

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MARINUS PHARMACEUTICALS, INC.,
Petitioner,

v.

OVID THERAPEUTICS, INC.,
Patent Owner.

PGR2023-00020
Patent No. 11,395,817 B2

DECLARATION OF RAMAN SANKAR, M.D., PH.D.

Declaration of Raman Sankar, M.D., Ph.D.
in support of Patent Owner’s Response to Post-Grant Review
of U.S. Patent No. 11,395,817

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EXHIBIT LIST

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

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Exhibit	Description
2011	Marinus Pharmaceuticals Announces Formation of Scientific Advisory Board (April 30, 2020), https://s25.q4cdn.com/443656056/files/doc_news/Marinus-Pharmaceuticals-Announces-Formation-of-Scientific-Advisory-Board-2020.pdf (last accessed June 19, 2023)
2012	Marinus Scientific Advisory Board, https://marinuspharma.com/about-marinus/scientific-advisory-board/ (last accessed June 19, 2023)
2013	Excerpt from the File History of U.S. Patent No. 11,395,817
2014	Declaration of Raman Sankar, M.D., Ph.D
2015	Transcript of Deposition of Dr. Michael A. Rogawski (November 15, 2023)
2016	Transcript of Deposition of Dr. Michael Saporito (November 7, 2023)
2017	European Medicines Agency, <i>Ztalmy Assessment Report</i> , EMA/267469/2023 (May 25, 2023)
2018	Tocris Bioscience, Ganaxolone Safety Data Sheet
2019	Lewis J. Fermaglich & Kathleen L. Miller, <i>A comprehensive study of the rare diseases and conditions targeted by orphan drug designations and approvals over the forty years of the Orphan Drug Act</i> , 18 Orphanet J. of Rare Diseases 163 (2023)
2020	Michele Simonato et al., <i>Issues for new antiepilepsy drug development</i> , Curr. Opin. Neurol. 195-200 (2013)

I. Introduction

1. I, Raman Sankar, M.D., Ph.D., have been retained by Ovid Therapeutics Inc. ("Ovid" or "Patent Owner") as an independent expert in the field of seizure disorders and epilepsy involving preclinical science, therapeutic development, and clinical practice. My qualifications in this area are set forth in my curriculum vitae in **Appendix A**. I am being compensated for the time I spend on this matter, but no part of my compensation depends on the outcome of this proceeding.

II. Professional Background and Qualifications

2. I am a neurologist with over 35 years of experience treating people with epilepsy and other neurological disorders. I see approximately 40-50 patients per month who are suffering from epilepsy. I currently have around 100-120 active patients under my care, including those who have suffered from status epilepticus ("SE").

3. I am currently a Professor of Neurology and Pediatrics and Chief Emeritus of Pediatric Neurology at the David Geffen School of Medicine at the University of California, Los Angeles ("UCLA").

4. I am also an attending neurologist at UCLA's Mattel Children's Hospital and the UCLA Medical Center Hospital and Clinics, providing patients with consult and in-patient services and epilepsy/long-term monitoring.

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5. I earned a B.S. in Chemistry in 1965 and a B.S. Tech. in Technology of Pharmaceuticals and Fine Chemicals in 1968 from the University of Bombay, and a Ph.D. in Pharmaceutical Sciences (Medicinal Chemistry) in 1974 from the University of Washington. From 1974-1975, I conducted postdoctoral research at the University of Washington School of Pharmacy. I was an Assistant Professor of Medicinal Chemistry from 1975-1980 and an Associate Professor from 1980-1982 at Xavier University College of Pharmacy. I was also an Adjunct Assistant Professor of Pharmacology at Tulane Medical School from 1979-1986.

6. I earned an M.D. in 1986 from Tulane Medical School. From 1986-1988, I was a Pediatric Intern-Resident at Children's Hospital of Los Angeles. From 1988-1989, I was a Resident in the Department of Neurology at the UCLA School of Medicine. From 1989-1991, I was a fellow in the Division of Pediatric Neurology at the UCLA School of Medicine. I am licensed to practice medicine in California. I am a Diplomate of the American Board of Psychiatry and Neurology with a special qualification in Child Neurology.

7. I became a Professor of Neurology at UCLA in 2005. Previously, I was a Clinical Instructor of Pediatric Neurology at the UCLA School of Medicine from 1991-1992, an Assistant Professor at the UCLA School of Medicine from 1992-1999, and an Associate Professor at the UCLA School of Medicine from 1999-2005.

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I also served as the Chief and Rubin Brown Endowed Chair of the Division of Pediatric Neurology at the UCLA School of Medicine from 2005-2022.

8. I have served on the Editorial Board of several journals related to epilepsy and neurology, including *Epilepsia*, *Epilepsy & Behavior*, *Journal of Pediatric Epilepsy*, *Contemporary Neurology*, and *Frontiers in Bioscience*.

9. I have performed extensive research in the fields of epilepsy and neurology, publishing over 200 peer-reviewed journal articles, book chapters, and books. Additionally, I have sponsored over 60 candidates for post-doctoral residency and 25 postdoctoral fellows. I conduct a significant amount of research in the laboratory related to the neurochemistry of gamma-aminobutyric acid type A ("GABA_A") systems during status epilepticus in the developing rat brain, including in the rat pilocarpine model for status epilepticus.

10. I have received professional awards for my clinical work, research, and teaching, including the Founders Award of the American Epilepsy Society, which is the highest honor bestowed by the society and recognizes outstanding lifetime achievement in the field of epilepsy. I have also received awards and recognition for my clinical work, research, and teaching, including election as a Fellow of the American Epilepsy Society (FAES) in 2018, election to the American Pediatric Society in 2013, appointment to the Commission on Neurobiology of the

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International League Against Epilepsy (ILAE) in September 2009, and election as a Fellow of the American Academy of Neurology (FAAN) in 2004. My research has been supported by grants from the National Institutes of Health, the Epilepsy Foundation of America, the Epilepsy Foundation of Greater Los Angeles, and awards from Valeant Pharmaceuticals, Sigma-Tau Pharmaceuticals, Inc., Cyberonics, Inc., and Johnson & Johnson Pharmaceutical Research Institute. Teaching awards that I have received include the Excellence in Teaching Award for the Department of Neurology from Resident Physicians in 2004 and the Lawrence Ferring Faculty Award for Teacher of the Year at the Xavier University College of Pharmacy in 1982.

III. Materials Considered

11. I have considered all the documents I cite in this Declaration, all the documents cited in the Patent Owner's Response to Post-Grant Review ("POR") of U.S. Patent No. 11,395,817 ("the '817 patent"), and all documents in the Petitioner's Petition for Post-Grant Review ("Petition") of the '817 patent in forming my opinions. I refer to the references and other documents cited in this Declaration using the same exhibit numbers and terminology as presented in the POR.

12. I may consider additional documents and information in forming any supplemental opinions. To the extent I consider additional documents or

information, including any expert declarations in this proceeding, I may offer further opinions.

IV. Background of the Technology

A. Status Epilepticus

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

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

15. SE does not fall neatly within the category of seizure disorders—it is a neurologic emergency that has limited and drastic treatment options. Ex. 2003, 2382.

Antiseizure medicines (“ASMs”) are the first line of defense against SE, but 30-57% of patients fail to respond to first-line therapy. *Id.* Moreover “53-55% of patients with SE do not respond to either first- or second-line treatment.” *Id.* These patients are generally provided an additional round of second-line ASMs or are placed in a medically-induced coma. *Id.*; *see also* Ex. 1004, 18287 (reporting up to 40% of SE patients suffer from refractory SE (“RSE”) and fail to respond to standard antiepileptic treatments).

16. SE patients resistant to treatment face dire outcomes with mortality rates as high as 35% and “nearly half of the surviving patients have subsequent neurologic deficits.” Ex. 2003, 2382. Marinus’s own CEO has stated that SE is a “difficult to treat seizure disorder with limited treatment options.” Ex. 1011, 1. Thus, one of the “key areas of unmet clinical needs in epilepsy” included “new AEDs for drug-resistant seizures and SE.” Ex. 1004, 18306.

B. Ovid’s Endeavors in Epilepsy and Seizure Disorder Treatment

17. Ovid is a leader in the development of therapies for the treatment of challenging neurological disorders. Ex. 2004, 3. Ovid has four candidates in various stages of clinical development: Soticlestat (in phase 3 clinical trials for treating Dravet syndrome and Lennox-Gastaut syndrome), GV101 (in phase 1 clinical trials for treating brainstem cavernous malformations), OV329 (in phase 1 clinical trials

for treating tuberous sclerosis complex, infantile spasms, and focal seizures), and OV350 & other K^+Cl^- cotransporter 2 ("KCC2") activators (in preclinical development for treating resistant epilepsies and other neuropathologies). *Id.*, 5.

18. Petitioner Marinus has employed Ovid's innovative epilepsy treatment discoveries and research as the foundation for its own development of ganaxolone products as therapeutics. Ovid's '817 patent is the basis for Marinus's clinical development efforts. The results generated in Marinus's clinical trials involving SE match the treatment methods outlined in the '817 patent. This validation demonstrates that Ovid's innovations in this field have provided a reliable roadmap upon which others can build upon.

19. For example, a June 22, 2022 research article published in *Epilepsia* 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]." Ex. 2003, 2381. In the article, the authors reported that "[r]eductions in seizure burden occurred rapidly in all three ganaxolone dose cohorts" tested. *Id.*, 2388. During the study, the three ganaxolone dose cohorts studied included 500 mg/day (low), 650 mg/day (medium), and 713 mg/day (high). *Id.*, 2383. These three ganaxolone doses are each encompassed by the '817 patent's claims. The primary endpoint of the phase 2 study was "the number of patients who did not require

escalation to a third-line IV anesthetic for RSE control within the first 24 h of ganaxolone initiation.” *Id.*, 2383. All three dose cohorts met the primary endpoint: “No patient who received ganaxolone added to the standard-of-care ASMs required treatment with IV anesthetics within 24 h of ganaxolone initiation (Table 2).” *Id.*, 2385. 82% of the treated patients achieved the secondary endpoint and “did not require treatment for SE with additional second-line IV ASMs or IV anesthetics through the 24 h following completion of the ganaxolone infusion.” *Id.*, 2386. In the four-week follow-up period, “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.

C. Marinus Touts the Unexpected Benefits of Ovid's Inventions

20. I understand that Marinus sought its own patent protection for the use of ganaxolone to treat SE. I understand that, during prosecution of its applications, Petitioner relied on the phase 2 data described above 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.

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21. 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.” *Id.*, 21. Marinus filed several applications claiming the benefit of this provisional application. During prosecution of these applications, the Office repeatedly rejected pending claims as obvious over Zhang (US2016/0228454). To overcome those rejections, Marinus submitted identical declarations from a Marinus scientist, stating 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.

22. The Marinus scientist stated that it was thus “completely unexpected” that maintaining a plasma concentration of about 500 ng/mL to about 1000 ng/mL ganaxolone for about 8 to about 12 hours was able to achieve “rapid and persistent suppression of SE.” Ex. 2007, 31 at ¶¶ 8-10; Ex. 2008, 27 at ¶¶ 8-10. This result was therefore “completely contrary” to Marinus’s and its scientist’s expectations. Ex. 2007, 31 at ¶ 10; Ex. 2008, 27 at ¶ 10.

V. The '817 Patent

A. The Specification

23. 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.

24. In the detailed description of the invention, the specification discloses a specific embodiment: “a method of treating an epileptic disorder such as status epilepticus includes administering ganaxolone or a pharmaceutically acceptable salt thereof to a patient in need thereof.” *Id.*, 8:11-14. There are four examples in the specification.

25. Example 3 provides a detailed description of the “Evaluation of the Ability of Allopregnanolone, Ganaxolone, and Gaboxadol to Block Benzodiazepine-Resistant Status Epilepticus.” *Id.*, 35:31-37:15. As depicted in the timeline shown in Figure 2, allopregnanolone, ganaxolone, and gaboxadol were administered to rats with escalating doses (0.5 mg/kg, 2 mg/kg, 5 mg/kg, 10 mg/kg, or 20 mg/kg) at 30 min after the onset of pilocarpine-induced convulsive SE. *Id.*, Fig. 2, 35:59-61, 36:22-24. Blinded behavioral observations were performed for two hours after compound administration, and the results obtained with these compounds were compared to those obtained from vehicle-treated control rats. *Id.*, 35:61-67. As

shown by Table 2 and Figures 3 and 4, administration of 20 mg/kg ganaxolone, but not that of allopregnanolone and gaboxadol, was effective to induce significant protection against SE, characterized by no observation of further convulsive seizures after 10 min of drug administration. *Id.*, Table 2, Figs. 3 and 4.

26. At a lower dose (10 mg/kg), ganaxolone also afforded protection against SE despite not reaching a statistically significant threshold. *Id.* Both 10 mg/kg and 20 mg/kg of ganaxolone treatment also promoted 24-hour survival of the experimental animals, although the effects were not statistically significant. *Id.* Furthermore, as shown in Figure 5, all doses of ganaxolone examined, except the lowest dose (0.5 mg/kg), reduced the number of observed seizures after treatment. *Id.*, Fig. 5.

27. Example 4 describes a "Prospective Study for the Characterization of the Ability of Allopregnanolone, Ganaxolone, and Gaboxadol to Block Benzodiazepine-Resistant Status Epilepticus." *Id.*, 37:17-22. This study builds upon Example 3 and is designed to further examine the potential synergistic effects of gaboxadol with other compounds, including ganaxolone, against benzodiazepine-resistant SE in the lithium-pilocarpine rat SE model. *Id.*, 37:28-32.

B. The Claims

28. I understand that 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.

29. Claim 22 further recites that “the pharmaceutical composition provides improvement to the patient after administration for more than 8 hours.” *Id.*, claim 22.

30. 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.

VI. Petitioner's Asserted References

A. Zhang (Ex. 1009)

31. Zhang (WO 2016/127170 A1) is a Marinus PCT publication titled “Intravenous Ganaxolone Formulations and Their Use in Treating Status Epilepticus

and Other Seizure Disorders” and focuses on intravenous ganaxolone formulations. Specifically, Zhang’s “disclosure provides an injectable ganaxolone formulation comprising ganaxolone, sulfobutyl ethyl- β -cyclodextrin; and water.” Ex. 1009, ¶ [0005]; *see also id.*, ¶¶ [0064]-[0068] (“Lyophilized Beta-Cyclodextrin-Ganaxolone Formulations.”).

32. Zhang identifies a variety of potential uses for the formulations, ranging from a seizure disorder to traumatic brain injury to seizures arising from neurodegenerative disorders, such as Parkinson’s disease. Ex. 1009, 1, ¶¶ [0005]-[0006]; *see also id.*, ¶¶ [0069]-[0073]. Zhang also contemplates combination treatment with its formulations. Ex. 1009, ¶¶ [0090]-[0103] (“Combination Treatment”).

33. Zhang does not describe administering ganaxolone to treat a human patient suffering from SE, improvement to a patient after administration for more than 8 hours, or any of the specific doses recited in claims 25-31. Instead, Zhang indicates that its ganaxolone formulations can be used to treat at least 31 diseases or disorders. Ex. 1009, ¶¶ [0069]-[0073] (status epilepticus, refractory status epilepticus, or super-refractory status epilepticus; PCDH19 female pediatric epilepsy; seizures including acute repetitive seizures, cluster seizures, infantile spasms, Lennox-Gastaut syndrome, West syndrome, catamenial epilepsy; provoked

seizures resulting from low blood sugar, electrolyte imbalance, high fever, brain infection (such as brain infections due to encephalitis, malaria, meningitis, toxoplasmosis, or amoebic infection), adverse reaction of prescription drugs, or alcohol or drug overdose; seizures arising from neurodegenerative disorders including Parkinson's disease, Alzheimer's Disease, Amyotrophic Lateral Sclerosis, and Huntington's disease; seizures arising from inflammatory disorders such as multiple sclerosis; and seizure disorders arising from lysosomal storage disorders, including Neimann-Pick-C, Tay Sachs, Batten, Sandhoff, and Gaucher disease).

34. Zhang includes eight examples. Six discuss formulations of ganaxolone (Examples 1-6); one discusses studies of the plasma levels of ganaxolone in rats after infusion with a ganaxolone-CAPTISOL solution (Example 7); and one discusses the effect of these ganaxolone formulations in the rat lithium-pilocarpine model for SE (Example 8). *Id.*, ¶¶ [0104]-[0136]. Example 8 is the only example in Zhang that alleges to evaluate the effects of ganaxolone in reducing seizures and it only does so in rats.

35. In Example 8, rats with lithium-pilocarpine-induced SE were dosed with vehicle (30% CAPTISOL), allopregnanolone (15 mg/kg), or a CAPTISOL-ganaxolone formulation administered intravenously (12 or 15 mg/kg) either 15 or 60 minutes post SE-onset. *Id.*, ¶¶ [0117], [0127]. The rats used in the study weighed

between 269 and 351 grams; therefore, the highest amount of ganaxolone administered to a rat in this study was 5.265 mg (15 mg/kg x .351 kg). *Id.*, ¶ [0120].

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

37. “Ganaxolone at 12 and 15 mg/kg produced qualitatively similar results.” *Id.*, ¶ [0134]. When dosed 15 minutes after SE-onset, ganaxolone “reduced EEG power across all frequency ranges to levels at or below baseline for at up to 5 h.” *Id.*, ¶ [0135]. “When dosed at 60 [minutes] post SE-onset, EEG power was also strongly reduced, but not below the baseline level for frequencies up to 70 Hz.” *Id.*, ¶ [0136]. Zhang reports no EEG data beyond 5 hours post administration of ganaxolone.

B. Saporito P1 (Ex. 1013)

38. Petitioner's Exhibit 1013 ("Saporito P1") is an undated document titled "Ganaxolone Administered Intravenously Prevents Behavioral Seizures and Promotes Survival in the Rat Lithium-Pilocarpine Model of Status Epilepticus." Ex. 1013, 1. Saporito P1 reports the percentage of rats protected from seizure after administration of a vehicle, 6, 9, and 12 mg/kg ganaxolone, or 15 mg/kg allopregnanolone. *See* Ex. 1013, Fig. 2. Saporito P1 also provides the survival rate in rats 24 hours after administration of a vehicle, 6, 9, and 12 mg/kg ganaxolone, or 15 mg/kg allopregnanolone. *See id.*, Fig. 3.

C. Saporito P2 (Ex. 1014)

39. Petitioner's Exhibit 1014 ("Saporito P2") is an undated document titled "Intravenous Administration of Ganaxolone Attenuates Electroencephalographic Seizures in a Diazepam Resistant Model of Status Epilepticus." Ex. 1014, 1. Saporito P2 reports the EEG seizure response in rats measured just over 5 hours after administration of a vehicle, 12 and 15 mg/kg ganaxolone, and 15 mg/kg allopregnanolone. *Id.*, Figs. 3-4.

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

40. Petitioner's Exhibit 1011 is a press release dated April 15, 2016, titled "Marinus Pharmaceuticals Receives FDA Orphan Drug Designation for Ganaxolone IV to Treat Status Epilepticus." Ex. 1011, 1. Marinus's Orphan Drug Press Release

states that “the U.S. Food and Drug Administration (FDA) has granted Orphan Drug Designation to the intravenous (IV) formulation of [Marinus's] CNS-selective GABA_A modulator, ganaxolone, for the treatment of status epilepticus.” *Id.*, 1. Marinus's Orphan Drug Press Release also notes that “[a] Phase 1 clinical trial evaluating the safety, tolerability and pharmacokinetics of ganaxolone IV is expected to initiate in the first half of 2016.” *Id.* In the press release, Marinus's CEO states that SE is a “difficult to treat seizure disorder with limited treatment options.” *Id.*

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

41. Petitioner's Exhibit 1022 is a press release dated June 22, 2016, titled “Marinus Pharmaceuticals Doses First Subject in Phase 1 Clinical Trial for Ganaxolone IV.” Ex. 1022, 1. Marinus's Phase I Press Release states that Marinus “has dosed the first subject in its Phase 1 clinical trial of ganaxolone IV, an intravenous (IV) formulation of Marinus' CNS-selective GABA_A modulator, for the treatment of status epilepticus (SE).” *Id.*

42. The press release also notes that the Phase 1 “study is designed to evaluate the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of ganaxolone IV in healthy volunteers, with data anticipated in the second half of 2016.” *Id.* Specifically, the press release states that the Phase 1 study “will include

a dose escalation of a bolus dosage of ganaxolone IV and a bolus dose of ganaxolone IV, followed by a continuous infusion.” *Id.*

VII. Person of Ordinary Skill in the Art

43. I have been instructed that a person of ordinary skill in the art (“POSA”) is a legal fiction that is used in many aspects of patent law. I have been instructed that a POSA is a hypothetical person at the time of the invention who is presumed to be aware of all pertinent prior art, thinks along conventional wisdom in the art, and is a person of ordinary creativity.

44. Based on my years of experience in the relevant field, it is my opinion that as of August 11, 2016, a POSA would have possessed a high level of skill, such as having an advanced degree, such as a medical degree or a Ph.D. in the field of pharmacology or other fields related to the development of pharmaceuticals, and have several years of experience as a practicing neurologist treating patients who suffer from seizure disorders including SE and/or several years of experience in researching treatments for such seizure disorders. A POSA would have been familiar with the pharmacokinetics and pharmacodynamics of pharmaceuticals. A POSA would easily have understood the references I discuss in this Declaration and would have had the capability to draw inferences from them.

45. As an expert, and certainly a POSA, in the relevant field since before 2016, I am qualified to provide an opinion as to what a POSA would have understood, known, or concluded as of 2016. I have reviewed the materials, conducted my analyses, and formed my opinions in my Declaration through the eyes of a POSA as of August 11, 2016.

VIII. Legal Standards

A. Claim Construction

46. I understand that the words of a claim are to be given their ordinary and customary meaning in light of the specification and prosecution history—that is, the meaning that the term would have to a POSA. I further understand that all the words of a claim are to be considered in judging the patentability of a claim against the prior art. I have been informed that the claims must be read in view of the specification, which is highly relevant to the claim construction analysis. The patentee may act as his own lexicographer by defining a claim term in the patent specification, either expressly or by implication.

47. I understand that the prosecution history is another important source of information when construing the claims. For example, an interpretation of a claim term that the patentee disavowed during prosecution must be excluded from the scope of that term.

48. I also understand that evidence extrinsic to the patent and its prosecution history may also be consulted, but that such materials should only be considered so long as they are not inconsistent with the claim language, the patent specification, and the prosecution history.

49. I have been informed that clinical efficacy clauses in method of treatment claims must be given patentable weight when they are material to patentability and express the inventive aspect of the claimed invention.

50. I understand that this is the case for both “method of treating” preambles, as well as “wherein” and “thereby” clauses that require achievement of particular clinical efficacies.

51. I understand that while certain claim limitations may be deemed “inherent” to the claimed methods, doing so requires showing that those limitations are the “necessary result” of the claimed method.

B. Anticipation

52. I understand that in order to anticipate a patent claim, a single prior art reference must disclose, either explicitly or inherently, each and every claim element. The identical invention must be shown in as complete detail in the prior art as in the claim. The elements as disclosed in the prior art must be arranged as required by the claim, but it must not satisfy an *ipsisimis verbis* test.

53. With respect to inherency, I have also been informed that a single prior art reference may “inherently anticipate” a claim if and only if a limitation that is not expressly described in the reference is necessarily present in the product or process that the reference describes, not merely probably or possibly present in that product or process. Stated differently, a limitation is inherently described only if it is the “necessary result” flowing from the prior art’s disclosure.

C. Obviousness

54. I understand that a claimed invention cannot be patented if the subject matter as a whole would have been obvious at the time the invention was made to a POSA. In applying this standard, I understand that I must consider: (i) the level of ordinary skill in the art; (ii) the scope and content of the prior art; (iii) the differences between the claimed invention and the prior art; and (iv) any secondary considerations indicating the invention would not have been obvious.

55. I also understand that a claim can be obvious in light of either a single prior art reference or multiple prior art references. Where multiple references are used, there must have been a motivation for a POSA to modify or combine the references to achieve the claimed invention.

56. I understand that the reason to combine references may come from a teaching, suggestion, or motivation, the references themselves, the knowledge of a

POSA, or the nature of the problem to be solved; and it may be explicit or implicit.

I also understand it is improper to rely on hindsight in making the determination of obviousness.

57. I also understand that obviousness does not require a certainty of success or absolute predictability of success, but only a reasonable expectation of success. Likewise, I understand that obviousness cannot be avoided by showing some degree of unpredictability so long as there was a reasonable probability of success.

IX. Claim Construction

A. "Treating status epilepticus comprising administering to a patient in need thereof"

58. A POSA would have understood that the phrase "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."

59. While the '817 patent's specification uses the word "patient" broadly, it also 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 (stating that "treating" or "treatment" refers to "alleviating, attenuating or delaying the appearance of clinical symptoms of a disease or condition in a subject that may be afflicted with or predisposed to the disease or condition, but

does not yet experience or display clinical or subclinical symptoms of the disease or condition"). The specification also states that "[t]he benefit to a subject to be treated may be statistically significant, mathematically significant, or at least perceptible to the subject and/or the *physician*." *Id.*, 29:46-48 (emphasis added). Indeed, the '817 patent's specification never correlates the terms "treating" or "treatment" to administering ganaxolone to rats for the purpose of conducting research. Moreover, the phrases "effective amount" and "therapeutically effective amount" are used in relation to the "disorder, disease, or condition *being treated*." *Id.*, 29:52-56 (emphasis added). A POSA interpreting the claim in light of the specification would thus have understood that "treating" refers to treating clinical and subclinical symptoms of a disease or a condition in a human patient, and not in the context of preclinical, research uses with a rat or other non-human animals.

60. As used in claim 22, a POSA would have understood that the term "patient" is being used more narrowly due to its use alongside the terms "treating" and "administering." Thus, when claim 22 recites "a patient in need thereof," a POSA would have understood that the someone "in need" would be a human patient suffering from SE, and would not be a rat or other animal receiving ganaxolone for research purposes.

Declaration of Raman Sankar, M.D., Ph.D.
in support of Patent Owner's Response to Post-Grant Review
of U.S. Patent No. 11,395,817

61. Further, in the context of claims 25-31, a POSA would have understood that the doses of ganaxolone recited in these claims would not be administered in a rat to treat SE. The doses in these claims (ranging from 500 mg to 1050 mg) are 130 to 200 times larger than the doses of ganaxolone administered to rats in Examples 3 (2.5 mg (20 mg/kg x 0.125 kg weight of rat)) and 4 (3.75 mg (30 mg/kg x 0.125 kg weight of rat)) of '817 patent. Ex. 1001, 35:44-48 ("male Sprague Dawley rats (n = 10 time or treatment/group, 100-125 g; Charles Rivers Laboratories)"); *id.*, 36:22-24 ("The doses administered for allopregnanolone, ganaxolone, or gaboxadol are 0.5 mg/kg, 2 mg/kg, 5 mg/kg, 10 mg/kg, or 20 mg/kg."); *id.*, 37:62-66 ("male Sprague Dawley rats (n = 13 time or treatment/group; 100-125 g at arrival from Charles Rivers Laboratories)"); *id.*, 37:45-60 (Table 3 providing highest dose of ganaxolone (GNX) as 30 mg/kg).

62. Additionally, the rats used in example 8 of Zhang weighed between 269 and 351 grams; therefore, the highest amount of ganaxolone administered to a rat in this study was 5.265 mg (15 mg/kg x .351 kg). Ex. 1009, ¶¶ [0117], [0120]. This is almost 100 times smaller than the smallest dose amount administered in claims 25-31, which further indicates that claims 25-31 are directed to treating a *human patient* suffering from SE rather than a rat.

63. The '817 patent specification also 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 of the '817 patent, the doses of ganaxolone recited in claims 25-31 relate to weight-based dosing in a rat spanning 4000 mg/kg (500 mg) to 8400 mg/kg (1050 mg) ganaxolone. Such weight-based doses are 100 to over 200 times higher than those described in the '817 patent specification for treating a patient. Thus, a 500 mg dose administered to a rat does not fall within the range disclosed in the specification. Therefore, a POSA would have understood that the "patient" being administered the dosage amounts recited in claims 25-31 would not have been a rat.

64. This understanding of the term "patient" not including rats in the context of the ganaxolone dosage amounts recited in claims 25-31 is further supported by evidence extrinsic to the patent. A POSA would have understood that the doses of ganaxolone recited in claims 25-31 would not result in treating SE in a rat because the doses are far beyond the effective dose of ganaxolone used as an anticonvulsant in rats and would be toxic to a rat because ganaxolone has been found to cause sedation, ataxia, unresponsiveness, and other central nervous impairment at much lower doses. Ganaxolone has been found to be "a potent anticonvulsant against

fully kindled stage 5 seizures induced by corneal kindling in rats” at an effective dose (“ED₅₀”) of 4.5 mg/kg administered intraperitoneally.¹ Ex. 1028, 1284. Therefore, a POSA would have understood that administering doses of ganaxolone to a rat that 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) would not have been used in a method to *treat* SE. Similarly, a POSA would have understood that administering several thousand mg/kg ganaxolone to a rat would instead be toxic to the rat. Studies evaluating the safety of administering ganaxolone to rats and its effects on a rat's central nervous system report that a rat's motor function is impaired starting at 5 mg/kg, sedation occurs at 15 mg/kg, loss of the 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; *see also* Ex. 2018, 3 (reporting lowest published toxic dose of ganaxolone administered subcutaneously to a rat (“TD₅₀”) is 3.46 mg/kg). A POSA thus would have understood that doses of ganaxolone at 100 times greater than those studied would result in extreme impairment to the rat's central nervous system. As

¹ Effective dose or ED₅₀ refers to the dose of a medication that produces a pharmacologic effect in 50% of the studied patient population that takes the medication.

such, a POSA would not have considered the claimed doses (500 mg/day to 1050 mg/day) to be treating SE when administered to a rat, as claims 25-31 requires.

B. “Improvement to the patient after administration for more than 8 hours”

65. A POSA would have understood the phrase “improvement to the patient after administration for more than 8 hours” as used in claim 22 to mean improvement to the human patient 8 hours after the full dose of ganaxolone is given, regardless of whether the dose of ganaxolone is given in a single administration or multiple administrations.

66. A POSA would have understood this to be the plain and ordinary meaning of the claim phrase because whether a patient with SE has sustained any improvement after administration of a drug is typically assessed at a point in time after a full dose is administered, rather than starting the clock after the first administration of only part of the dose. This is because the full dose of the drug is generally required to provide the expected effect.

67. Thus, a POSA would have understood the claim phrase “improvement to the patient after administration for more than 8 hours” as used in claim 22 to mean improvement to the human patient 8 hours after the full dose of ganaxolone is given.

X. Ground 1: Claims 22 and 25-31 Are Not Anticipated by Zhang

68. I have considered whether claims 22 and 25-31 are anticipated by Zhang and conclude that Zhang does not disclose each and every element of these claims either expressly or inherently.

A. Zhang does not describe “treating status epilepticus comprising administering to a patient in need thereof”

69. Claims 22 and 25-31 depend from claim 21, which recites “administering to a patient in need thereof a pharmaceutical composition comprising ganaxolone or a pharmaceutically acceptable salt thereof wherein the pharmaceutical composition is administered intravenously.” Under the correct interpretation of this claim as described above, “treating status epilepticus comprising administering to a patient in need thereof” requires treating a human patient suffering from SE. *See supra* § IX.A.

70. There is nothing in Zhang that describes treating a human patient, let alone one suffering from SE. I understand that Petitioner cites to ¶¶ [0005] and [0031], both of which relate to a formulation of ganaxolone, and ¶¶ [0104]-[0136], which are directed to Zhang's Examples. Pet., 35-38. None of these passages describes treating a human patient suffering from SE. There is no disclosure in Zhang that describes intravenously administering ganaxolone to a human patient suffering from SE.

71. Instead, Zhang's discloses animal data. Examples 7 and 8 disclose data from ganaxolone administered to rats with pilocarpine-induced SE. *See* ¶¶ [0116]-[0136]. It is common knowledge to a POSA that animal models do not translate directly to human treatment. For example, in the rat lithium pilocarpine model, SE is chemically induced using pilocarpine, while in humans, SE typically comes about due to a variety of clinical circumstances such as infection, inadvertently missing doses of anti-seizure medicines, trauma, stroke, or carcinomatous meningitis. Because SE is chemically induced in rats using pilocarpine, 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. Moreover, one cannot directly compare doses of ganaxolone administered to rats with doses administered to humans because rats metabolize compounds at a much faster rate than humans by the hepatic microsomal system. As a result, higher doses (in mg/kg) of a compound are typically administered to rats than humans. Therefore, data from the rat lithium pilocarpine model only provides information as to what compounds could potentially be used to treat SE in humans and does not provide specific information regarding effective doses of any such compound in humans. Nothing in Zhang describes the administration of ganaxolone for treating a human suffering from SE.

72. Therefore, Zhang does not describe treating a human patient suffering from SE, as required by claims 22 and 25-31.

B. Zhang does not describe “improvement to the patient after administration for more than 8 hours” from claim 22

73. Claim 22 recites that the claimed pharmaceutical composition administered intravenously provides “improvement to the patient after administration for more than 8 hours.” Under the correct construction of this claim as described above, “improvement to the patient after administration for more than 8 hours” requires improvement to the 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. *See supra* § IX.B.

74. I understand that Petitioner and Dr. Rogawski both concede that “Zhang does not expressly disclose that its ganaxolone formulation” provides this therapeutic effect. Pet., 45; *see also* Ex. 1003, ¶ 93. For example, 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.

75. I understand that Petitioner instead relies on alleged 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 formations in the manner taught in Zhang.” Pet., 44-45; Ex. 1003, ¶ 93.

76. As an initial point, Zhang cannot establish any effect in a human patient, inherent or otherwise, because ganaxolone was not administered to a human patient. Moreover, neither Petitioner nor Dr. Rogawski, however, cites any evidence in support. Zhang discloses that any effect of ganaxolone in reducing EEG power diminishes by 5 hours. *See* Ex. 1009, ¶¶ [0135]-[0136]. In fact, 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).

77. Zhang provides no data regarding seizure reduction beyond 5 hours. Zhang does not establish that ganaxolone provides seizure reduction for 8 hours after administration.

78. Zhang therefore does not inherently anticipate claim 22 because it does not show that the claim limitation—improvement after administration for more than 8 hours—would inevitably occur.

79. I understand that, in the alternative, Petitioner cites to paragraph 74 of Zhang, 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.” Pet., 45. But 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].

80. The dosing schedules of paragraph 74 of Zhang are not identified as being relevant to any method of treatment. Instead, Zhang discusses a wide variety of treatment options, including the disease or disorder treated (e.g., “seizures, traumatic brain injury, stroke” in paragraph 74 specifically, and at least 31 diseases or disorders in Zhang generally, *see id.*, ¶¶ [0069]-[0073]), the type of administration (e.g., “intramuscularly or intravenously”), and dose amount. *Id.*, ¶ [0074]. Paragraph 74 of Zhang does not even refer to treating SE. It only states that the β -cyclodextrin ganaxolone “injections may be given at intervals of 1 to 24 hours.” Ex. 1009, ¶ [0074]. There is nothing in Zhang that establishes that repeated administration of ganaxolone at intervals of 2 hours would necessarily and inevitably provide sustained treatment to an SE patient, let alone a human one, for more than 8 hours. And importantly, Zhang does not even monitor the rat subjects for 8 hours after final administration of the total dose, as the claim requires. *See* § IX.B.

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

81. 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 and Dr. Rogawski's calculations assume that these claimed ranges relate to the following weight-based dose amounts in a 70-kg human patient: 500-1000 mg/day relates to 7.14-14.29 mg/kg/day, 625-650 mg/day relates to 8.93-9.29 mg/kg/day, 650-675 mg/day relates to 9.29-9.64 mg/kg/day, 675-700 mg/day relates to 9.64-10 mg/kg/day, 625-700 mg/day relates to 8.93-10 mg/kg/day, 700-725 mg/day relates to 10-10.36 mg/kg/day, and 1025-1050 mg/day relates to 14.64-15 mg/kg/day. Zhang, however, does not describe any of the ranges recited in claims 25-31.

82. I understand that Petitioner points to a single range of doses in paragraph 85, where Zhang states that “[i]n certain embodiments each bolus dose comprises about 1 mg/kg to about 20 mg/kg ganaxolone.” Pet., 46-47 (quoting Ex. 1009, ¶ [0085]). As discussed above, Zhang's general disclosure is not specific to any disease state, dosage strength, or dosing regimen. Zhang indicates that the methods of treatment “also include administering multiple injections . . . over a

period of 1 to 10 days” and that “[t]he injections may be given at intervals of 1 to 24 hours.” Ex. 1009, ¶ [0074].

83. Zhang’s range of “from about 1 mg/kg to about 20 mg/kg” dosed from every 1 to 24 hours for one day leads to a potential dose range of about 1 mg/kg/day to about 480 mg/kg/day or, as a weight-based dose range for a 70 kg adult human, 70 mg/day to 33,600 mg/day.

84. 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” as Petitioner claims. Decision, 30.

85. Zhang’s disclosure of anywhere from 70 mg/day to 33,600 mg/day for a 70 kg adult human encompasses broad dosage ranges that would be ineffective to treat SE patients and would not result in improvement to the patient as required by claims 25-31.

86. Therefore, Zhang’s extremely broad disclosure, untethered to a particular disease state and any effective dose ranges, does not describe any of the ranges recited in claims 25-31.

87. Moreover, Zhang’s Example 8 provides data in the rat-lithium pilocarpine model and only at ganaxolone doses of 12 mg/kg and 15 mg/kg. As

discussed above, 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. As a result, higher doses (in mg/kg) of a compound are typically administered to rats than humans.

88. Therefore, the data in Example 8 of Zhang does not describe treating SE using any of the doses described in claims 25-31.

XI. Ground 2: Claims 22 and 25-31 Are Not Obvious in View of Zhang

89. I considered whether claims 22 and 25-31 would have been obvious in view of Zhang. Based on the disclosure of Zhang, a POSA would not have been motivated or reasonably expected ganaxolone to treat SE, to provide improvement to a patient after administration for more than 8 hours, or to treat SE using the dose ranges recited in claims 25-31. Therefore, a POSA would not have found that claims 22 and 25-31 would have been obvious in view of Zhang.

A. Claim 22 Would Not Have Been Obvious in View of Zhang

90. As described above, a POSA would have understood based on the limited data provided in Zhang and what was known in 2016 about the pharmacokinetics of ganaxolone that Zhang does not describe the method of treatment in claim 22. A POSA further would have understood that claim 22 would not have been obvious in view of Zhang because Zhang provides no motivation to

meet the limitation of claim 22 and no reasonable expectation of success in using intravenous administration of ganaxolone to achieve the results as recited in claim 22.

1. No motivation

91. 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." As discussed above in Section X.B, nowhere does Zhang disclose "improvement to the patient after administration for more than 8 hours."

92. As described above in Section X, Zhang never ties its disclosure in paragraph 74 that a β -cyclodextrin-ganaxolone injection "may be given at intervals of 1 to 24 hours" to treating SE or Zhang's Example 8. Zhang never discloses data from the administration of ganaxolone in humans. There is nothing in Zhang that would have motivated a POSA to arrive at the limitation of claim 22.

2. No reasonable expectation of success

93. Additionally, 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." Nothing in Zhang suggests the subject matter of claim 22 or that a POSA would have arrived at the recited claims with a reasonable expectation of success.

94. As discussed above in Section X.B, a POSA would not have had a reasonable expectation of success based on Zhang's disclosure. Zhang's Example 8 discloses that the effect of ganaxolone on reducing EEG power is largely diminished by 5 hours and that ganaxolone showed a significant reduction at 3-5 hours in only one low frequency group (0-5 Hz). Ex. 1009, ¶¶ [0135]-[0136]. Zhang provides no data regarding seizure reduction beyond 5 hours. Thus, Zhang itself shows an *absence* of any effect by 5 hours.

95. 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." Paragraph 74 of Zhang states that ganaxolone can be administered "at intervals of 1 to 24 hours." Ex. 1009, ¶ [0074]. Paragraph 74 of Zhang does not state or provide any indication that multiple administration can prolong an effect from a single administration, let alone a prolonged effect on SE.

96. Even so, the correct interpretation of claim 22, as discussed above in Section IX.B, requires improvement to the 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. *See supra* § IX.B.

97. As described above, Zhang provides no data regarding seizure reduction beyond 5 hours. Zhang teaches nothing that would establish that ganaxolone provides seizure reduction for 8 hours after administration. Zhang therefore provides nothing to indicate to a POSA that there would have been a reasonable expectation of success in treating SE as recited in claim 22 because it does not show that the claim limitation—improvement after administration for more than 8 hours—would occur or would have been expected to occur.

98. As discussed above in Section X.B, there is no reason that a POSA would have had a reasonable expectation of success that the administration of the full dose of ganaxolone broken into multiple, repeated administrations would result in “improvement to the patient after administration for more than 8 hours” if a single administration of the full dose for SE suppresses seizures for up to 2 hours.

B. Claims 25-31 Would Not Have Been Obvious in View of Zhang

99. As described above, a POSA would have understood that Zhang's extremely broad disclosure, untethered to a particular disease state and any effective dose ranges, does not describe any of the ranges recited in claims 25-31. A POSA further would have understood that claims 25-31 would not have been obvious in view of Zhang because Zhang provides no motivation to meet the limitations of these

claims and no reasonable expectation of success in using intravenous administration of ganaxolone at the claimed dose ranges to achieve the results as recited.

1. No motivation

100. A POSA would not have been motivated to choose the specific dose ranges for treating SE that are recited in claims 25-31 from the broad dose range provided in paragraph 85 of Zhang (i.e., “about 1 mg/kg to about 20 mg/kg ganaxolone”). *See* Ex. 1003, ¶¶ 99-109.

101. I understand that Petitioner 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. But, in my opinion from the perspective of a POSA, Zhang provides no suggestion or motivation to choose the specific dose ranges recited in claims 25-31 to treat SE from this extremely broad range of doses that could be for any one of the 31 diseases and disorders Zhang’s omnibus disclosure contemplates.

102. Paragraph 85 of Zhang merely refers to administering various dose ranges and numerous dosing regimens of ganaxolone without identifying any disease or disorder to be treated. *See* Ex. 1009, ¶ [0085]. As described above in Section X.C, Zhang’s disclosure of anywhere from 70 mg/day to 33,600 mg/day for a 70 kg adult

encompasses a broad dosage range, including doses that a POSA would have understood to be ineffective to treat SE patients and not result in improvement to the patient as required by claims 25-31. Thus, Zhang provides no suggestion or motivation to choose the specific dose ranges recited in claims 25-31 to treat SE as required by the claims.

2. No reasonable expectation of success

103. In my opinion, a POSA would not 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. I understand that Petitioner states that although 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. I disagree.

104. I understand that both Petitioner and Dr. Rogawski 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.

105. But, as described above in Section X.A, this result would not have provided a reasonable expectation of success for the specific doses of claims 25-31 in a human patient. Moreover, as described above, 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 dose ranges recited in claims 25-31. *See supra* § X.A. The lack of efficacy data in humans is significant because of the difficulties in treating SE, as explained above. *See supra* §§ IV.A, X.A; *infra* XI.C.3; *see also* Ex. 1011, 1 (recognizing that SE is a "difficult to treat seizure disorder with limited treatment options").

106. Therefore, based on Zhang's disclosure, a POSA would not have had a reasonable expectation of success in treating a human patient suffering from SE with the doses recited in claims 25-31.

C. Objective Indicia of Nonobviousness

1. The claimed methods demonstrate unexpected results

107. The methods of treating SE by administering ganaxolone recited in claims 22 and 25-31 were unexpected, and the recited doses were critical to the claimed inventions. Statements by Petitioner and Petitioner's own work after the filing date of the '817 patent confirm that the treatment methods recited in claims 22 and 25-31 provided unexpected results over what a POSA would have expected in view of Zhang.

108. As described above, *see* Section IV.C, Marinus itself and one of its own scientists expected that high ganaxolone exposure for at least four days would be required to "break SE" in view of the same Zhang document being asserted against

its claims during prosecution of Petitioner's U.S. App. Nos. 17/186,569 and 17/729,427.

109. In an article describing a phase 2 clinical trial “sponsored and supported by [Petitioner]” examining the use of intravenous ganaxolone for the treatment of refractory SE, it was discovered that “[r]eductions in seizure burden occurred rapidly in all three ganaxolone dose cohorts” tested. Ex. 2003, 2381, 2388. During the study, the three ganaxolone dose cohorts studied included 500 mg/day (low), 650 mg/day (medium), and 713 mg/day (high). *Id.*, 2383. For each dose cohort, “ganaxolone infusion was initiated as an IV bolus (over 3 min) with continuous infusion of decreasing infusion rates for 48-96 h followed by an 18-h taper.” *Id.* The primary endpoint of the study was “the number of patients who did not require escalation to a third-line IV anesthetic for RSE control within the first 24 h of ganaxolone initiation” and the study's secondary endpoints included “the number of patients who maintained SE cessation 24 h after ganaxolone taper and at week 4, time to cessation of SE, and ganaxolone safety/tolerability and pharmacokinetics.” *Id.*, 2383-84.

110. 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). Additionally, 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. 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.* The authors reported that the data “suggest that ganaxolone has the potential to provide significant clinical benefit to patients with RSE.” *Id.*

111. The “rapid” seizure cessation, 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.

112. Upon seeing these unexpected clinical study results, a POSA also would have 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. In my opinion, these unexpected results therefore support the nonobviousness of claims 25-31.

113. 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. In my opinion, this unexpected result supports the nonobviousness of claim 22.

114. 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.

115. 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. Specifically, 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.* Additionally, the article describing Petitioner's phase 2 trial specifically ties the 713 mg/day dose to these results. Ex. 2003, 2386; *see also id.*, 2384 (Figure 2 stating that “[h]igh dose GNX achieves and maintains target plasma levels (≥ 500 ng/ml) for ~8 h, designed to sustain SE cessation”).

116. 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 scientist's (who meets the definition of a person of ordinary skill

in the art) expectations and were markedly superior over the other doses encompassed by Zhang's extremely broad disclosure.

117. These statements also surprisingly revealed that ganaxolone could result in "improvement to the patient after administration for more than 8 hours" in view of the results reported in Example 8 of Zhang, 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).

118. Based on Petitioner's above admissions and in my opinion, the improvement recited in claim 22 and the dose ranges recited in claims 25-31 provided unexpected results over the closest prior art, Zhang. These unexpected results thus support the nonobviousness of claims 22 and 25-31.

2. Long-felt but unmet need for the claimed methods of treatment

119. 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, SE "[b]ecomes more treatment refractory with

progression.” *Id.* As Petitioner agrees, “[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.

120. The prior art contains many statements acknowledging the long-felt need for a drug that could treat SE. Reddy recognized 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.

121. In my opinion, and from the perspective of a POSA, ganaxolone administered according to the methods in claims 22 and 25-31 filled this unmet need. *See supra* § IV.A. As demonstrated in Petitioner’s phase 2 clinical trial, and as described above, the claimed improvement and dose ranges of ganaxolone resulted in rapid seizure cessation and reduction in seizure burden. Ex. 2003, 2386, 2388. Additionally, Petitioner’s ongoing phase 3 clinical trial for the use of intravenous

ganaxolone to treat RSE uses the same dose selection as its phase 2 clinical trial, further confirming that the claimed methods fulfill the previously unmet need for a drug that could treat SE. Ex. 2002, 28.

3. Failure of others in treating SE

122. The '817 patent's claimed methods stand out amongst repeated failed attempts to treat SE. Intravenous benzodiazepines, such as lorazepam and diazepam, are among the "first-line therapies" for treating SE, but as Petitioner admits, "[a] significant drawback to these therapies is that their efficacy decreases dramatically as the duration of SE increases, and there can be a complete loss of efficacy after a certain amount of time." Pet., 11 (citing Ex. 1004, 18287). When there is a complete loss of efficacy, "more drastic second-line (phenytoin and fosphenytoin) and third-line therapies (propofol or phenobarbital) must be employed, but are not always successful." Ex. 1004, 18287; *see also* Ex. 1009, ¶ [0001]; Pet., 11-12. In my opinion the development of the claimed methods in view of these multiple failures support the nonobviousness of claims 22 and 25-31.

XII. Ground 3: Claims 22 and 25-31 Are Not Obvious in View of Zhang, Saporito P1, and Saporito P2

123. I considered whether claims 22 and 25-31 would have been obvious in view of Zhang, Saporito P1, and Saporito P2.

124. Based on the disclosure of Zhang, Saporito P1, and Saporito P2,² a POSA would not have expected ganaxolone to treat SE, to provide improvement to a patient after administration for more than 8 hours, or to do so using the dose ranges from claims 25-31.

A. No reference discloses “treating status epilepticus comprising administering to a patient in need thereof” from claims 22 and 25-31

125. As discussed above in Section X.A, 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 required by claims 22 and 25-31.

126. Additionally, Saporito P1 and P2 do not describe intravenously administering to a human patient a pharmaceutical composition comprising ganaxolone or a pharmaceutically acceptable salt thereof. Saporito P1 reports on a study conducted by Marinus to investigate the effects of IV-administered ganaxolone in the *rat lithium-pilocarpine model*. Ex. 1013, 1. Saporito P2 also reports only data in rats, not in humans. Ex. 1014, 1.

² I understand that Patent Owner is challenging the status of Saporito P1 and Saporito P2 as prior art to the '817 patent. Regardless of whether Saporito P1 and Saporito P2 are in fact prior art, my opinion is that the '817 patent would not have been obvious over the combination of Zhang, Saporito P1, and Saporito P2.

127. As discussed above, it is common knowledge to a POSA that animal models do not translate directly to human treatment. For example, in the rat lithium pilocarpine model, SE is chemically induced using pilocarpine, while in humans, SE typically comes about due to a variety of clinical circumstances such as an infection, inadvertently missing doses of anti-seizure medicines, trauma, stroke, or carcinomatous meningitis. Because SE is chemically induced in rats using pilocarpine, 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. Moreover, one cannot directly compare doses of ganaxolone administered to rats with doses administered to humans because rats metabolize compounds at a much faster rate than humans by the hepatic microsomal system. As a result, higher doses (in mg/kg) of a compound are typically administered to rats than humans. Therefore, data from the rat lithium pilocarpine model only provides information as to what compounds could potentially be used to treat SE in humans and does not provide information regarding specific doses that would have been effective to treat a human SE patient. A POSA would have understood that the data disclosed in Saporito P1 and Saporito P2 do not disclose intravenously administering to a human patient a pharmaceutical composition comprising ganaxolone or a

pharmaceutically acceptable salt thereof or provide the information necessary for a POSA to reach those limitations.

128. Neither Saporito P1 nor Saporito P2 discloses intravenously administering ganaxolone to a human patient suffering from SE. A POSA would have understood that no combination of Zhang, Saporito P1, and Saporito P2 discloses “treating status epilepticus comprising administering to a patient in need thereof” under the correct construction. *See* §§ IX.A; X.A.

B. Claim 22 Would Not Have Been Obvious in View of Zhang, Saporito P1, and Saporito P2

1. No motivation

129. As discussed above in Section XI.A.1, 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.” As discussed above in Section XI.A.1, nowhere does Zhang disclose “improvement to the patient after administration for more than 8 hours.”

130. Additionally, as described above in Section XII.A, neither Saporito P1 nor Saporito P2 provide the additional details necessary to arrive at the limitation of claim 22. Both references provide only data from rats, not humans, and a POSA would have understood that this data does not translate directly to human treatment.

131. Thus, there is nothing in Zhang, Saporito P1, Saporito P2, or any combination of these references that would have motivated a POSA to combine these references to arrive at the limitation of claim 22.

2. No reasonable expectation of success

132. As discussed above in Section XI.A, Zhang does not disclose “improvement to the patient after administration for more than 8 hours,” as claim 22 requires. 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.”

133. As discussed in Section XI.A.2 above, 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. Saporito P1 and Saporito P2 do not cure Zhang’s deficiency. Neither reference shows that a ganaxolone SE treatment would provide “improvement to the patient after administration for more than 8 hours.” *See* Ex. 1013; Ex. 1014.

134. Like Zhang’s Example 8, Figures 3 and 4 in Saporito P2 demonstrate that the effect of ganaxolone on reducing EEG power is largely diminished by 6 hours, after which there is no additional data. Ex. 1014, 1. Similarly, for Figure 2 in

Saporito P1, the rats “were observed for the presence or absence of convulsive seizures (stage 3 or greater) for an additional 2 hours” after ganaxolone administration and rats that “did not exhibit a convulsive seizure during that time period were considered protected.” Ex. 1013, 1. Saporito P1 does not contain any data beyond 2 hours after administration.

135. Thus, like Zhang, Saporito P1 and Saporito P2 do not provide any data beyond 6 hours. They would not have provided a POSA with a reasonable expectation of success in achieving “improvement to the patient after administration for more than 8 hours.”

136. I understand that Petitioner argues that “Saporito P1 shows that ganaxolone promoted survival in the rats, measured 24 hours after the onset of CSE, suggesting improvement after 8 hours.” Pet., 56. This has no support in Saporito P1 itself. 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. A POSA would have understood that 24-hour survival of rats as reported in Saporito P1 does not necessarily suggest improvement in treating SE in humans after 8 hours.

C. Claims 25-31 Would Not Have Been Obvious over Zhang, Saporito P2, and Saporito P2

1. No motivation

137. As discussed above in Section XI.B.1, 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).

138. Neither Saporito P1 nor Saporito P2 would have provided a motivation for choosing the dose ranges recited in claims 25-31.

2. No reasonable expectation of success

139. As discussed above in Section XI.B.2, a POSA would not 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.

140. Neither Saporito P1 nor Saporito P2 would have provided a reasonable expectation of success in choosing the dose ranges recited in claims 25-31.

D. Objective Indicia of Nonobviousness

141. As discussed above in Section XI.C, objective indicia of nonobviousness indicate that the inventions recited in claims 22 and 25-31 would not have been obvious.

XIII. Ground 4: Claims 22 and 25-31 Are Not Obvious over Zhang, Marinus Orphan Drug Press Release, and Marinus Phase I Press Release

142. I considered whether claims 22 and 25-31 would have been obvious in view of Zhang, the Marinus Orphan Drug Press Release, and the Marinus Phase I Press Release.

143. Based on the disclosure of Zhang, the Marinus Orphan Drug Press Release, and the Marinus Phase I Press Release, a POSA would not have expected ganaxolone to treat SE, to provide improvement to a patient after administration for more than 8 hours, or to do so using the dose ranges from claims 25-31.

A. Claim 22 Would Not Have Been Obvious over Zhang, Marinus Orphan Drug Press Release, and Marinus Phase I Press Release

1. No motivation

144. 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 claim 22.

145. As discussed above in Section XI.A.1, 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." As discussed above in Section XI.A.1, nowhere does Zhang disclose "improvement to the patient after administration for more than 8 hours."

146. Additionally, nothing in Zhang would motivate a POSA to seek out additional publications related to the treatment of SE by administering ganaxolone to a patient in need. As described above, Zhang's disclosure is limited to rat data and does not describe the use of ganaxolone to treat a patient with SE. Thus, there is nothing that would motivate a POSA to combine these references to arrive at the limitation of claim 22.

2. No reasonable expectation of success

147. A POSA would not 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" as required for claim 22 based on Zhang in combination with Marinus's Orphan Drug Press Release and/or Marinus's Phase I Press Release.

148. For the reasons discussed above in Section XI.A.2, Zhang does not provide a reasonable expectation of success for claim 22. Additionally, 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 successfully provide "improvement to the patient after administration for more than 8 hours," as recited in claim 22. 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.

149. Indeed, 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. *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.”). Efficacy could not have been tested or established 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* § XI.B.2; *see also* Ex. 1011, 1 (recognizing that SE is a “difficult to treat seizure disorder with limited treatment options”).

150. Additionally, the fact that the FDA granted orphan drug status to Marinus for the use of ganaxolone to treat SE does not demonstrate anything about the efficacy of the drug. Less than 14% of drugs granted orphan drug designation ultimately receive in FDA approval. Ex. 2019, 3.

151. The same is true for the fact that Marinus was allowed to proceed to Phase I clinical trials for the use of ganaxolone to treat SE. Indeed, the success rate of *phase III* clinical studies for anti-epileptic drugs is only about 10%. Ex. 2020, 2.

A POSA therefore would not have found the Press Releases indicative of the efficacy of ganaxolone for the treatment of SE.

152. Therefore, the Press Releases, even in combination with Zhang, would not have provided a POSA with a reasonable expectation of success. *See supra* XI.A.2.

B. Claims 25-31 Would Not Have Been Obvious over Zhang, Marinus Orphan Drug Press Release, and Marinus Phase I Press Release

1. No motivation

153. 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 25-31.

154. As discussed above in Section XI.B.1, a POSA would not have been motivated to choose the narrower dose ranges recited in claims 25-31 from the broader dose range disclosed in Zhang (1 mg/kg to 20 mg/kg).

155. Additionally, nothing in Zhang would motivate a POSA to seek out additional publications related to the treatment of SE by administering ganaxolone to a patient in need. As described above, Zhang's disclosure is limited to rat data and does not describe the use of ganaxolone to treat a patient with SE. Thus, there is nothing that would motivate a POSA to combine these references to arrive at the limitation of claims 25-31.

2. No reasonable expectation of success

156. A POSA would not have had a reasonable expectation of success that intravenous 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.

157. For the reasons discussed above in Section XI.B.2, Zhang does not provide a reasonable expectation of success for claims 25-31. Additionally, 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 successfully treat SE when administered at the doses recited in claims 25-31. Neither Press Release discloses any information about ganaxolone's efficacy in treating SE in a human or otherwise. *See* Ex. 1011, 1; Ex. 1022, 1.

158. Indeed, both Press Releases predate phase 1 clinical trials for testing the safety, tolerability, and pharmacokinetics of ganaxolone IV—notably, not for its efficacy in treating SE. *See* Ex. 1011, 1 (“A Phase 1 clinical trial evaluating the safety, tolerability and pharmacokinetics of ganaxolone IV is expected to initiate in the first half of 2016.”); Ex. 1022, 1 (“We look forward to reporting the results on this Phase 1 study later this year.”). The lack of efficacy data in humans is significant because of the noted difficulties in treating SE. *See supra* § XI.B.2; *see also* Ex.

1011, 1 (recognizing that SE is a “difficult to treat seizure disorder with limited treatment options”).

159. Additionally, the fact that the FDA granted orphan drug status to Marinus for using ganaxolone to treat SE does not demonstrate anything about the efficacy of the drug. Less than 14% of drugs granted orphan drug designation ultimately result in an FDA approval. Ex. 2019, 3

160. The same is true for the fact that Marinus was allowed to proceed to Phase I clinical trials. Indeed, the success rate of *phase III* clinical studies for anti-epileptic drugs is only about 10%. Ex. 2020, 2. A POSA therefore would not have found the Press Releases indicative of the efficacy of ganaxolone for the treatment of SE.

161. The Press Releases, even in combination with Zhang, would not have provided a POSA with a reasonable expectation of success. *See supra* XI.B.2.

C. Objective Indicia of Nonobviousness

162. As discussed above in Section XI.C, objective indicia of nonobviousness indicate that the inventions recited in claims 22 and 25-31 would not have been obvious.

Declaration of Raman Sankar, M.D., Ph.D.
in support of Patent Owner's Response to Post-Grant Review
of U.S. Patent No. 11,395,817

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

Declaration of Raman Sankar, M.D., Ph.D.
in support of Patent Owner's Response to Post-Grant Review
of U.S. Patent No. 11,395,817

Respectfully submitted,



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Date: November 28, 2023