution Decision, claims 22 and 25-31 are narrowly drawn to the use of a particular compound, ganaxolone, to treat a particular disease, SE. Decision, 47. Additionally, Petitioner has failed to put forth any evidence that treating SE with ganaxolone was unpredictable, that a large quantity of experimentation would have been necessary to show that ganaxolone was effective to treat SE, that the scope of claims 22 and 25-31 are unduly broad, that the guidance in the '817 patent's specification is insufficient, or that the prior art identifies particular concerns with the claimed treatment method. *Id.* All Petitioner points to is a lack of working examples. *See* Petition, 78. Any attempt by Petitioner to add additional arguments and evidence to its enablement analysis should be deemed waived. *Intelligent Bio-Systems, Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367 (Fed. Cir. 2016) (“It is of the utmost importance that petitioners in the IPR proceedings adhere to the requirement that the initial petition identify ‘with particularity’ the ‘evidence that supports the grounds for the challenge to each claim.’”) (quoting 35 U.S.C. § 312(a)(3)); *see also* 35 U.S.C. § 322(a)(3).

Even so, as discussed in Section VII.A.1, 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.

Based on the above, Petitioner has not demonstrated that the challenged claims are not enabled.

## **IX. Conclusion**

Petitioner has not established by a preponderance of the evidence that claims 22 and 25-31 of the '817 patent are unpatentable. Accordingly, the Board should determine that claims 22 and 25-31 of the '817 patent are not unpatentable.

Respectfully submitted,

Dated: November 30, 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 Response** contains 18,569 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: November 30, 2023

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

The undersigned certifies that a copy of the foregoing **Patent Owner's Response** was served electronically via email on November 30, 2023, in its entirety on the following:

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Petitioner has consented to electronic service by email.

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