

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

OVID THERAPEUTICS INC.,
Petitioner,

v.

MARINUS PHARMACEUTICALS, INC.,
Patent Owner.

Case IPR2024-00726
Patent 11,110,100 B2

**PETITION FOR AN *INTER PARTES* REVIEW OF
U.S. PATENT NO. 11,110,100**

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EXHIBIT LIST

Exhibit	Description
1001	U.S. Patent No. 11,110,100 B2 to Marinus Pharmaceuticals, Inc. (“the ‘100 patent”)
1002	Declaration and Curriculum Vitae of Dr. Raman Sankar, M.D., Ph.D. (the “Sankar Declaration”)
1003	U.S. Patent No. 11,395,817 B2 (“During”)
1004	NCT03350035 Clinical Trial Study Details, ClinicalTrials.gov (Nov. 17, 2017), https://clinicaltrials.gov/study/NCT03350035?term=NCT03350035&rank=1&tab=history&a=1 (last visited Sept. 28, 2023) (“NCT03350035”)
1005	J. Tsai et al., Phase I study to determine the pharmacokinetics, pharmacodynamics, and safety of IV ganaxolone in healthy adults, Final Programme of the 6th London-Innsbruck Colloquium on Status Epilepticus and Acute Seizures, 74-75 (Apr. 6-8, 2017) (“Tsai 2017”)
1006	J. Tsai et al., Phase I Study to Determine the Pharmacokinetics, Pharmacodynamics, and Safety of IV Ganaxolone in Healthy Adults 80 Annals of Neurology S77-78 (Supp. 20 2016) (“Tsai 2016”)
1007	Ganaxolone Phase 1 Data Supports Progressing to Phase 2 in Patients with Status Epilepticus, Clinical Leader (Oct. 19, 2016), https://www.clinicalleader.com/doc/ganaxolone-phase-data-progressing-phase-patients-epilepticus-0001 (last visited Sept. 28, 2023) (“Clinical Leader 2016”)
1008	R. Eugene Ramsay et al., Pharmacokinetic and Pharmacodynamic (PK/PD) Relationship of Intravenous Ganaxolone in Refractory Status Epilepticus (Nov. 25, 2019), https://aesnet.org/abstractslisting/pharmacokinetic-and-pharmacodynamic-(pk/pd)-relationship-of-intravenous-ganaxolone-in-refractory-status-epilepticus (“Ramsay 2019”)

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1009	A. Husain et al., Intravenous Ganaxolone Achieves Rapid and Dose-Dependent Sustained Improvement in EEG Seizure Burden in Patients with Refractory Status Epilepticus, 37 J. Clin. Neurophysiol. 332 (July 2020) (“Husain 2020”)
1010	Treatment of Refractory Status Epilepticus Prevents Need for Induced Coma with Intravenous Anesthetics in Phase 2 Trial, Practical Neurology (Oct. 18, 2019), https://practicalneurology.com/news/treatment-of-refractory-status-epilepticus-prevents-need-for-induced-coma-with-intravenous-anesthetics-in-phase-2-trial (last visited Sept. 28, 2023) (“Practical Neurology 2019”)
1011	R. Eugene Ramsay, Pharmacokinetic and Pharmacodynamic (PK/PD) Relationship of Intravenous Ganaxolone in Refractory Status Epilepticus, Marinus Pharmaceuticals (Dec. 7, 2019), https://marinuspharma.com/wp-content/uploads/2020/09/AES-2019-GNX-in-RSE-Ph2-Poster-vFINAL.pdf (last visited Sept. 28, 2023) (“AES Poster 2019”)
1012	Doodipala S. Reddy et al., Experimental Models of Status Epilepticus and Neuronal Injury for Evaluation of Therapeutic Interventions, 14 Int’l J. Mol. Sci. 18284-318 (2013) (“Reddy”)
1013	Marinus Pharmaceuticals Receives FDA Orphan Drug Designation for Ganaxolone IV to Treat Status Epilepticus, Marinus Pharmaceuticals (Apr. 15, 2016), https://ir.marinuspharma.com/news/news-details/2016/Marinus-Pharmaceuticals-Receives-FDA-Orphan-Drug-Designation-for-Ganaxolone-IV-to-Treat-Status-Epilepticus/default.aspx (last visited Sept. 28, 2023)
1014	Marinus Corporate Presentation June 2023, Marinus Pharmaceuticals (June 2023), https://s25.q4cdn.com/443656056/files/doc_financials/2023/Corporate-Deck-June-FINAL.pdf (last visited June 19, 2023)
1015	Eugen Trinka et al., A definition and classification of status epilepticus – Report of the ILAE Task Force on Classification of Status Epilepticus, 56 Epilepsia 1515-1523 (2015) (“Trinka 2015”)

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1016	Henrikas Vaitkevicius, Intravenous ganaxolone for the treatment of refractory status epilepticus: Results from an open-label, dose-finding, phase 2 trial, 63 Epilepsia 2381-91 (2022) (“Vaitkevicius 2022”)
1017	John D. Hixson, Stopping Antiepileptic Drugs: When and Why?, 12 Current Treatment Options in Neurology 434-442 (2010) (“Hixson 2010”)
1018	Simon Shorvon, The Management of Status Epilepticus, 70 J. Neurol. Neurosurg. Psychiatry ii22-ii27 (Supp. II 2001) (“Shorvon 2001”)
1019	Durgul Ozdemir et al., Efficacy of continuous midazolam infusion and mortality in childhood refractory generalized convulsive status epilepticus, 14 Seizure 129-132 (2005) (“Ozdemir 2005”)
1020	Edward P. Monaghan et al., Initial Human Experience with Ganaxolone, a Neuroactive Steroid with Antiepileptic Activity, 38 Epilepsia 1026-1031 (1997) (“Monaghan 1997”)
1021	Richard B. Carter et al., Characterization of the Anticonvulsant Properties of Ganaxolone (CCD 1042; 3 α -Hydroxy-3 β -methyl-5 α -pregnan-20-one), a Selective, High-Affinity, Steroid Modulator of the γ -Aminobutyric Acid _A Receptor, 280 J. Pharmacol. Experimental Therap. 1284-1295 (1997) (“Carter 1997”)
1022	WO 2007/062266 A2 (“Shaw”)
1023	Michael R. Sperling et al., Randomized, double-blind, placebo-controlled phase 2 study of ganaxolone as add-on therapy in adults with uncontrolled partial-onset seizures, 58 Epilepsia 558-564 (2017) (“Sperling 2017”)
1024	Marinus Pharmaceuticals Doses First Subject in Phase 1 Clinical Trial for Ganaxolone IV, Marinus Pharmaceuticals (June 22, 2016), https://ir.marinuspharma.com/news/news-details/2016/Marinus-Pharmaceuticals-Doses-First-Subject-in-Phase-1-Clinical-Trial-for-Ganaxolone-IV/default.aspx (last visited Sept. 28, 2023) (“Marinus’s Phase 1 Press Release”)

Exhibit	Description
1025	Julia Tsai et al., Phase 1 Study to Determine the Pharmacokinetics, Pharmacodynamics, and Safety of IV Ganaxolone in Healthy Adults (“2016 Phase 1 Poster”)
1026	Eileen Broomall et al., Pediatric Super-Refractory Status Epilepticus Treated with Allopregnanolone, 76 Ann Neurol. 911-915 (2014) (“Broomall 2014”)
1027	Dorota Zolkowska et al., Intramuscular allopregnanolone and ganaxolone in a mouse model of treatment-resistant status epilepticus 59 Epilepsia 220-227 (Supp. 2 2018) (“Zolkowska 2018”)
1028	Henrikas Vaitkevicius et al., First-in-man allopregnanolone use in super-refractory status epilepticus, 4 Annals of Clinical Translational Neurol. 411-414 (2017) (“Vaitkevicius 2017”)
1029	Excerpts from the File History of the ’100 Patent
1030	Raman Sankar, Treatment of status epilepticus: Physiology, pharmacology, and future directions, Epilepsia Open 1-8 (May 2023), https://onlinelibrary.wiley.com/doi/epdf/10.1002/epi4.12725 (“Sankar 2023”)
1031	U.S. Provisional Application No. 62/882,648 (“the ’648 Provisional Application”)
1032	WO 2021/026124 A1 (“WO ’124”)
1033	Marinus Pharmaceuticals Presents Clinical Data of Ganaxolone in Pediatric Epilepsies at Antiepileptic Drug and Device Trials XIII Conference, Marinus Pharmaceuticals (May 18, 2015), https://ir.marinuspharma.com/news/news-details/2015/Marinus-Pharmaceuticals-Presents-Clinical-Data-of-Ganaxolone-in-Pediatric-Epilepsies-at-Antiepileptic-Drug-and-Device-Trials-XIII-Conference/default.aspx (last viewed Sept. 28, 2023)
1034	Geoffrey M. Currie, Pharmacology, Part 2: Introduction to Pharmacokinetics, 46 J. Nuclear Med. Tech. 221-30 (Sept. 2018) (“Currie 2018”)

Exhibit	Description
1035	Excerpts from the File History of U.S. Patent Application No. 15/673,737
1036	141st Annual Meeting of the American Neurological Society, Annals of Neurology, S1-S265, https://onlinelibrary.wiley.com/doi/10.1002/ana.24759 (last accessed Feb. 8, 2024)

I. Introduction

U.S. Patent No. 11,110,100 (“the ’100 patent”) claims methods of treating status epilepticus (“SE”) by administering an effective dose of ganaxolone intravenously as a bolus followed by continuous infusion 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. Before the ’100 patent’s earliest claimed priority date, Ovid had filed patent applications describing (and later claimed in U.S. Patent No. 11,395,817 (“During”)) daily doses of ganaxolone that inherently disclose the same ganaxolone plasma concentration that the ’100 patent’s inventors purport to have “unexpectedly discovered” resulted in SE suppression. Marinus also had already begun reporting the results of its Phase 1 clinical trial to support treating SE with ganaxolone and had published protocols on ClinicalTrials.gov for its Phase 2 clinical trial that administered ganaxolone intravenously as a bolus dose followed by continuous infusion to treat SE (“NCT03350035”). This prior art renders the claims of the ’100 patent obvious. Yet Marinus did not disclose the Phase 1 results or Phase 2 protocol to the PTO during prosecution of the ’100 patent.

Should Marinus argue that the claimed ganaxolone plasma concentration is not inherent to the previously disclosed daily doses of ganaxolone in During and assert that pharmacokinetic data is required, the ’100 patent cannot be afforded the priority date of Marinus’s provisional application. The provisional application never

describes the plasma concentration that Marinus asserts resulted in the “completely unexpected” suppression of SE and allowance of the claims. Indeed, Marinus’s provisional application expressly reported that pharmacokinetic data related to administering doses of ganaxolone found to suppress SE was “*unavailable*” at the time of the provisional application’s filing. And there are no blaze marks amid the rest of the specification that would have guided a POSA to the method of treatment that Marinus actually claimed. Thus, if Marinus argues During is not patent-defeating, Marinus should not be permitted to rely on its priority filing for § 112 support.

Without the benefit of the provisional application’s filing date, the ’100 patent’s claims are undoubtedly obvious over the results of Marinus’s Phase 2 clinical trials that were public before Marinus’s PCT application was filed. The Phase 2 clinical trial results describe administering ganaxolone as a bolus followed by continuous infusion at daily amounts that achieve the recited plasma concentration and result in the suppression of SE.

Ovid thus respectfully submits that trial should be instituted and that all claims of the ’100 patent should be found unpatentable.

II. Requirements for an IPR (37 C.F.R. § 42.104)

A. Grounds for Standing

Ovid certifies that the '100 patent is available for IPR. This petition is being filed more than nine months after the grant of the patent on September 7, 2021. Ovid has not filed a civil action challenging the validity of any claim of the '100 patent and is not barred or estopped from requesting review of the challenged claims on the identified grounds. Ovid has not yet been served with any complaint for infringement of the '100 patent.

B. Challenges and Precise Relief Requested

Ovid requests an IPR of the challenged claims on the grounds in the table below and requests that each challenged claim be found unpatentable. An explanation of how the challenged claims are unpatentable under the statutory grounds identified below is provided in the form of a detailed description that follows, showing where each element can be found in the cited prior art and the relevance of that prior art. Additional explanations and support for each ground is set forth in Ex. 1002, the Declaration of Dr. Raman Sankar, M.D., Ph.D.

Ground	Claims	Basis for Rejection
1	1-21	Obviousness under 35 U.S.C. § 103 over During (Ex. 1003) and NCT03350035 (Ex. 1004)
2	1-21	Obviousness under 35 U.S.C. § 103 over During and Marinus's Phase 1 Clinical Trial Results (Tsai 2017 (Ex. 1005), Tsai

		2016 (Ex. 1006), and Clinical Leader 2016 (Ex. 1007))
3	1-21	Obviousness under 35 U.S.C. § 103 over During, NCT03350035, and the Phase 2 Clinical Trial Results (Practical Neurology 2019 (Ex. 1010), Ramsay 2019, AES 2019 Poster (Ex. 1011), Husain 2020 (Ex. 1009)

III. Background

A. Status Epilepticus (“SE”)

Epilepsies and seizure disorders cover a variety of neurological disorders resulting from abnormal electrical activity in the brain. Ex. 1002, ¶12. A seizure is an atypical electrical discharge in the brain that results in changes in consciousness, sensation, and behavior. Ex. 1012, 18285; Ex. 1002, ¶12. Epilepsy is a chronic condition characterized by recurring, unprovoked seizures. Ex. 1012, 18285; Ex. 1002, ¶12.

Status epilepticus (“SE”) is a seizure disorder defined by continuous seizure activity or multiple seizures lasting longer than 30 minutes without regaining consciousness. Ex. 1012, 18287; Ex. 1002, ¶13. SE can be life-threatening and, if not treated immediately, may result in brain damage, cognitive impairment, or even death. Ex. 1013, 1; Ex. 1002, ¶13. SE is “the second most common neurologic emergency in the U.S.,” having “150,000 cases per year” and is often treated in the emergency room. Ex. 1014, 22; Ex. 1002, ¶13.

SE can be characterized by various behavioral signs or symptoms that evolve over time (i.e., semiology)—e.g., convulsive SE is associated with excessive abnormal muscle contractions and/or impaired mental status. SE can also have electroencephalographic correlates detectable on an electroencephalogram (“EEG”) recording. *See, e.g.*, Ex. 1015, 1519; Ex. 1002, ¶14. The EEG results affect the choice and aggressiveness of clinical approaches taken by physicians. Ex. 1015, 1518; Ex. 1002, ¶14. Moreover, SE’s EEG pattern and semiology are highly dynamic and may change over short periods of time. Ex. 1015, 1518; Ex. 1002, ¶14.

SE has limited and drastic treatment options and is unlike other classes of seizure disorders. Ex. 1016, 2382; Ex. 1002, ¶15. Antiseizure medicines (“ASMs”) are the first line of defense against SE, but 30-57% of patients fail to respond. Ex. 1016, 2382; Ex. 1002, ¶15. Moreover, “53-55% of patients with SE do not respond to either first- or second-line treatment.” Ex. 1016, 2382; Ex. 1002, ¶15. Patients who do not respond to treatment are often placed in a medically-induced coma. Ex. 1016, 2382; *see also* Ex. 1012, 18287 (reporting up to 40% of SE patients suffer from refractory SE and fail to respond to standard antiepileptic treatments); Ex. 1002, ¶15.

Patients who have refractory SE (“RSE”) are typically treated through administering certain drugs using an intravenous bolus dose, followed by continuous infusion for around 12 hours and tapering of the drug. Ex. 1002, ¶16. A bolus dose

is an amount of drug administered within a specific timeframe to quickly raise the drug's blood-plasma concentration to an effective level. *Id.*, ¶16. After the bolus is administered, continuous infusion is used to maintain the plasma concentration level. *Id.*, ¶16.

Using a bolus dose followed by continuous infusion is common in emergency situations, where using only continuous infusion would take too long to reach a steady-state plasma concentration. *Id.*, ¶16. The continuous infusion must then be tapered to avoid patients experiencing withdrawal seizures or recurrence of SE. Ex. 1017, 439; Ex. 1002, ¶16.

This type of administration has been used to treat RSE with at least propofol, thiopental, and midazolam. In 2001, propofol was used to treat RSE with a bolus dose, followed by continuous infusion and a slow taper. Ex. 1018, Fig. 2; Ex. 1002, ¶17. Thiopental was similarly administered, in conjunction with monitoring EEG, to treat RSE. Ex. 1018, Fig. 2; Ex. 1002, ¶17.

In 2009, researchers studied the efficacy of midazolam for treating childhood refractory generalized convulsive SE. Ex. 1019, 129; Ex. 1002, ¶18. Subjects with RSE were administered midazolam as a “0.2 mg/kg . . . bolus, followed by a continuous infusion starting at 1 mg/kg/min up to 5 mg/kg/min increasing by 1 mg/kg/min every 15 min until complete control of seizures was achieved.” Ex. 1019, 130. The midazolam infusion rate was “gradually decreased until tapering was

completed when patient had remained seizure free for a period of 24 h.” Ex. 1019, 130). EEG was used “after the seizures had been controlled to monitor the suppression of seizure discharge.” Ex. 1019, 130.

B. Development of Allosteric Modulators of GABA_A for Treating Seizure Disorders, Including SE

1. Ganaxolone

Ganaxolone is a neuroactive steroid that allosterically modulates the brain’s γ -aminobutyric acid type A (GABA_A) receptor complex. Ex. 1020, 1026; Ex. 1002, ¶19. Ganaxolone’s antiseizure effects have been evaluated for over 20 years. *See, e.g.*, Ex. 1020; Ex. 1021; Ex. 1002, ¶19.

In 1997, researchers reported ganaxolone’s potential for antiepileptic activity in humans. *See* Ex. 1020; Ex. 1002, ¶20. In the study, 96 healthy volunteers were orally administered ganaxolone ranging from 50 to 1,500 mg, and researchers “systematically characterized” the pharmacokinetics of ganaxolone. Ex. 1020, 1026; Ex. 1002, ¶20. The pharmacokinetic analysis revealed a “linear and proportional increase in the area under the curve (AUC) and C_{max} values with increasing dose within the expected therapeutic dose range.” Ex. 1020, 1026; *see also id.*, 1031; Ex. 1002, ¶20. The maximum daily dose administered was 1,500 mg/day. *Id.*, 1031.

In 2007, Marinus evaluated ganaxolone’s ability to treat epilepsy and other central nervous system disorders in various dosage forms. Ex. 1022, ¶¶[0002], [00174]; Ex. 1002, ¶21. For example, Marinus administered 200 mg of ganaxolone

as an oral suspension (50 mg/mL) to six healthy subjects and analyzed ganaxolone's pharmacokinetic properties. *Id.*, ¶[00546]; Ex. 1002, ¶21. This study yielded a “mean $C_{\max}$ of 37 ± 25 ng/ml and an $AUC_{(0-24)}$ of 184 ± 104 ng*h/ml.” *Id.*, ¶[00546]; Ex. 1002, ¶21.

In 2017, Marinus reported the results of an earlier Phase 2 study of the safety and efficacy of ganaxolone as an add-on therapy in adults with partial-onset seizures. Ex. 1026, 558; Ex. 1002, ¶22. This study demonstrated that 1,500 mg/day ganaxolone was effective at reducing partial-onset seizure frequency. Ex. 1023, 558; *see also id.*, 561, 562; Ex. 1002, ¶22. Ganaxolone was titrated at 600 mg/day for 2 days, followed by 900 mg/day for 2 days, 1,200 mg/day for 2 days, and then 1,500 mg/day. *Id.*, 559; Ex. 1002, ¶22. The 1,500 mg/day dose was administered for an 8-week maintenance period. *Id.*, 559; Ex. 1002, ¶22. The study found the doses of ganaxolone were “generally safe and well tolerated” and exhibited “no clinically relevant laboratory or [electrocardiography (“ECG” or “EKG”)] changes during the study.” *Id.*, 558, 563; Ex. 1002, ¶22. The study also notes that it was known that, “[f]ollowing oral administration, ganaxolone is rapidly absorbed” and the plasma concentration “sharply decreases . . . over the first 12 h and then by a terminal half-life of approximately 20 hours.” *Id.*, 559.

In 2016, Marinus began clinical trials for an intravenous formulation of ganaxolone for treating SE. Ex. 1024, 1; Ex. 1002, ¶23. Marinus's Phase 1 trial was

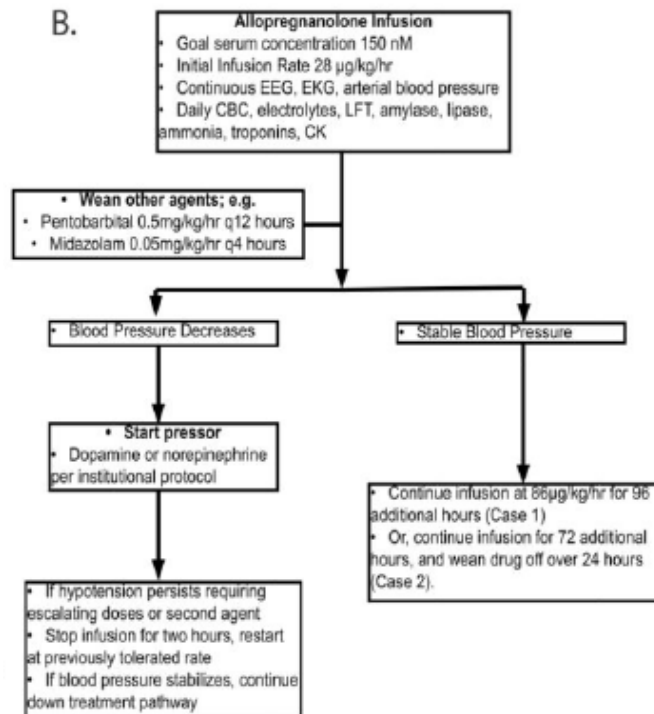
designed to investigate the safety, pharmacokinetics (“PK”), and pharmacodynamics (“PD”) of IV ganaxolone administered as both an ascending bolus dose (Stage 1 with dose cohorts A, B, C, and D) and as a bolus dose followed by a continuous infusion (Stage 2 with dose cohort A). Ex. 1024, 1; Ex. 1025, 1; Ex. 1002, ¶23. In a poster describing the Phase 1 study presented by Marinus scientists at the Annual Meeting of the American Neurological Association, the authors indicated that the doses for cohorts A and B of the bolus dose were based on Marinus’s “GNX focal onset seizure study,” described above. Ex. 1025, 1 Ex. 1002, ¶23. Moreover, the poster indicates that “[a]n interim PK analysis was conducted after each cohort and this PK data was used to predict the PK to inform dose and infusion rate in subsequent cohorts, as well as dosing in Stage 2.” Ex. 1025, 1; Ex. 1002, ¶23.

2. Allopregnanolone

Allopregnanolone is another neurosteroid and allosteric modulator of GABA_A receptors whose antiseizure activity has been tested in SE patients. Ex. 1026, 1; Ex. 1002, ¶24. Ganaxolone is the 3 β -methyl analog of allopregnanolone, (Ex. 1027, 220), and, as reported by Marinus, was “designed to have similar GABA modulation effects to allopregnanolone without unwanted steroidal effects” (Ex. 1033, 1). Ex. 1002, ¶24.

Broomall 2014 reports the use of continuous infusion of an intravenous solution of allopregnanolone to treat SE in two pediatric patients. Ex. 1026, 1. In one

patient, an intravenous solution of allopregnanolone (0.5 mg/mL in 0.9% NaCl with 6% Captisol) was infused over 5 days according to the protocol in Fig. 1B (shown below). *Id.*, 3; Ex. 1002, ¶25. In the other patient, allopregnanolone was infused according to the protocol in Fig. 1B but tapered off between hours 96 and 120. Ex. 1026, 3; Ex. 1002, ¶25. The target infusion rate for both patients was 86 µg/kg/h, which would result in a steady-state plasma level of 150 nM. This target steady-state level is equivalent to 48 ng/mL. Ex. 1026, 3; Ex. 1002, ¶25.



In Vaitkevicius 2017, two adult SE patients were given a 120-hour continuous infusion of allopregnanolone. Ex. 1028, 411; Ex. 1002, ¶26. One patient received 670.8 mg allopregnanolone as a 5.6 mg/h continuous infusion over 5 days. Ex. 1028, 412; Ex. 1002, ¶26. Panels E-H in Figure 2 of Vaitkevicius 2017 (below) show EEG

patterns demonstrating reduced seizure activity at 12, 24, 36, and 48 hours after discontinuation of phenobarbital while on allopregnanolone infusion. Ex. 1028, 413; Ex. 1002, ¶26.



A 2018 study further assessed the potential of allopregnanolone and ganaxolone to treat SE when administered intramuscularly and found that both neurosteroids were effective in terminating behavioral seizures. Ex. 1027, 221, 225; Ex. 1002, ¶27. 3 mg/kg of both allopregnanolone and ganaxolone terminated SE in 92% and 75% of animals, prevented mortality in 85% and 50% of animals, and had comparable plasma $C_{\max}$ values of 645 and 550 ng/mL. Ex. 1027, 220, 223, 225 (Table 1); Ex. 1002, ¶27.

IV. The '100 Patent

A. The Patent Family

Marinus's '100 patent issued on September 7, 2021, from U.S. Patent Application No. 17/186,569 ("the '569 application"). Ex. 1001, cover. It claims priority to U.S. Provisional Application No. 62/882,648 ("the '648 application"),

filed on August 5, 2019, and is a continuation of International Application No. PCT/US2020/044843 (“’843 PCT”), which and was filed on August 4, 2020. *Id.*, cover, 1:5-9.

B. The Specification

The ’100 patent discloses methods of treating SE with ganaxolone by administering an intravenous bolus and a continuous intravenous infusion. *Id.*, 3:27-30; Ex. 1002, ¶29. The specification states that “[s]uppression of SE typically breaks the seizures (i.e., suppresses or reduces seizure activity)” and that “[c]linically, suppression of SE can be reduction in seizure burden (i.e., the percent of time during which there is electrographic seizure activity).” Ex. 1001, 16:7-13.

The ’100 patent contains three examples. Example 1 reports the prior-art results Phase 1 clinical trial that investigated the safety, pharmacokinetics, and pharmacodynamics of an intravenous bolus of ganaxolone and continuous intravenous infusion of ganaxolone in healthy subjects. *Id.*, 47:19-24; Ex. 1002, ¶30 *see infra*, § VIII.C.

Example 2 details an “ongoing, double-blind, randomized placebo-controlled Phase 2 study designed to evaluate the safety, tolerability, and efficacy of adjunctive IV GNX in subjects with SE who have failed initial treatment with benzodiazepines and at least one AED” and presents preliminary results from 5 subjects in the study. Ex. 1001, 47:50-54:50; Ex. 1002, ¶ 31. *Infra*, § VIII.B.

Example 3 relates to “[a]n open-label, dose range finding study in which IV ganaxolone was added to standard-of-care IV AEDs in SE patients who had failed initial benzodiazepines and at least one 2nd line IV AED but had not progressed to IV anesthetics.” Ex. 1001, 54:54-58, 56:19-30; Ex. 1002, ¶32.

C. The Claims

The '100 patent contains 21 claims. Claim 1, the only independent claim, recites:

1. A method of treating status epilepticus (SE), comprising administering to a subject in need thereof an effective amount of ganaxolone to suppress SE, wherein the effective amount of ganaxolone is administered as an intravenous bolus plus continuous infusion 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. 1001, claim 1.

The remaining 20 claims depend from claim 1. Dependent claims 2, 3, 11 and 12 recite modifications to the administration of the intravenous bolus dose (dosage and duration). For illustration purposes only, claim 2 is presented below:

2. The method of claim 1, wherein the intravenous bolus comprises about 5 mg to about 40 mg of ganaxolone.

Id., claim 2.

Dependent claims 4, 5, 7, and 9 recite modifications to the administration of the continuous intravenous infusion (dosage and duration). For illustration purposes only, claim 4 is presented below:

4. The method of claim 1, wherein the continuous intravenous infusion comprises infusion of about 20 mg of ganaxolone per hour to about 80 mg of ganaxolone per hour.

Id., claim 4.

Dependent claims 6, 8, 10, 13, 15, 17, and 20 recite decreasing or tapering the amount of the continuous intravenous infusion. For illustration purposes only, claim 6 is presented below:

6. The method of claim 5, wherein the amount of ganaxolone infused into the subject by the continuous intravenous infusion is decreased from about 80 mg to about 40 mg per hour to about 20 mg per hour.

Id., claim 6.

Dependent claims 14, 18, 19, and 21 specify that the subject has RSE. For illustration purposes, claim 14 is presented below:

14. The method of claim 1, wherein the subject has refractory status epilepticus.

Id., claim 14.

Dependent claim 16 recites that “the total daily dose of ganaxolone administered is from about 500 mg to about 900 mg.” *Id.*, claim 16.

D. The Prosecution History

The original claims of the '569 application were canceled in a preliminary amendment and replaced. Ex. 1029, 135-40. New claim 55, the only independent claim, recited the following:

55. (New) A method of treating status epilepticus (SE), comprising administering to a subject in need thereof an effective amount of ganaxolone to suppress SE for a period of at least 8 hours, wherein the effective amount of ganaxolone is administered as an intravenous bolus plus continuous infusion to produce and maintain a ganaxolone plasma concentration of at least about 500 ng/ml for at least about 8 hours.

Id., 137.

The only Office Action included two rejections relevant here: (1) lack of enablement because the specification did not “reasonably provide enablement for all doses above 500 ng/mL” and (2) obviousness over US 2016/0228454 A1, a Marinus patent publication. *Id.*, 188-92.

For enablement, Marinus amended the claims to recite “a ganaxolone plasma concentration of about 500 ng/ml to about 1000 ng/ml.” *Id.*, 205-15.

For obviousness, Marinus submitted a declaration by one of the inventors, Dr. Joseph Hulihan, that states that “we unexpectedly discovered that SE could be rapidly and persistently suppressed using less ganaxolone and for a much shorter period of time than was anticipated.” *Id.*, 218. The declaration also alleges the study “surprisingly revealed” that “it is important to maintain” a ganaxolone plasma concentration of about 500 ng/ml to about 1000 ng/ml “for about 8 to about 12 hours to achieve persistent suppression, i.e., to break SE,” and that “seizures rapidly recurred” when the plasma concentration dropped below this range. *Id.*

According to the declaration, this “surprising and unexpected discovery” provides the clinical advantages of effectively breaking SE with “enhanced safety “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 claims were also amended to add the upper limit of “about 12 hours” mirroring the alleged unexpected results. *Id.* at 205-15.

In response, a Notice of Allowance issued finding that “[t]he declaration under 37 CFR 1.132 filed 07/08/2021 is sufficient to overcome the rejection of [the pending claims] based upon US 2016/0228454” and that “[t]he declaration shows the cessation of SE using the parameters of the claims. This differentiates from the prior art in the duration of treatment needed to achieve cessation of SE.” *Id.*, 248-50.

V. Legal Standards

A. Priority

For a patent to claim priority from the filing date of its provisional application, it must satisfy § 119(e)(1):

An application for patent filed under section 111(a) or section 363 for an invention *disclosed in the manner provided by section 112(a)* . . . in a provisional application filed under section 111(b), by an inventor or inventors named in the provisional application, *shall have the same effect, as to such invention, as though filed on the date of the provisional application* filed under section 111(b).

35 U.S.C. § 119(e)(1) (emphasis added); *see also Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015).

“In other words, the specification of the provisional must ‘contain a written description of the invention and the manner and process of making and using it, in such full, clear, concise, and exact terms,’ 35 U.S.C. § 112[(a)], to enable an ordinarily skilled artisan to practice the invention *claimed* in the *non-provisional* application.” *New Railhead Mfg., L.L.C. v. Vermeer Mfg. Co.*, 298 F.3d 1290, 1294 (Fed. Cir. 2002).

B. Obviousness

Under Section 103 of the Patent Act, a patent “may not be obtained . . . if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains.” 35 U.S.C. § 103 (2011).

Under Section 103, “the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved.” *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). “Against this background, the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others,

etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented.” *Id.* at 17-18.

VI. Level of Ordinary Skill in the Art

A person of ordinary skill in the art (“POSA”) for the ’100 patent at the time of the patent’s earliest filing date would have had a medical degree or a Ph.D. in pharmacology or fields related to the development of pharmaceuticals and would have been familiar with the PK and PD of pharmaceuticals. A POSA also would have had 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. *See also* Ex. 1002, ¶50.

VII. Claim Construction (37 C.F.R. § 42.104(b)(3))

The term “to produce and maintain a ganaxolone plasma concentration of about 500 ng/ml to about 1000 ng/ml” of independent claim 1 should be construed as nonlimiting. Claim language without any bearing on the claimed methods should be deemed non-limiting when it does not result in ‘a manipulative difference in the steps of the claim.’” *In re Copaxone Consol. Cases*, 906 F.3d 1013, 1023 (Fed. Cir. 2018); *see also Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1375-76 (Fed. Cir. 2001) (finding preamble language “a method for treating a cancer patient to effect regression of a taxol-sensitive tumor, said method being associated with reduced hematologic toxicity” “is only a statement of purpose and intended

result”); *Syntex (U.S.A.) LLC v. Apotex, Inc.*, 407 F.3d 1371, 1378 (Fed. Cir. 2005); *Minton v. Nat’l Ass’n of Sec. Dealers, Inc.*, 336 F.3d 1373, 1381 (Fed. Cir. 2003)).

Claim 1 requires administering “an effective amount of ganaxolone to suppress SE” and further specifies that the effective amount should be “administered as an intravenous bolus plus continuous infusion.” *See* Ex. 1001, claim 1. The claim language is clear: the dosing amount must be an “effective amount of ganaxolone to suppress SE.” As Dr. Sankar explains, to determine what amount of ganaxolone is effective to suppress SE, a POSA would have administered ganaxolone as a bolus followed by continuous infusion and then monitored the patient’s EEG activity to confirm the suppression of SE. Ex. 1002, ¶55-56. Therefore, a POSA would have understood that it is the end result (i.e., suppression of SE) that defines the amount of ganaxolone administered, meaning the claimed plasma concentration (i.e., “about 500 ng/ml to about 1000 ng/ml”) does not change the method of the claims and is superfluous. *Id.*, ¶56.

As Dr. Sankar explains, in practice, a POSA would not have used the ganaxolone plasma concentration as an indicator of SE suppression because it could take several hours or even days to receive blood plasma concentration results after taken from a patient. *Id.*, ¶57.

The plasma-concentration language in claim 1 is similar to non-limiting claim language in other cases. For example, in *In re Copaxone Consolidated Cases*, the

Federal Circuit found the following emphasized claim language to be non-limiting:

“A method . . . comprising administering to the human patient a therapeutically effective regimen . . . , *the regimen being sufficient to alleviate the symptom of the patient.*” 906 F.3d at 1022-23. The court found that the emphasized phrase “does not change the express dosing amount or method already disclosed in the claims, or otherwise result in a manipulative difference in the steps of the claim.” *Id.* at 1023. The claim language was found to be clear in that “the dosing ha[d] to be [a] ‘therapeutically effective regimen’” and “the addition of ‘the regimen being sufficient to’ be therapeutically effective [is] superfluous.” *Id.* at 1023; *see also Bristol-Myers Squibb*, 246 F.3d at 1375-76.

This interpretation of the claim is also consistent with the ’100 patent’s specification, which links “effective amount” with SE suppression:

During the treatment, the subject can be monitored for plasma concentration of neurosteroid (e.g. ganaxolone) and *using EEG for seizure activity*. If the subject appears to show signs of SE re-lapse, *the amount of ganaxolone administered can be adjusted accordingly*.

Ex. 1001, 17:6-11; *see also id.*, 23:64-24:1. The specification therefore confirms that whether an effective amount of ganaxolone has been administered to suppress SE is determined by monitoring EEG for seizure activity and adjusting the ganaxolone dose, as needed. *See* Ex. 1002, ¶58.

Based on the above, a POSA would have understood that the ganaxolone plasma concentration recited in claim 1 is non-limiting.

VIII. Marinus Is Not Entitled to Its Priority Date

The '100 patent claims priority to '843 PCT, filed on August 4, 2020, which claims priority to the '648 application (Ex. 1031), filed on August 5, 2019. The '100 patent is not entitled to the filing date of the '648 provisional application from which it claims priority because the '648 application does not provide written description support for the '100 patent's claims.

Claim 1 requires that the effective amount of ganaxolone is administered as an IV bolus plus continuous infusion “to produce and maintain a ganaxolone plasma concentration of about 500 ng/ml to about 1000 ng/ml for about 8 hours to about 12 hours.” To the extent the ganaxolone plasma concentration recited in independent claim 1 is construed to be limiting or not a natural result of an obvious method, Marinus' priority application does not include any data to support this limitation. Ex. 1002, ¶61.

During the '100 patent's prosecution, one inventor submitted a declaration stating that it was “unexpectedly discovered” that SE could be rapidly and persistently suppressed by “administering ganaxolone as an intravenous bolus and continuous intravenous infusion to achieve and maintain a ganaxolone plasma concentration of about 500 ng/ml to about 1000 ng/ml for about 8 to about 12 hours.”

Ex. 1029, 216-19. The applicant stated that “the combination of ganaxolone plasma concentration and time period are important to for the therapeutic effect of ‘breaking’ SE.” *Id.*

Nothing in the ’648 application provides evidence that the inventors were in possession of the “combination” that was admittedly important for the unexpected results as of the filing date of the ’648 application. Ex. 1002, ¶62. That is, the provisional application “does not demonstrate that the inventor possessed more than a mere wish or hope that [the claimed invention] would work, and thus it does not demonstrate that [the inventor] actually invented what he claimed.” *Nuvo Pharms. (Ire.) Designated Activity Co. v. Dr. Reddy’s Labs. Inc.*, 923 F.3d 1368, 1381 (Fed. Cir. 2019).

Example 3 and Figures 12-15 of the ’100 patent are missing from the ’648 application. Ex. 1001, 13-17, 54:52-57:7. Indeed, Example 3 and Figures 12-15 were not added until the filing of WO ’124. *See* Ex. 1032, ¶¶[0238]-[0248], 123-127. In the declaration, the inventor specifically identified “Figure 15” of the ’100 patent (which depicts the correlation between PK and efficacy for the three dose groups) as support for the alleged unexpected results. Ex. 1029, 216-19. However, neither Figure 15 nor the experimental data depicted by Figure 15 were disclosed in the ’648 application.

In Example 2, the '648 application describes a clinical trial protocol and pharmacokinetic modeling data from 5 patients, which “suggested that exposure levels of GNX at approximately 1000 ng/mL were associated with rapid and complete SE suppression, and lower GNX exposures at <500 ng/mL were associated with seizure relapse.” Ex. 1031, ¶¶[0188]-[0203]. However, none of these experiments maintained ganaxolone plasma concentration at least about 500 ng/ml to at least about 100 ng/ml for about 8 to about 12 hours, as the '100 patent claims require. Ex. 1002, ¶63. Also, because seizure activity relapsed within about 5-6 hours (when plasma concentrations of GNX decreased < 500 ng/ml), these experiments provide no support for persistent suppression of SE, which the inventors allege was “unexpectedly” achieved with the claimed plasma concentration and time period. *See* Ex. 1029, ¶218.

The '648 application also describes the results from a single patient who was subjected to a modified protocol that would allow for the total daily dose of ganaxolone to increase from 500 to 715 mg and would purportedly allow for ganaxolone exposure to be maintained at >500 ng/ml for approximately 8 hours. *Id.*, ¶¶[0204], [0208]. This single patient “experienced rapid RSE cessation following GNX treatment . . . and was successfully weaned off GNX without seizure relapse.” *Id.*, ¶[0208]. The '648 application, however, expressly admits that “[p]harmacokinetic data were *unavailable at the time of this report.*” *Id.*, ¶[0204].

The inventors thus could not have been in possession of an invention that did not exist at the time the '648 application was filed. *See Chiron Corp. v. Genentech, Inc.*, 363 F.3d 1247, 1255 (Fed. Cir. 2004) (finding claims were not entitled to priority claim because inventors, “by definition, could not have possession of, and disclose, the [claimed subject matter] that did not even exist at the time of the 1984 application”). Thus, no data in the provisional application would have demonstrated to a POSA that the ganaxolone plasma concentration was maintained “at least about 500 ng/ml for at least about 8 hours to about 12 hours” in this single patient. Ex. 1002, ¶¶64-66.

Moreover, when the applicant amended the pending claims to recite that the ganaxolone plasma concentration of “about 500 ng/ml to about 1000 ng/ml is maintained for about 8 hours to about 12 hours”—i.e., the plasma concentration and administration alleged to be “unexpected”—all but one of the paragraphs in the application that the applicant relied on for written description support for the amendment were not included in the provisional application. *See* Ex. 1029, 211 (citing Ex. 1029, ¶¶[0009], [0012], [0013], [0015], [0020], [0062], [0076], [0077], and [0107]). The only paragraph cited that was included in the provisional application, paragraph [0107], relates to the “total daily dose of ganaxolone administered,” not achieving a specific ganaxolone plasma concentration for about 8 to about 12 hours. *Compare* Ex. 1029 at 52, ¶[0107] *with* Ex. 1031, ¶[0111].

The lack of citation by Marinus is unsurprising because the '648 application was not about reaching the claimed ganaxolone plasma concentration and treatment duration. The '648 application instead discusses administering ganaxolone “in a manner which provides a plasma concentration of ganaxolone of about 50 ng/ml to about 3500 ng/ml over a time period of about 24 hours to about 120 hours” (Ex. 1031, ¶[0021]) or administering ganaxolone in a treatment for as long as “e.g., from about 30 minutes to about 120 hours” or “[i]n certain embodiments . . . about 1 to about 5 days (e.g., about 24 hours, about 36 hours, about 48 hours, about 72 hours, about 96 hours, or about 120 hours.”) (*id.*, ¶[0118]). Indeed, the '648 application reports hundreds of combinations of ganaxolone plasma concentration ranges and treatment durations of varying degrees (*see, e.g., id.*, ¶¶[0028]-[0030]), but notably never describes the claimed plasma concentration and treatment duration that “unexpectedly” resulted in suppression of SE. This only further underscores that the '648 application does not “clearly allow [a POSA] to recognize that the inventor invented what is claimed” or provide any guides or “blaze marks” to single out the plasma concentration limitation to support the later-added claims. *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1348, 1351 (Fed. Cir. 2010) (en banc).

Therefore, to the extent that Marinus argues that the ganaxolone plasma concentration limitation carries independent patentable weight, the earliest priority

date that any of the claims of the '100 patent are entitled to is the August 4, 2020 filing date of WO '124.

IX. The Scope and Content of the Prior Art

A. During (Ex. 1003)

U.S. Patent No. 11,395,817 (“During” or Ex. 1003) is a U.S. patent that issued under § 151, possesses a different inventive entity than the '100 patent, and was effectively filed on August 11, 2016, which is before the earliest effective filing date of the '100 patent. During is thus 35 U.S.C. § 102(a)(2) prior art.

During describes “methods 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. 1003, Abstract. During states that allosteric modulators include ganaxolone. *Id.*, 6:22-23; Ex. 1002, ¶68.

During discloses that “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.” Ex. 1003, 8:11-14. During discloses that ganaxolone can be administered in doses by weight of the patient ranging within 10 to 40 mg/kg. *Id.*, 8:14-22. During also describes additional doses of ganaxolone from 50 to 2000 mg. *Id.*, 8:22-34. According to During, ganaxolone “can be administered, e.g., once daily, twice daily, three times daily, or four times daily” and can be

administered “as soon as possible after the onset of seizures.” *Id.*, 8:39-44; Ex. 1002, ¶¶69-71.

During also more broadly discloses that “an allosteric modulator or a pharmaceutically acceptable salt thereof is administered at dosages ranging from about 0.001 mg/kg to about 30 mg/kg of body weight of a patient in need thereof.” Ex. 1003, 6:47-50. With respect to these allosteric modulators, During discloses specific exemplary daily dose ranges between 500 and 1000 mg/day. *Id.*, 7:49-57; Ex. 1002, ¶72.

During’s Example 3 includes a detailed description of the “[e]valuation of the ability of allopregnanolone, ganaxolone, and gaboxadol to block benzodiazepine-resistant status epilepticus.” Ex. 1003, 35:33-37:15. In this study, allopregnanolone, ganaxolone, and gaboxadol were administered to rats in doses of 0.5 mg/kg, 2 mg/kg, 5 mg/kg, 10 mg/kg, or 20 mg/kg. *Id.*, 36:22-24. As shown in Table 2 and Figures 3 and 4, the 20 mg/kg ganaxolone dose was effective to induce significant protection against SE and resulted in no observation of further convulsive seizures after 10 min of drug administration. At a lower dose (10 mg/kg), ganaxolone afforded protection against SE despite not reaching a statistically significant threshold. Ex. 1002, ¶73. Each of these disclosures were present in the originally filed application dated August 10, 2017. *Compare* Ex. 1003 *with* Ex. 1035.

During's claims also recite methods of treating SE by administering the following intravenous doses of ganaxolone: "about 150 mg to 1000 mg/day," "about 500 mg to 1000 mg/day," "about 625 mg to 650 mg/day," "about 650 mg to 675 mg/day," "about 675 mg to 700 mg/day," "about 625 mg to 700 mg/day," "about 700 mg to 725 mg/day," "about 1025 mg to 1050 mg/day." Ex. 1003, 40:18-33 (claims 24-31); Ex. 1002, ¶74.

B. NCT03350035 Clinical Trial (Ex. 1004)

NCT03350035 is a version of a clinical trial protocol that was first published on ClinicalTrials.gov on November 17, 2017, and last updated on November 22, 2017, which are both before the earliest effective filing date of the '100 patent. Ex. 1004, 2.

As explained by Dr. Sankar, a POSA would have considered ClinicalTrials.gov to be a reliable and trustworthy source of information about scheduled, ongoing, and completed clinical trials and would have found the posting dates listed on ClinicalTrials.gov to be trustworthy and authoritative. Ex. 1002, ¶¶75-76. Indeed Dr. Sankar uses ClinicalTrials.gov in his clinical work. *Id.*, ¶75 (citing Ex. 1030, 5). NCT03350035 is thus prior art under § 102(a)(1). *See, e.g., Samsung Bioepis Co. Ltd v. Regeneron Pharma.*, IPR2023-00442, Paper 10 at *17 (PTAB July 19, 2023) (finding Phase 2 study posted on ClinicalTrials.gov to be prior

art); *Grünenthal GMBH, v. Antecorp Bioventures II LLC*, PGR2019-00003, Paper 7 at *22 (PTAB May 7, 2019) (same).

NCT03350035 is “a double-blind, randomized, placebo-controlled study to evaluate the safety, tolerability, and efficacy of adjunctive IV ganaxolone in subjects with SE.” Ex. 1004, 3. Under “Arms and Interventions,” NCT03350035 discloses that ganaxolone was administered as an “IV loading dose with continuous infusion (maintenance dose) for 2-4 days followed by a 24-hour taper.” *Id.*, 3-4; Ex. 1002, ¶77.

C. Marinus’s Phase 1 Clinical Trial Results

Tsai 2017, Tsai 2016, and Clinical Leader 2016 (“Marinus Phase 1 CTRs”) each describe Marinus’s Phase 1 study conducted to determine the PK, PD, and safety of intravenous ganaxolone in healthy adults. Each was published more than one year before the effective filing date of the ’100 patent and are prior art under § 102(a)(1), with no exceptions available under § 102(b). None of these disclosures were submitted to the PTO during prosecution of the ’100 patent.

1. Tsai 2017 (Ex. 1005)

Tsai 2017 is abstract P72 in the Final Programme of the 6th London-Innsbruck Colloquium on Status Epilepticus and Acute Seizures. Ex. 1005, 74-75. Tsai 2017 was available no later than April 6, 2017, which is before the earliest effective filing date of the ’100 patent, and is thus § 102(a)(1) prior art.

Tsai 2017 describes the results of a Phase 1 study evaluating the “safety, pharmacokinetics (PK), and pharmacodynamics (PD) of [ganaxolone (GNX)] IV administered as a bolus dose and continuous infusion to healthy patients.” Ex. 1005, 74. Tsai 2017 describes the protocol as assessing “PK changes in EEG, BIS, and sedation scores, and safety . . . following a single bolus and bolus dosing followed by continuous infusion of GNX IV.” *Id.* The pharmacokinetic results of the Phase 1 study report that:

GNX concentrations in plasma were generally proportional to the administered dose. Potential anti-convulsant plasma concentrations were achievable with a bolus dose. After the IV bolus dose or cessation of the IV infusion dose, concentrations of GNX in plasma declined in a multi-phasic manner.

Id., 75.

Tsai 2017 concludes that “GNX administered as a rapid IV bolus or bolus with continuous infusion was generally safe and well tolerated” and that “[p]redictable PK from this study enables dosing guidance for GNX IV.” *Id.*; Ex. 1002, ¶¶78-80.

2. Tsai 2016 (Ex. 1006)

Tsai 2016 is abstract S208 in Volume 80, Supplement 20 of the 2016 Annals of Neurology Journal. Ex. 1006, S77-78. Tsai 2016 published on October 14, 2016, which is before the earliest effective filing date of the ’100 patent and is thus prior

art under § 102(a)(1). *See, e.g.*, Ex. 1036 (noting that *Annals of Neurology*, Volume 80, Issue S20 “First published: 14 October 2016”).

Tsai 2016 describes the results of a Phase 1 study whose objective was “to evaluate the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of ganaxolone (GNX) IV administered as a bolus dose and continuous infusion to healthy participants.” Ex. 1006, S77-S78. The study proceeded in two stages, where Stage 1 “will determine the PK, change in quantitative and qualitative EEG (PD), and safety . . . following single bolus doses of IV GNX” and Stage 2 “will determine the PK, safety, and PD of bolus IV dosing followed by continuous infusion.” *Id.*, S78; Ex. 1002, ¶¶81-82.

3. Clinical Leader 2016 (Ex. 1007)

Clinical Leader 2016 was published on October 19, 2016, which is before the earliest effective filing date of the '100 patent, and is thus § 102(a)(1) prior art. Ex. 1007, 1.

Clinical Leader 2016 states that Marinus’s Phase 1 study “was designed to determine the pharmacokinetics (PK), pharmacodynamics (PD), and safety of ganaxolone IV administered as an ascending bolus dose (Stage 1) or continuous infusion (Stage 2).” Ex. 1007, 1. Clinical Leader 2016 also states that Marinus had “announced that in its Phase 1 dose-escalation study, ganaxolone intravenous (IV) achieved dose levels targeted for efficacy in patients with status epilepticus (SE) and

other indications.” *Id.*, 1. In the press release, Marinus’s Chief Medical Officer states that Marinus is “pleased with the results from our Phase 1 study which has provided predictable PK to enable dosing of ganaxolone IV in clinical studies in SE.” *Id.*

The Phase 1 results are described as demonstrating that “[e]very dose regimen of ganaxolone IV administered, either bolus or continuous infusion, was generally safe and well tolerated and reached targeted dose levels in a short period of time.” *Id.*, 1. Moreover, “[g]anaxolone IV plasma concentrations were generally proportional to the administered dose, with potential anti-convulsant plasma concentrations achievable with a bolus dose. Additionally, the continuous infusion of ganaxolone IV achieved the targeted PK levels.” *Id.*

Clinical Leader 2016 also states that the Phase 1 data “was presented . . . in a poster entitled, ‘Phase 1 study to determine the pharmacokinetics, pharmacodynamics, and safety of IV ganaxolone in healthy adults,’ at the 141st Annual Meeting of the American Neurological Association (ANA), October 16-18, 2016.” *Id.*; Ex. 1002, ¶¶83-84.

D. Phase 2 Clinical Trial Results

Practical Neurology 2019, Ramsay 2019, the AES 2019 Poster, and Husain 2020 (“Phase 2 CTRs”) describe the results of a Phase 2, open-label, dose-escalation study where IV ganaxolone was used to treat RSE patients. Each were published before the PCT filing date of the ’100 patent. To the extent that the ’100 patent is

not entitled to the priority date of the provisional application, these disclosures are prior art under § 102(a)(1).

1. Practical Neurology 2019 (Ex. 1010)

Practical Neurology 2019 published on October 18, 2019, which is before the August 4, 2020 priority date of the '100 patent. Ex. 1010, 1. Practical Neurology 2019 lists none of the inventors of the '100 patent as authors nor does it indicate that the subject matter disclosed was directly or indirectly obtained from any named inventors of the '100 patent. Practical Neurology 2019 is thus § 102(a)(1) prior art should the '100 patent not be given its August 5, 2019 priority date.

Practical Neurology 2019 describes the results of a Phase 2 clinical trial, whose “results were presented at the Neurocritical Care Society 17th Annual Meeting in Vancouver, BC.” Ex. 1010, 2. The study’s results describe identifying “[a] target dose of ganaxolone, supported by pharmacokinetic (PK) data. *Id.*, 1. Moreover, “[t]he PK data show that the target dose of ganaxolone (713 mg/day) achieved plasma drug concentrations greater than 500 ng/mL for approximately 8 hours, the longest and highest duration of the 3 dosing groups.” *Id.*, 2. The study found that “[a] dose-response relationship among the dose groups was apparent.” *Id.*; Ex. 1002, ¶¶85-87.

2. Ramsay 2019 (Ex. 1008)

Ramsay 2019 published on November 25, 2019, before the filing date of the PCT related to the '100 patent. Ex. 1008, 1. To the extent that the '100 patent is not entitled to the priority date of the provisional application, Ramsay 2019 is prior art under § 102(a)(1).

Julia Tsai is the only author of Ramsay 2019 who is also a named inventor of the '100 patent. Ex. 1008, 1. There is no indication, however, that the disclosures of Ramsay 2019 directly or indirectly originated from Julia Tsai.

Ramsay 2019 describes that “PK/PD evidence of a rapid, durable, and drug exposure-dependent clinical response to IV GNX administration in patents with refractory status epilepticus (RSE) in a Phase 2 open-label study.” *Id.*, 1-2. Ramsay 2019 states that the study assessed “two dose levels of IV GNX . . . in subjects with RSE.” *Id.*, 2. “Cohort-A (n=5) and Cohort-B (n=5) were dosed with 500 mg/day and 714 mg/day of continuous IV GNX, respectively, for up to four days” and the infusion was designed to “produce initial high plasma levels of GNX for several hours followed by stepped decreases of GNX dosing.” *Id.*

“RSE was stopped rapidly (within minutes) upon the start of IV GNX in all subjects who failed 1-4 IV ASMs (Figure 1). This response was associated with plasma GNX levels >500 ng/mL.” Cohort-A maintained ganaxolone plasma concentrations “~500 ng/mL for approximately 4 hours with good seizure

suppression.” *Id.* “Seizure relapse or abnormal EEG activity was noted at ~5-6 hours into the infusion in four out of 5 subjects which corresponded to when GNX plasma levels decreased to < 500 ng/mL.” *Id.* Cohort-B maintained ganaxolone plasma concentrations of “~500 ng/mL for ~8 hrs.” *Id.* “Good seizure control was maintained in all subjects throughout the entire dosing period even when GNX plasma levels decreased < 500 ng/mL and no subjects progressed to IV anesthetics.” *Id.*

Ramsay 2019 concluded that “the durability of pharmacological response appears to correlate with GNX exposure and ability to maintain target plasma drug levels for an adequate amount of time.” *Id.*; Ex. 1002, ¶¶88-92.

3. AES 2019 Poster (Ex. 1011)

Marinus’s website includes a poster under the heading “AES 2019” with the same name as the Ramsay 2019 abstract. Ex. 1011, 1. This is the same poster presented with the Ramsay 2019 abstract on December 7, 2019. Ex. 1008, 1 (noting that the information in Ramsay 2019 was presented on December 7, 2019, at 6 pm).

The AES 2019 Poster presents the results of the Phase 2 study described in Ramsay 2019 from three dose groups, where “Target Dose [713 mg/day] Achieves 500 ng/mL for ~8 hours.” Ex. 1011, 1; Ex. 1002, ¶¶93-94.

4. Husain 2020 (Ex. 1009)

Husain 2020 is abstract F53 published in Volume 37, Number 4 of the Journal of Clinical Neurophysiology and was submitted for the 2020 American Clinical Neurophysiology Society (ACNS) Annual Meeting. Ex. 1009, 2. Husain 2020 published on July 1, 2020, which is before the filing date of the PCT application related to the '100 patent. To the extent that the '100 patent is not entitled to the priority date of the provisional application, Husain 2020 is prior art under § 102(a)(1).

Julia Tsai and Alex Aimetti are the only two (of eight) authors of Husain 2020 who are also named inventors on the '100 patent. *Id.*, 3. There is no indication that the disclosures of Husain 2020 directly or indirectly originated from Julia Tsai or Alex Aimetti.

Husain 2020 describes a Phase 2, open-label, dose-escalation study where IV ganaxolone was used to treat RSE patients. *Id.*, 3. The “evaluable patients were allocated to three dose cohorts: 500 mg/day GNX (Low, n=4), 650 mg/day GNX (Medium, n=4), or 713 mg/day GNX (Target, n=7).” *Id.*

Husain 2020 observed “rapid reduction in seizure burden” within 0-5 minutes of ganaxolone administration and “an 80% sustained reduction” within 10-15 minutes post-ganaxolone administration. *Id.*, 3. “Only evaluable patients in the Target dose achieved at least an 80% sustained reduction in seizure burden for the

entire analysis window (24 hrs) whereas seizure activity partially returned in the Low and Medium doses at times aligning with decreased GNX exposure.” *Id.*; Ex. 1002, ¶¶95-97.

X. Claims 1-21 of the ’100 Patent Are Unpatentable as Obvious

A. All Claims of the ’100 Patent Are Unpatentable Even If They Are Entitled to the Priority Date of the ’648 Application

1. Ground 1: All Claims of the ’100 Patent Would Have Been Obvious Over During and NCT03350035

a. Claim 1

i. Motivation to Combine

As Dr. Sankar states, and as is clear from their disclosures, During and NCT03350035 both relate to administering ganaxolone to treat SE. Ex. 1002, ¶99; Ex. 1003, 8:11-14, 8:22-34, 35:31-37:15; Ex. 1004, 3-4.

In particular, During’s Example 3 evaluates ganaxolone’s ability to block benzodiazepine-resistant SE and shows that 20 mg/kg ganaxolone provides significant improvement in seizure protection. Ex. 1003, 35:33-35; Ex. 1002, ¶100. Claims 24-31 of During recite methods of treating SE by administering specific dose ranges ganaxolone within the range of 150 mg to 1000 mg/day, including “about 700 mg to 725 mg/day.” Ex. 1003, 40:18-33; Ex. 1002, ¶100.

Further, and as described above in Section III.B.1, the prior art demonstrated that 1,500 mg/day ganaxolone (after titrating up from 600 mg/day) administered orally was effective at reducing partial-onset seizure frequency. *See, e.g.*, Ex. 1023,

561, 562; Ex. 1002, ¶101. The prior art directly taught that doses of ganaxolone in partial-onset seizure studies inform those for SE. Ex. 1025, 1 (Table 1 stating “Cohort B” dose is “Therapeutic dose based on GNX (FOS [focal/partial onset seizure]); over 2 min”). A POSA would have been motivated to target even lower doses based on the ganaxolone’s oral administration because a POSA would have known that ganaxolone administered intravenously would have higher bioavailability than ganaxolone administered orally. Ex. 1002, ¶101; Ex. 1034, 222. Therefore, a POSA also would have been motivated to select a lower dose within the range of 600 to 1,500 mg/day to suppress SE, such as During’s disclosed doses of 625-725 mg/day or 1025-1050 mg/day ganaxolone. Ex. 1002, ¶101.

NCT03350035 describes a protocol for evaluating the safety, tolerability, and efficacy of adjunctive IV ganaxolone in subjects with SE and describes administering ganaxolone as an “IV loading dose with continuous infusion (maintenance dose) for 2-4 days followed by a 24-hour taper.” Ex. 1004, 3-4; Ex. 1002, ¶102. As Dr. Sankar explains, a POSA would have understood that the “loading dose” is the same as a “bolus dose.” Ex. 1002, ¶102.

Thus, During and NCT03350035 specifically address using ganaxolone to treat SE, with During describing specific dose ranges effective to treat SE and NCT03350035 describing administering ganaxolone as an IV bolus dose with continuous infusion to treat SE. Ex. 1002, ¶¶103; Ex. 1003, 8:11-14, 35:33-37:15,

40:18-33; Ex. 1004, 3-4. A POSA thus would have been motivated to administer an effective amount of ganaxolone as an intravenous bolus followed by continuous intravenous infusion to suppress SE. Ex. 1002, ¶104.

ii. Reasonable Expectation of Success

As explained above in Section IX.A.1, During describes administering various ganaxolone doses to treat SE, which includes suppressing SE, and NCT03350035 describes a protocol for evaluating the safety, tolerability, and efficacy of adjunctive IV ganaxolone in humans with SE by administering ganaxolone as an intravenous bolus followed by continuous intravenous infusion. Ex. 1003, 7:40-58, 8:11-34, 40:20-33; Ex. 1004; Ex. 1002, ¶106.

The prior art thus expressly describes a method of treating SE by administering ganaxolone as an intravenous bolus plus continuous infusion. Ex. 1002, ¶107; Ex. 1003, 8:11-14, 35:33-37:15, 40:18-33; Ex. 1004, 3-4. During also expressly describes “an effective amount of ganaxolone to suppress SE.” For instance, During discloses that doses of ganaxolone to treat SE can range from 50 mg to 2000 mg (Ex. 1003, 8:22-34) and can be “administered parenterally in escalating doses as soon as possible after onset of seizures” (*id.*, 8:42-44).

A POSA would have understood that During’s doses encompass doses effective for suppressing SE based on previous studies related to treating SE and other seizure disorders using ganaxolone or its analog (allopregnanolone) Ex. 1002,

¶108. For example, as described above in Section III.B.1, the prior art demonstrated that 1,500 mg/day ganaxolone (after titrating up from 600 mg/day) administered orally was effective at reducing partial-onset seizure frequency. *See, e.g.*, Ex. 1023, 561, 562; Ex. 1002, ¶108. The prior art directly taught that ganaxolone doses in partial-onset seizure studies inform those for SE. Ex. 1025, 1. Accordingly, a POSA would have reasonably expected that a dose of 1,500 mg/day would be effective to suppress SE.

Dosing information for allopregnanolone also would have provided a POSA with a reasonable expectation that the dose range (50-2000 mg) expressly provided by During encompasses doses that are effective to suppress SE. Ex. 1002, ¶109. Specifically, as explained in Section III.B.2, ganaxolone is an analog of allopregnanolone and both are allosteric modulators of the GABA_A receptor. *See* Ex. 1033, 1; Ex. 1002, ¶109. Doses of allopregnanolone had been correlated to doses of ganaxolone in the SE mouse model. Ex. 1002, ¶110; *see also* Ex. 1027, 223, 225 (Table 1). For example, Zolkowska 2018's study in the SE mouse model, both allopregnanolone and ganaxolone were found that allopregnanolone and ganaxolone terminate SE in mice and have comparable plasma C_{max} values at the same dose. Ex. 1027, 223, 225 (Table 1). A 2017 study also found that 670.8 mg allopregnanolone administered as a 5.6 mg/h continuous infusion over 5 days "successfully treated" patients with SRSE. Ex. 1028, 411-12. For these additional reasons, a POSA would

have had further reason to administer ganaxolone intravenously at doses around 670.8 mg or above with a reasonable expectation of suppressing SE. Ex. 1002, ¶¶110-111; *see also* Ex. 1027; Ex. 1028.

There is no question that a POSA would have reasonably expected that doses falling within During's express range (50-2000 mg) would have suppressed SE. Ex. 1003, 8:22-34; Ex. 1002, ¶112. Any other optimization within this range would have been routine. *See Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1371 (Fed. Cir. 2007) (finding that the fact that the patent owner "engaged in routine, verification testing to optimize selection of one of several known and clearly suggested" options "proves nothing more than routine optimization that would have been obvious").

NCT03350035's dosing regimen of a bolus followed by continuous infusion is not new in treating SE. As explained in Section III.A, patients who did not respond to first or second-line ASMs would have been administered certain drugs using an intravenous bolus dose, followed by continuous intravenous infusion and then tapering. Ex. 1002, ¶114. Simultaneously, a POSA would have monitored the patient's EEG readout for seizure activity and adjusted the dose to control seizures. *Id.* This was a common approach used to treat SE with drugs such as propofol, thiopental, and midazolam. *Id.* A POSA would have thus been motivated to apply NCT03350035's dosing regimen to the doses in During with a reasonable expectation of successfully suppressing SE. By monitoring the patient's EEG

readout, a POSA would have optimized the ganaxolone dose administered via intravenous bolus and continuous intravenous infusion to suppress SE.

As explained in Section VII, this the ganaxolone plasma concentration limitation of claim 1 is superfluous and should be given no patentable weight. But even if considered to be a limitation, the doses of ganaxolone described in the prior art that provide an effective amount of ganaxolone to suppress SE would necessarily result in the ganaxolone plasma concentration limitation of claim 1. Ex. 1002, ¶¶112-115. Specifically, a POSA would have understood that doses of ganaxolone effective to suppress SE disclosed in During and supported by previous studies related to ganaxolone's or allopregnanolone's use to treat SE or other seizure disorders, would necessarily result in a ganaxolone plasma concentration of about 500 ng/mL to about 1000 ng/mL, as claim 1 requires. Ex. 1002, ¶115; Ex. 1003, 7:40-8:8, 8:11-34. Therefore, the ganaxolone plasma concentration limitation is the "natural result flowing from" the administration of an effective amount of ganaxolone to suppress SE and is inherent. *Persion Pharms. LLC v. Alvogen Malta Ops. Ltd.*, 945 F.3d 1184, 1191 (Fed. Cir. 2019); *see also Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1354 (Fed. Cir. 2012).

Thus, During and NCT03350035 disclose each claim element, and a POSA would have been motivated to administer ganaxolone to treat SE according to claim 1 with a reasonable expectation of success. Ex. 1002, ¶116.

b. Dependent Claims 2, 3, 11, and 12

For at least the reasons described in Section X.A.1.a.i, a POSA would have been motivated to combine During and NCT03350035 to arrive at the claimed inventions. Further, and for at least the reasons discussed in Section X.A.1.a.ii, it would have been routine and obvious for a POSA to optimize the prior-art ganaxolone dosing regimen to arrive at the intravenous bolus dose as recited in claims 2, 3, 11, and 12 with a reasonable expectation of success, based on the prior-art disclosures and the standard practices that a POSA would have employed to effectively suppress SE.

During states that “dosages” of allosteric modulators, including ganaxolone, may include “1 mg to 30 mg.” Ex. 1003, 6:51-54. This range directly overlaps with the bolus doses of claims 2 (from about 5 mg to about 40 mg) and 3 (about 30 mg). *See Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1311 (Fed. Cir. 2006) (“Where a claimed range overlaps with a range disclosed in the prior art, there is a presumption of obviousness.”); *E.I. DuPont de Nemours & Co. v. Synvina C.V.*, 904 F.3d 996, 1006 (Fed. Cir. 2018). Further, a bolus is used for the rapid achievement of the desired effects and is used when a fast response is required, especially in emergency situations, such as SE. *See* Section III; Ex. 1002, ¶¶117-118. A POSA would have been motivated to use a bolus dose to suppress SE, i.e., to achieve plasma levels required to achieve the desired clinical effect. Indeed, Marinus’s own Phase 1

CTRs indicated that “potential anti-convulsant plasma concentrations were achievable with a bolus dose” of ganaxolone. Ex. 1007, 1; Ex. 1002, ¶118. A POSA treating an SE patient would have relied on EEG readouts (Ex. 1002, ¶¶14-16; *supra* Section III.A) to make adjustments to the bolus dose to effectively achieve suppression of SE. This is especially true given that ganaxolone had already been shown to be safe and well tolerated at doses up to 1,500 mg/day (*see, e.g.*, Ex. 1023, 558, 563 (finding that 1,500 mg/day ganaxolone exhibited “no clinically relevant laboratory or [electrocardiography (“ECG”)] changes during the study”)). Ex. 1002, ¶119. Moreover, the time limits in claim 12 to administer a bolus “for about 1 minute to about 5 minutes” is a standard time for administering a bolus and cannot provide patentable weight. Ex. 1002, ¶119.

Thus, a POSA would have determined the amount of a bolus dose of ganaxolone based on the prior-art disclosures of daily amounts of ganaxolone that can treat SE and other seizure disorders and then optimized the amount of that bolus dose by monitoring a patient’s EEG readout to determine what amount is effective to control seizure activity. Ex. 1002, ¶120. Such routine optimization would have been obvious to a POSA. *See Pfizer*, 480 F.3d at 1371.

With an understanding of During and NCT03350035, the specific amount and timing of the intravenous bolus disclosed in claims 2, 3, 11, and 12, would have been obvious. *See* Ex. 1002, ¶121.

c. Dependent Claims 4, 5, 7, and 9

For at least the reasons described in Section X.A.1.a.i, a POSA would have been motivated to combine During and NCT03350035 to arrive at the claimed invention. Further, and for at least the reasons discussed in X.A.1.a.ii, it would have been routine and obvious for a POSA to optimize the prior-art ganaxolone dosing regimen to arrive at the rate of continuous intravenous infusion as recited in claims 4, 5, 7, and 9 with a reasonable expectation of success, based on the prior-art disclosures and the standard practices that a POSA would have employed to effectively suppress SE.

As explained above in Section X.A.1.a.i, a POSA would have been led by During and previous uses of ganaxolone to treat other seizure disorders to target a ganaxolone dose between 600 mg/day and 1500 mg/day ganaxolone to suppress SE. Ex. 1002, ¶120. A POSA then would have been able to determine an hourly rate of infusion based on monitoring a patient's EEG readout to continue to control seizure activity after administering the intravenous bolus as described above in Section IX.A.1.b. Ex. 1002, ¶123. Further modification to achieve the rates of continuous intravenous infusion of claims 4 (about 20 mg/hr to about 80 mg/hr), 5 (about 80 mg/hr for at least 2 hours), 7 (50 mg/hr for about 6 hours to about 10 hours), and 9 (20 mg/hr for about 12 hours to about 24 hours) would have been a routine practice

and obvious to a POSA at the relevant time. Ex. 1002, ¶¶124-25; *see also Pfizer*, 480 F.3d at 1371.

Thus, upon reading During and NCT03350035, the hourly rate of ganaxolone infused into the subject by continuous intravenous infusion, and any further modifications would have been obvious. *See* Ex. 1002, ¶126.

d. Dependent Claims 6, 8, 10, 13, 15, 17, and 20

For at least the reasons described in Section X.A.1.a.i, a POSA would have been motivated to combine During and NCT03350035 to arrive at the claimed invention. Further, and for at least the reasons discussed in IX.A.1.a.ii, it would have been routine and obvious for a POSA to optimize the ganaxolone dosing regimen by decreasing or tapering the rate of continuous intravenous infusion as recited in claims 6, 8, 10, 13, 15, 17, and 20 with a reasonable expectation of success, based on the prior-art disclosures and the standard practices that a POSA would employ to effectively suppress SE.

As of August 2019, it was well known in the art that a reduction or decrease in the amount of an ASM infused into a subject by continuous intravenous infusion, or taper, was desirable to reduce the risk of the patient having withdrawal seizures or recurrence of SE. *See supra* Section III.A; Ex. 1002, ¶128. In light of During and NCT03350035, it would have been obvious for a POSA to reduce or decrease the

amount of ganaxolone infused into the subject by continuous intravenous infusion as recited in the claims. *See* Ex. 1002, ¶¶129-130.

e. Dependent Claims 14, 16, 18, 19, and 21

For at least the reasons described in Section X.A.1.a.i, a POSA would have been motivated to combine During and NCT03350035 to arrive at the claimed invention. Further, and for at least the reasons discussed in IX.A.1.a.ii, a POSA also would have had a reasonable expectation of success in treating a subject having RSE (as recited in claims 14, 18, 19, and 21) or treating SE using a total daily dose of ganaxolone of 500 mg to 900 mg (as recited in claim 16).

During specifically discloses administering ganaxolone to treat SE, including RSE. Ex. 1003, 2:13-22, 4:6-16, 10:28-42. A POSA at the relevant time would also have known that a subset of patients with SE have RSE. Ex. 1002, ¶132. Thus, upon reading During and NCT03350035, it would have been obvious to a POSA that subjects in need of the disclosed ganaxolone treatment method includes patients with RSE. *Id.*

As described above, *see supra* Section X.A.1.a, it also would have been obvious to a POSA from the disclosures of During and previous studies related to the use of ganaxolone to treat SE and other seizure disorders, that the total daily dose of ganaxolone effective to suppress SE would be from about 500 mg to about 900 mg.

Therefore, claims 14, 16, 18, 19, and 21 would have been obvious over During and NCT03350035. *See* Ex. 1002, ¶¶133-134.

2. Ground 2: All Claims of the '100 Patent Would Have Been Obvious Over During and Marinus's Phase 1 CTRs

a. Claim 1

i. Motivation to Combine

During and Marinus's Phase 1 CTRs both relate to the use of ganaxolone to treat SE. Ex. 1002, ¶136; Ex. 1003, 8:11-14, 8:22-34, 35:31-37:15; Ex. 1004, 3-4.

Specifically, During describes administering ganaxolone to treat SE along with specific doses of ganaxolone, including doses of about 500 mg to 1000 mg/day and about 700 mg to 725 mg/day ganaxolone. *See supra* § X.A.1.a; Ex. 1003, 8:11-14, 35:33-35 (Example 3), 40:18-33 (claims 24-31); Ex. 1002, ¶137.

Marinus's Phase 1 CTRs each describe the results of a phase 1 study to evaluate the safety, PK, and PD of ganaxolone administered as a bolus dose and continuous infusion to healthy participants. Ex. 1006, S77-S78; Ex. 1005, 74. Tsai 2017 reports the Phase 1 pharmacokinetic results as showing that ganaxolone plasma concentrations were generally proportional to the administered dose. Ex. 1005, 75. Tsai 2017 concludes that "GNX administered as a rapid IV bolus or bolus with continuous infusion was generally safe and well tolerated" and that "[p]redictable PK from this study enables dosing guidance for GNX IV." *Id.* Similar results were presented in Clinical Leader 2016. Ex. 1007, 1. Thus, these disclosures demonstrate

that there was nothing unpredictable about dosing ganaxolone as a bolus followed by continuous infusion, and that a POSA would have been motivated to optimize the dose to suppress SE. Ex. 1002, ¶138.

Thus, During and Marinus's Phase 1 CTRs specifically address the use of ganaxolone to treat SE, with During describing specific dose ranges effective to treat SE and Marinus's Phase 1 CTRs addressing the use of ganaxolone as an IV loading dose (or bolus) with continuous infusion. Based on these disclosures, a POSA would have been motivated to administer an effective amount of ganaxolone as an intravenous bolus followed by continuous intravenous infusion to suppress SE. A POSA also would have been specifically motivated to optimize the dose to suppress SE Ex. 1002, ¶¶139-41.

ii. Reasonable Expectation of Success

A POSA would have had a reasonable expectation of success to achieve the claimed subject matter in view of During and Marinus's Phase 1 CTRs. During describes administering various dose amounts of ganaxolone to treat SE and Marinus's Phase 1 CTRs each describe phase 1 study results evaluating the safety, PK, and PD of ganaxolone administered as a bolus dose and continuous infusion to healthy participants. §§ IX.A.1 and IX.B.1; Ex. 1002, ¶¶143-44; Ex. 1003, 8:11-14; Ex. 1006, S77-S78; Ex. 1005, 74. Marinus's Phase 1 CTRs further disclose that ganaxolone plasma concentrations were "generally proportional to the administered

dose” and that “[p]otential anti-convulsant plasma concentrations were achievable with a bolus dose.” Ex. 1005, 75; *see also* Ex. 1007, 1.

Additionally, for the same reasons described in Section X.A.1.a, a POSA aware of these disclosures in During and Marinus’s Phase 1 CTRs would have considered previous studies related to treating SE and other seizure disorders using ganaxolone or its analog (allopregnanolone), and then used standard practices for treating emergency conditions like SE to optimize the dosing regimen to suppress SE. Ex. 1002, ¶¶145-50. This would have led a POSA to select the 625-725 mg/day or 1025-1050 mg/day doses of ganaxolone disclosed in During for treating SE. Ex. 1002, ¶¶139-40; *see Pfizer*, 480 F.3d at 1371.

A POSA also would have had a reasonably expected that these doses would suppress SE because Marinus’s Phase 1 CTRs found that ganaxolone plasma concentrations were “generally proportional to the administered dose” and that “[p]otential anti-convulsant plasma concentrations were achievable with a bolus dose.” Ex. 1005, 75; *see also* Ex. 1007, 1; Ex. 1002, ¶¶147-54.

Given the disclosures of During and Marinus’s Phase 1 CTRs, a POSA would have been motivated to administer ganaxolone to treat SE according to claim 1 with a reasonable expectation of success.

b. Dependent Claims 2, 3, 11, and 12

For at least the reasons described in Section X.A.2.a.i, a POSA would have been motivated to combine During and Marinus's Phase 1 CTRs to arrive at the claimed invention. Further, and for at least the reasons discussed in Sections X.A.2.a.ii and X.A.1.b, it would have been routine and obvious for a POSA to optimize the ganaxolone dosing regimen by modifying the intravenous bolus dose as recited in claims 2, 3, 11, and 12 with a reasonable expectation of success, based on the prior-art disclosures and the standard practices that a POSA would employ to effectively suppress SE. Therefore, claims 2, 3, 11, and 12 would have been obvious over During and Marinus's Phase 1 CTRs. *See* Ex. 1002, ¶¶155-57.

c. Dependent Claims 4, 5, 7, and 9

For at least the reasons described in Section X.A.2.a.i, a POSA would have been motivated to combine During and Marinus's Phase 1 CTRs to arrive at the claimed invention. Further, and for at least the reasons discussed in Sections X.A.2.a.ii and X.A.1.c, it would have been routine and obvious for a POSA to optimize the ganaxolone dosing regimen by modifying the rate of continuous intravenous infusion as recited in claims 4, 5, 7, and 9 with a reasonable expectation of success, based on the prior-art disclosures and the standard practices that a POSA would employ to effectively suppress SE. Therefore, claims 4, 5, 7, and 9 would

have been obvious over During and Marinus's Phase 1 CTRs. *See* Ex. 1002, ¶¶158-60.

d. Dependent Claims 6, 8, 10, 13, 15, 17, and 20

For at least the reasons described in Section X.A.2.a.i, a POSA would have been motivated to combine During and Marinus's Phase 1 CTRs to arrive at the claimed invention. Further, and for at least the reasons discussed in X.A.2.a.iib and X.A.1.d, it would have been routine and obvious for a POSA to optimize the ganaxolone dosing regimen by decreasing or tapering the rate of continuous intravenous infusion as recited in claims 6, 8, 10, 13, 15, 17, and 20 with a reasonable expectation of success, based on the prior-art disclosures and the standard practices that a POSA would employ to effectively suppress SE. Therefore, claims 6, 8, 10, 13, 15, 17, and 20 would have been obvious over During and Marinus's Phase 1 CTRs. *See* Ex. 1002, ¶¶161-63.

e. Dependent Claims 14, 16, 18, 19, and 21

For at least the reasons described in Section X.A.2.a.i, a POSA would have been motivated to combine During and Marinus's Phase 1 CTRs to arrive at the claimed invention. Further, and for at least the reasons discussed in Sections X.A.2.a.ii and X.A.2.e, a POSA also would have had a reasonable expectation of success in treating a subject having RSE (as recited in claims 14, 18, 19, and 21) or treating SE using a total daily dose of ganaxolone of 500 mg to 900 mg (as recited

in claim 16). Therefore, claims 14, 16, 18, 19, and 21 would have been obvious over During and Marinus's Phase 1 CTRs. *See* Ex. 1002, ¶¶164-66.

B. All Claims of the '100 Patent Are Unpatentable Over Marinus' Own Phase 2 Publications

1. Ground 3: All Claims of the '100 Patent Would Have Been Obvious in View of During, NCT03350035, and the Phase 2 CTRs

a. Claim 1

i. Motivation to Combine

As Dr. Sankar states, During, NCT03350035, and the Phase 2 CTRs each relate to the use of ganaxolone to treat SE. Ex. 1002, ¶¶167-68.

As discussed above in Section X.A.1.a, During teaches administering ganaxolone to treat SE along with specific dose ranges of ganaxolone, including about 700-725 mg/day ganaxolone. Ex. 1003, 8:11-14, 35:33-35 (Example 3); 40:18-33 (claims 24-31); Ex. 1002, ¶169.

As discussed above in Section X.A.1.a, NCT03350035 describes a protocol for evaluating the safety, tolerability, and efficacy of adjunctive IV ganaxolone in humans with SE and discloses administering ganaxolone as an intravenous bolus dose followed by continuous infusion and tapering. Ex. 1004, 3-4; Ex. 1002, ¶170.

The Phase 2 CTRs each describe Phase 2 clinical trial results for treating RSE with ganaxolone. *See* Ex. 1008, 1; Ex. 1009, 1; Ex. 1010, 1-2; Ex. 1011, 1; *see also* Ex. 1002, ¶171. In particular, and as Dr. Sankar describes, each reports that the target

dose of ganaxolone (713 mg/day) achieved plasma concentrations above 500 ng/ml for approximately 8 hours and also resulted in good seizure control. *See* Ex. 1002, ¶171 (citing Ex. 1008, 2; Ex. 1009, 3; Ex. 1010, 1-2; Ex. 1011, 1).

Thus, During specifically addresses the use of ganaxolone to treat SE, including specific dose ranges, NCT03350035 also specifically addresses the use of ganaxolone to treat SE as an IV loading dose (or bolus) with continuous infusion, and the Phase 2 CTRs specifically address administering 713 mg/day ganaxolone to achieve a plasma concentration of > 500 ng/ml for about 8 hours and suppression of SE.

Based on During's disclosures (directed to ganaxolone's evaluation of the ability of ganaxolone to block benzodiazepine-resistant SE and disclosure of dose ranges), the disclosures in NCT03350035 (directed to the administration of ganaxolone as an IV bolus dose with continuous infusion in subjects with SE) and the Phase 2 CTRs (directed to administering 713 mg/day ganaxolone to achieve a plasma concentration of > 500 ng/ml for about 8 hours and suppressing SE), a POSA would have been motivated to use ganaxolone to suppress SE. Ex. 1002, ¶¶172-73.

ii. Reasonable Expectation of Success

Based on the combination of During, NCT03350035, and the Phase 2 CTRs, a POSA would have expected that ganaxolone administered as an IV loading dose with continuous infusion would suppress SE and produce and maintain a ganaxolone

plasma concentration of about 500 ng/ml to about 1000 ng/ml for about 8 hours to about 12 hours.

As discussed above in Section X.A.1.a, During teaches administering ganaxolone to treat SE along with specific dose ranges of ganaxolone, including about 700-725 mg/day ganaxolone. Ex. 1003, 8:11-14, 35:33-35 (Example 3); 40:18-33 (claims 24-31); Ex. 1002, ¶¶174-75.

NCT03350035 specifically addresses the use of ganaxolone as an IV loading dose (i.e., bolus) with continuous infusion in subjects with SE. Ex. 1004, ; Ex. 1002, ¶176.

And the Phase 2 CTRs describe Phase 2 results for treating RSE with ganaxolone. Each of Phase 2 CTR reports that the target dose of ganaxolone (713 mg/day) achieved plasma concentrations above 500 ng/ml for approximately 8 hours and resulted in good seizure control. Ex. 1002, ¶177; Ex. 1008, 2; Ex. 1009, 3; Ex. 1010, 1-2; Ex. 1011, 1.

Because a POSA would have known that administering ganaxolone as an intravenous bolus plus continuous infusion at or around 713 mg/day would produce and maintain a ganaxolone plasma concentration of about 500 ng/ml to about 1000 ng/ml for about 8 hours to about 12 hours in a typical patient, it would have been obvious to administer ganaxolone to suppress SE in the manner recited in claim 1. Thus, given the disclosures of During, NCT03350035, and the Phase 2 CTRs, a

POSA would have been motivated to administer ganaxolone to suppress SE according to claim 1 with a reasonable expectation of success. Ex. 1002, ¶178.

b. Dependent Claims 2, 3, 11, and 12

For at least the reasons described in Section X.B.1.a.i, a POSA would have been motivated to combine During, NCT03350035, and the Phase 2 CTRs to arrive at the claimed invention. Further, and for at least the reasons discussed in Sections X.B.1.a.ii and X.A.2.b, it would have been routine and obvious for a POSA to optimize the ganaxolone dosing regimen by modifying the intravenous bolus dose as recited in claims 2, 3, 11, and 12 with a reasonable expectation of success, based on the prior-art disclosures and the standard practices that a POSA would employ to effectively suppress SE. Therefore, claims 2, 3, 11, and 12 would have been obvious over During, NCT03350035, and the Phase 2 CTRs. *See* Ex. 1002, ¶¶179-81.

c. Dependent Claims 4, 5, 7, and 9

For at least the reasons described in Section X.B.1.a.i, a POSA would have been motivated to combine During, NCT03350035, and the Phase 2 CTRs to arrive at the claimed invention. Further, and for at least the reasons discussed in Sections X.B.1.a.ii and X.A.2.c, it would have been routine and obvious for a POSA to optimize the ganaxolone dosing regimen by modifying the rate of continuous intravenous infusion as recited in claims 4, 5, 7, and 9 with a reasonable expectation of success, based on the prior-art disclosures and the standard practices that a POSA

would employ to effectively suppress SE. Therefore, claims 4, 5, 7, and 9 would have been obvious over During, NCT03350035, and the Phase 2 CTRS. *See* Ex. 1002, ¶¶182-84.

d. Dependent Claims 6, 8, 10, 13, 15, 17, and 20

For at least the reasons described in Section X.B.1.a.i, a POSA would have been motivated to combine During, NCT03350035, and the Phase 2 CTRs to arrive at the claimed invention. Further, and for at least the reasons discussed in Sections X.B.1.a.ii and X.A.2.d , it would have been routine and obvious for a POSA to optimize the ganaxolone dosing regimen by decreasing or tapering the rate of continuous intravenous infusion as recited in claims 6, 8, 10, 13, 15, 17, and 20 with a reasonable expectation of success, based on the prior-art disclosures and the standard practices that a POSA would employ to effectively suppress SE. Therefore, claims 6, 8, 10, 13, 15, 17, and 20 would have been obvious over During, NCT03350035, and the Phase 2 CTRs. *See* Ex. 1002, ¶¶185-87.

e. Dependent Claims 14, 16, 18, 19, and 21

For at least the reasons described in Section X.B.1.a.1, a POSA would have been motivated to combine During, NCT03350035, and the Phase 2 CTRs to arrive at the claimed invention. Further, and for at least the reasons discussed in Sections X.B.1.a.ii and X.A.2.e, a POSA also would have had a reasonable expectation of success in treating a subject having RSE (as recited in claims 14, 18, 19, and 21) or

treating SE using a total daily dose of ganaxolone of 500 mg to 900 mg (as recited in claim 16). Therefore, claims 14, 16, 18, 19, and 21 would have been obvious over During, NCT03350035, and the Phase 2 CTRs. *See* Ex. 1002, ¶¶188-90.

C. No Secondary Considerations of Nonobviousness

During prosecution the applicant submitted a declaration by one of the named inventors of the '100 patent to overcome an obviousness rejection. In that declaration, the inventors stated that “[i]t was completely unexpected that providing ganaxolone at a serum concentration of about 500 ng/ml to about 1000 ng/ml for a short duration of only about 8 to about 12 hours, resulted in persistent SE suppression. In fact, it was completely contrary to our expectations.” Ex. 1029, 216-19.

A POSA would not have found this result to be surprising or unexpected at least in view of During’s disclosure of similar doses of ganaxolone to treat SE (e.g., (e.g., “625 to 700 mg/day” or “1025 to 1050 mg/day”). Ex 1002, ¶192. As Dr. Sankar explains, these doses would inherently reach the same ganaxolone plasma concentration that the inventor of the '100 patent contends were “unexpected.” *Id.* Therefore, it would not have been unexpected for a POSA to achieve suppression of SE by administering an effective amount of ganaxolone via an intravenous bolus plus continuous infusion to produce and maintain a ganaxolone plasma concentration of about 500 ng/ml to about 1000 ng/ml for about 8 hours to about 12

hours. *See, e.g., Santarus, Inc. v. Par. Pharm., Inc.*, 694 F.3d 1344, 1354 (Fed. Cir. 2012); *see also In re Kao*, 639 F.3d 1057, 1070 (Fed. Cir. 2011). This applies to each obviousness ground (Grounds 1, 2, and 5).

Ovid is not aware of any other secondary considerations of nonobviousness that are relevant to the obviousness analysis or that have been alleged by Marinus.

XI. Discretionary Denial is Not Warranted

In deciding to institute an IPR, the Board may use its discretion to grant or deny institution under § 325(d) by considering whether “the same or substantially the same prior art or arguments previously were presented to the Office.” 35 U.S.C. § 325(d).

Section 325(d) identifies “two separate issues” for the Board to consider in exercising its discretion to deny institution: (1) “whether the petition presents to the Office the same or substantially the same art previously presented to the Office”; and (2) “whether the petition presents to the Office the same or substantially the same arguments previously presented to the Office.” *Solvay USA Inc. v. WorldSource Enters., LLC*, IPR2020-00768, Paper 12 at 7 (PTAB Sept. 25, 2020) (citation omitted). The Board may consider *Becton, Dickinson* factors (a)-(f), which apply “a two-part framework, first considering *Becton, Dickinson* factors (a), (b), and (d) to determine whether the same or substantially the same art or arguments were previously presented to the Office, and if so, evaluating *Becton, Dickinson*

factors (c), (e), and (f) to determine whether the Petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims.” *Solvay*, IPR2020-00768, Paper 12 at 7 (citing *Adv. Bionics, LLC v. Med-El Elektromedizinische Geräte GmbH*, IPR2019-01469, Paper 6 at 7-11 (PTAB Feb. 13, 2020)).

The prior art and arguments presented in this petition are not the same or substantially the same as those previously presented to the Office. To the extent they are, the Examiner plainly erred in a manner material to the challenged claims’ patentability. Discretionary denial is thus not warranted.

A. The Art and Arguments Presented Are Not the Same or Substantially the Same as Those Previously Presented to the Office.

Neither the art nor arguments presented are the same or substantially the same as the art and arguments previously presented to the Office.

During prosecution, the Examiner considered none of During,¹ NCT03350035, Tsai 2017, Tsai 2016, Clinical Leader 2016, Practical Neurology 2019, Ramsay 2019, the AES 2019 Poster, or Husain 2020. Nor did the applicant disclose any of these references to the Office. Although the application included discussion of Marinus’s phase 1 trials, the applicant did *not* inform the PTO of the

¹ The PCT application to which During claims priority was listed in an applicant-submitted IDS and marked as considered by the Examiner, but the Examiner did not cite this PCT application in its sole obviousness rejection. *See* Ex. 1029, 189-92, 195-96.

prior-art status of its results. Moreover, these prior-art publications are not the same or substantially the same as those previously presented or relied on during prosecution. Marinus did not submit the publications asserted in this proceeding, which published *before* the '648 application was filed. *Compare* Ex. 1024 *with* Exs. 1005, 1006, 1007; Ex. 1029, 181-82.

The Office was not presented with any arguments regarding the novelty or non-obviousness of the current or pending claims over any of the prior art relied on in this petition because the Examiner did not make any rejections over this art. The Examiner instead made a single obviousness rejection over Marinus's patent application publication, US 2016/0228454. *See* Ex. 1029, 189-92.

B. The Examiner Erred in a Manner Material to the Patentability of the Challenged Claims.

The Examiner materially erred with respect to claim interpretation, by failing to recognize that the ganaxolone plasma concentration limitations recited in the '100 patent are non-limiting and do not carry independent patentable weight as they are inherent to the dosing regimen rendered obvious by the prior art. *Cf.* M.P.E.P. § 2111.02 The Examiner provided no construction of any claim terms on the record.

C. The Petition Relies on Additional Evidence that Was Not Available to the Examiner During Prosecution.

This petition relies on additional evidence that was not available to the Examiner during prosecution. For example, the Examiner did not have the benefit

of the disclosure of Phase 1 or Phase 2 study protocols and data or the explanations provided in Dr. Sankar's declaration, which explains how a POSA would have used an intravenous bolus plus continuous infusion and then monitored the patient's EEG to treat an emergency condition such as SE. The additional evidence presented here is another reason why discretionary denial is not appropriate. *See, e.g., Adv. Energy Indus. v. Reno Techs.*, IPR2021-01397, Paper 7, at *7-9 (PTAB Feb. 16, 2022) (refusing to exercise discretionary denial by relying-in-part on additional evidence submitted in expert declaration).

XII. Conclusion

Ovid has established a reasonable likelihood of prevailing for claims 1-21 of the '100 patent. Ovid respectfully requests that the Board review and finds these claims unpatentable.

XIII. Payment of Fees

Ovid authorizes charge of fees to Deposit Account 06-0916.

XIV. Mandatory Notices Under 37 C.F.R. § 42.8(A)(1)

A. Real Party-In-Interest Under 37 C.F.R. § 42.8(b)(1)

Ovid Therapeutics Inc. is the real party-in-interest.

B. Related Matters Under 37 C.F.R. § 42.8(b)(2)

Petitioner is not aware of any disclaimers, reexamination certificates, or other related matters other than this petition for an IPR.

C. Lead and Back-Up Counsel Under 37 C.F.R. § 42.8(b)(3)

Ovid provides the following designation of counsel:

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D. Service Information

Please address all correspondence and service to the address listed above.

Ovid consents to electronic service by email at anthony.tridico@finnegan.com.

Respectfully submitted,

Dated: March 26, 2024

/Anthony C. Tridico/
Anthony C. Tridico
Reg. No. 45,958

CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(d), I, Anthony C. Tridico, certify that **Petition for an *Inter Partes* Review of U.S. Patent No. 11,110,100** contains 13,995 words, excluding those portions identified in 37 C.F.R. § 42.24(a)(1), as measured by the word-processing system used to prepare this paper.

Dated: March 26, 2024

/Anthony C. Tridico/
Anthony C. Tridico
Reg. No. 45,958

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§42.6(e) and 42.105(a), the undersigned certifies that on March 26, 2024, a copy of the foregoing **Petition for an *Inter Partes* Review of U.S. Patent No. 11,110,100, the associated power of attorney, and Exhibits 1001-1036** were served by FedEx Priority Overnight on the correspondence address of record indicated in the Patent Office's public Patent Center system for U.S. Patent No. 11,110,100:

Hogan Lovells US LLP
IP Group, Columbia Square
555 Thirteenth Street, N.W.
Washington, DC 20004

A courtesy copy of the foregoing was also served by FedEx Priority Overnight on the Patent Practitioner indicated in the Patent Office's public Patent Center system for U.S. Patent No. 11,110,100:

Robert H. Underwood
Hogan Lovells US LLP
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Boston, MA 02110

Date: March 26, 2024

By: /William Esper/
William Esper
Case Manager and PTAB Coordinator
Finnegan, Henderson, Farabow,
Garrett & Dunner, LLP