

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

PATENT OWNER'S PRELIMINARY RESPONSE

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LIST OF EXHIBITS

Exhibit No.	Exhibit Description
2001	Declaration of Dr. Maciej Gasior
2002	Declaration of Dr. Henrikas Vaitkevicius
2003	Abstracts for the 17 th Annual Meeting, Neurocritical Care Society, Vancouver, BC, October 15–18, 2019, <i>Neurocritical Care</i> 31:S1–S341 (2019) (doi:10.1007/s12028-019-00857-7), available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7100118/ (“Neurocritical Care Abstracts”)
2004	Marinus Press Release Dated October 17, 2019 (“Neurocritical Care Press Release”)
2005	Marinus Press Release dated December 7, 2019 (“AES Press Release”)
2006	American Clinical Neurophysiology Society 2020 Annual Meeting & Courses Final Program, February 5–9, 2020, available at https://www.acns.org/UserFiles/file/am20-FP-v23.pdf (“ACNS Program”)
2007	Marinus Press Release dated February 3, 2020 (“ACNS Press Release”)
2008	Declaration of Anne Koch Baland with Attachments
2009	RESERVED
2010	RESERVED
2011	Declaration of Dr. Michael A. Rogawski
2012	WO 2016/127170A1 (“Zhang”)
2013	WO 2018/031748A1 (“During PCT”)
2014	Supplemental Response filed May 11, 2022, in 17/024,127 (from During’s File History)
2015	RESERVED
2016	RESERVED
2017	Petition for Post Grant Review of U.S. Patent No. 11,395,817 (During), Paper 2 in PGR2023-00020

Exhibit No.	Exhibit Description
2018	U.S. Provisional Patent Application 62/882,648 and its file history
2019	U.S. Application No. 2016/0228454 (“Zhang US”)
2020	Declaration of Raman Sankar, M.D., PH.D., Ex. 2014 in PGR2023-00020
2021	https://ovidrx.com/our-company/leadership/ , accessed June 20, 2024
2022	Reddy and Kuruba, “Experimental Models of Status Epilepticus and Neuronal Injury for Evaluation of Therapeutic Interventions,” <i>Int. J. Mol. Sci.</i> 14:18284–318 (2013) (“Reddy” or “Reddy & Kuruba”)
2023	Seinfeld et al., “Status Epilepticus,” in <i>Additional Perspectives on Epilepsy: The Biology of a Spectrum Disorder</i> (Cold Spring Harbor Laboratory Press, 2016, ed. Gregory L. Holmes and Jeffrey L Noebels) (“Seinfeld”)
2024	Imtiyaz et al., “The Evolution of the Pilocarpine Animal Model of Status Epilepticus,” <i>Heliyon</i> 6:e04557 (2020) (“Imtiyaz”)
2025	Press Release: “Marinus Pharmaceuticals Doses First Subject in Phase I Clinical Trial for Ganaxolone IV,” Published on June 22, 2016, Available at: https://ir.marinuspharma.com/news/news-details/2016/Marinus-Pharmaceuticals-Doses-First-Subject-in-Phase-1-Clinical-Trialfor-Ganaxolone-IV/default.aspx (“June 22, 2016, Press Release” or “Marinus’s Phase 1 Press Release”)
2026	Press Release: “Marinus Pharmaceuticals Receives FDA Orphan Drug Designation for Ganaxolone IV to Treat Status Epilepticus,” Published April 15, 2016, Available at: https://ir.marinuspharma.com/news/news-details/2016/Marinus-Pharmaceuticals-Receives-FDA-Orphan-Drug-Designation-for-Ganaxolone-IV-to-Treat-Status-Epilepticus/default.aspx (“April 15, 2016, Press Release” or “Marinus’s Orphan Drug Press Release”)
2027	WIPO Publication No. WO 2007/062266 (“Shaw”)

Exhibit No.	Exhibit Description
2028	American Academy of Neurology (“AAN”) 2016 Annual Meeting Scientific Abstract Listing and Meeting Information, AAN 2016 Annual Meeting, Vancouver, BC, Canada, April 15–21, 2016, Available at: https://issuu.com/americanacademyofneurology/docs/16am_abs_trac_listingdigi_v1424 (“AAN Meeting Brochure”)
2029	Saporito et al., “Ganaxolone Administered Intravenously Prevents Behavioral Seizures and Promotes Survival in the Rat Lithium-Pilocarpine Model of Status Epilepticus,” Poster, presented April 17, 2016, at the 2016 AAN Annual Meeting (“Saporito P1” or “Saporito Poster 1” or “2016 AAN Poster 1” or “2016 AAN Saporito Poster 1”), with single page version on page 1 and enlarged version spanning pages 4-5
2030	Saporito et al., “Intravenous Administration of Ganaxolone Attenuates Electroencephalographic Seizures in a Diazepam Resistant Model of Status Epilepticus,” Poster, presented April 19 and April 20, 2016, at the 2016 AAN Annual Meeting (“Saporito P2” or “Saporito Poster 2” or “2016 AAN Poster 2” or “2016 AAN Saporito Poster 2”), with single page version on page 1 and enlarged version spanning pages 4-5
2031	Tsai et al., “Phase I Study to Determine the Pharmacokinetics, Pharmacodynamics, and Safety of IV Ganaxolone in Healthy Adults,” Abstract of Poster Presented at the 6 th London-Innsbruck Colloquium on Status Epilepticus and Acute Seizures April 6–8, 2017, Salzburg, Austria (“Tsai”)
2032	RESERVED
2033	Supplemental Information to Vaitkevicius et al., “Intravenous Ganaxolone for the Treatment of Refractory Status Epilepticus: Results from an Open-Label, Dose-Finding Phase 2 Trial,” <i>Epilepsia</i> 63:2381-91 (2022) (“ <i>Epilepsia</i> Supplemental Information” or “ <i>Epilepsia</i> SI”)
2034	Wylie et al., Status Epilepticus. [Updated 2022 May 15]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK430686/ (“Wylie”)

Exhibit No.	Exhibit Description
2035	Trinka et al., “A definition and classification of status epilepticus—Report of the ILAE Task Force on Classification of Status Epilepticus.” <i>Epilepsia</i> , 56(10):1515-1523 (2015) (“Trinka”)
2036	Transcript of Deposition of Dr. Raman Sankar, February 9, 2024 (“Sankar Deposition Transcript”) in PGR2023-00020

Pursuant to 37 C.F.R § 42.107(a), patent owner Marinus Pharmaceuticals, Inc. (“Patent Owner” or “PO” or “Marinus”) submits this Preliminary Response in response to the Petition for Inter Partes Review (“IPR”) of U.S. Patent no. 11,110,100 (the “’100 patent”) filed by Ovid Therapeutics, Inc. (“Petitioner” or “Ovid”).

I. INTRODUCTION AND SUMMARY OF THE ARGUMENT

Petitioner’s arguments are primarily based on attempting to read express limitations to required clinical effects out of the ’100 patent’s claims, even though those limitations were critical in obtaining allowance of the claims over the prior art. The prior art does not teach those clinical result limitations so, when Petitioner chooses to address them at all, it is forced to find them in non-prior art references discussing the results of Patent Owner Marinus’s Phase 2 clinical trials. Because those references are not prior art, Petitioner is left with nothing that teaches these critical limitations, so it chooses to pretend they are not limitations at all or that they are somehow “inherently” met by prior art. But inherency is a high standard and cannot be met here, where the evidence shows that there are prior art dosing regimens that do not lead to the claimed results. With these fatally flawed arguments, Petitioner has failed to show a reasonable likelihood that any of the claims are obvious, and institution should be denied.

We summarize the specific flaws in Petitioner’s various Grounds below.

Petitioner's primary reference for all the Grounds (During, Ex. 1003) teaches no more, and in fact less, than art the Examiner cited in an obviousness rejection during prosecution. Petitioner combines During with reference(s) related to Marinus's own clinical work on ganaxolone to treat SE: results of a Phase 1 trial (Ground 2); the pre-initiation announcement of a Phase 2 trial (Ground 1); and particular results of that Phase 2 trial (Ground 3).

First, institution should be denied because Petitioner's arguments with respect to Grounds 1, 2, and 3 rely on Petitioner's faulty claim construction that "[t]he 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." Both Patent Owner and the Examiner expressly relied on the limitations in this term to distinguish over the prior art during prosecution. Furthermore, they give the claim meaning and purpose. There is no support for Petitioner's attempt to read out this express limitation of the claims.

Second, to prevail on Ground 3 Petitioner must establish: 1) that the Challenged Claims are not entitled to priority; 2) that each of the Phase 2 references it relies on qualify as printed publications for the purposes of § 102(a)(1); and 3) that the § 102(b)(1) exceptions do not apply. Petitioner has failed to establish any let alone all three of these requirements. Therefore, institution should be denied on Ground 3.

Third, while Petitioner barely pays lip service to the proper claim construction, it cannot prevail on Grounds 1 and 2 under that construction. Petitioner's only argument under the proper construction improperly relies on the doctrine of inherency, without any attempt to show that the claimed plasma levels and claimed timeframe would necessarily be met by administering ganaxolone according to the prior art. Moreover, objective evidence that the Office considered during prosecution (and specifically relied on for allowance) confirms the non-obviousness of the Challenged Claims.

Finally, compounding all its other errors, Petitioner relies on an expert whose opinions here are contrary to opinions he gave in a prior proceeding between the parties. The art Petitioner relies on here is also cumulative over the art that was already before the Examiner when he found the claims allowable, and Petitioner has shown no material error. Discretionary denial is thus also appropriate here.

In sum, Ovid's Petition is both legally and factually deficient. Petitioner has not demonstrated that it is more likely than not that any of the Challenged Claims are unpatentable. Institution should be denied.

II. BACKGROUND OF THE TECHNOLOGY

A. Status Epilepticus (“SE”)

Seizures are a potentially serious medical condition that afflict millions of people worldwide. Ex. 2022, 2. A seizure is defined as an abnormal electrical discharge in the brain that causes alteration in consciousness, sensation, and behavior. *Id.*; Ex. 2011, ¶ 20. One of the most common seizure disorders is epilepsy, which is a chronic condition in which patients experience recurrent, unprovoked seizures. *Id.*

Status epilepticus (“SE”) is a neurological condition in which a patient experiences a prolonged seizure or a series of multiple seizures without recovery in between them. *Id.*; Ex. 2011, ¶ 21. These prolonged seizures, which go on for five minutes or longer, are not likely to resolve on their own and instead require medical intervention. *Id.*; Ex. 2023, 1-2.

Many different triggers, including stroke, traumatic brain injury, central nervous system infections, alcohol or drug withdrawal, or the cessation of anti-seizure medications, can cause SE. Ex. 2011, ¶ 22; Ex. 2024, 1; Ex. 2023, 2. Often, however, the cause is unknown, making the condition even more complicated. Ex. 2011, ¶ 22; Ex. 2023, 2.

While people with epilepsy may experience SE, SE is distinct from epilepsy. While treatments for most types of epilepsy are intended to prevent seizures from

occurring at all, treatments for SE are intended to stop the prolonged or repeated seizure activity that a patient is currently experiencing. Ex. 2011, ¶ 23.

SE is a life-threatening medical emergency and generally must be treated in a hospital. *Id.*, ¶ 24. The prolonged seizures that are characteristic of SE can cause severe brain damage and a high rate of mortality, which can range from 7–39%, depending on the age and other medical conditions of the patient. *Id.*; Ex. 2023, 7. Even where not fatal, SE can cause significant damage to the brain, which may be associated with cognitive and other neurological impairments. Ex. 2011, ¶ 24; Ex. 2022, 1.

SE can be characterized by behavioral manifestations and/or electrophysiological activity. Ex. 2011, ¶ 25; Ex. 2034; Ex. 2035; Ex. 2029; Ex. 2030. In the case of convulsive SE, behavioral manifestations include generalized tonic-clonic movements of the extremities and impaired mental status. *Id.* During an SE episode, the electrophysiological activity is detectable on an electroencephalogram (EEG) recording. *Id.*

Currently, approved first-line therapies for SE include benzodiazepines such as lorazepam and diazepam. Ex. 2011, ¶ 26; Ex. 2022, 4. A significant drawback to these therapies is that their efficacy decreases dramatically as the duration of SE increases, and there can be a complete loss of efficacy after a certain amount of time. *Id.* Second-line therapies, including phenytoin, fosphenytoin, levetiracetam,

or valproic acid, can be administered if the first-line therapies fail. *Id.*

Unfortunately, the second-line therapies may not work either, which puts patients in significant danger of worse outcomes, including death. *Id.* Making matters worse, up to 40% of SE, referred to as “refractory SE,” does not respond to the standard first- or second-line treatments, and is then treated with anesthetic drugs that come with their own set of risks. *Id.* Because of the serious medical risks associated with treatment failures, the development of new treatments for SE is critical. Ex. 2011, ¶ 27; Ex. 2024, 1.

B. Patent Owner Marinus’s Development of Ganaxolone as a Treatment for SE

Ganaxolone is a synthetic neurosteroid compound that is a CNS-selective GABA_A modulator. Ex. 2011, ¶ 28. Patent Owner Marinus has been working on the development of ganaxolone for the treatment of seizure disorders including SE for over 15 years. *Id.* Petitioner Ovid, on the other hand, has not engaged in any clinical development of ganaxolone.

Early on, Marinus evaluated various dosage forms of ganaxolone for the treatment of epilepsy. Ex. 2011, ¶ 29; Ex. 2027. Marinus was also working to develop ganaxolone specifically for treatment of SE. Ex. 2011, ¶ 29; Ex. 2005; Ex. 2026. By 2016, Marinus had published its earlier work using the rat-lithium pilocarpine model to predict the efficacy of IV-administered ganaxolone for SE in

humans. Ex. 2011, ¶ 29; Ex. 2012; Ex. 2028 at 46, 99, 128; Ex. 2029; Ex. 2030.

Marinus's animal research examined the impact of IV-administered ganaxolone on both the electrical (EEG) and behavioral effects of SE. Ex. 2011, ¶ 29; Ex. 2029; Ex. 2030. As to the electrical effects, the research found that the ganaxolone "elicits a sustained (≥ 5 hours) block of SE independent of treatment time after SE onset," indicating that the drug effectively terminated and treated SE as assessed by EEG. *Id.* As to the behavioral effects, the research found that IV-administered ganaxolone "halted CSE [convulsive status epilepticus] and produced a dose-dependent reduction in seizures associated with CSE when administered at 3 different doses over four separate time points after the first observed convulsive seizure." *Id.* Ganaxolone also promoted survival, measured 24 hours after CSE onset. *Id.*

With these animal results in hand, Marinus turned its attention to clinical trials to examine whether ganaxolone is safe and effective for treatment of SE in humans. In 2016, Marinus issued a press release announcing that "the U.S. Food and Drug Administration (FDA) granted Orphan Drug Designation to the intravenous (IV) formulation of its CNS-selective GABA_A modulator, ganaxolone, for the treatment of [SE]." Ex. 2011, ¶ 30; Ex. 2026. The press release noted that "[a] Phase 1 clinical trial evaluating the safety, tolerability and pharmacokinetics of ganaxolone IV is expected to initiate in the first half of 2016." *Id.* In June

2016, Marinus reported that it had dosed the first human subjects, healthy volunteers, in a Phase 1 clinical trial for ganaxolone IV. Ex. 2011, ¶ 30; Ex. 2025. In 2017, Marinus reported results from that Phase 1 trial, which showed that ganaxolone “administered as a rapid IV bolus or bolus with continuous infusion was generally safe and well tolerated” in healthy volunteers and that “there were no safety issues that limit getting to a potentially efficacious plasma concentration in a short period of time.” Ex. 2011, ¶ 30; Ex. 2031.

After seeing positive results in its Phase 1 clinical trial in healthy volunteers, Marinus set out to determine whether ganaxolone would be effective at treating SE in patients who were suffering from the condition. Ex. 2011, ¶ 31. Marinus conducted a Phase 2 clinical trial where it evaluated specific dosing regimens for ganaxolone in the treatment of refractory status epilepticus (RSE) and published the results of that trial in a paper appearing in the journal *Epilepsia*. *Id.*; Ex. 1016. Ganaxolone requires a solubilizing agent for IV administration. Ex. 2011, ¶ 51; Ex. 1001, 30:31-32; 33:40-48. Marinus used Captisol® as the solubilizing agent in its formulation used in the clinical trial. Ex. 2011, ¶ 51; Ex. 1001, 48:9-12; 1016, 3. The FDA has daily limits for the amount of Captisol®, which limits the daily amount of ganaxolone. Ex. 2011, ¶ 51; Ex. 1001, 48:9-12, 50:28-30. Facing these constraints, Marinus designed complex dosing regimens for the Phase 2 trial.

Patients suffering from RSE were given ganaxolone infusions starting with

an IV bolus over 3 minutes, followed by continuous infusion of decreasing infusion rates for 48-96 hours and then an 18-hour taper. *Id.*; Ex. 1016, 1. The detailed dosing information is provided a Supplemental Table to the *Epilepsia* paper (Ex. 2033) and is reproduced below. Ex. 2011, ¶ 32, Ex. 2033.

Vaitkevicius et al. **Supplemental Material**

Supplemental Table 1. Ganaxolone dosing used in this study

Cohort	Initial Bolus ^a	Additional Boluses PRN	Day 1 Infusion Rates	Day 2 - 4 Infusion Rates	18-h Taper ^b
High (713 mg/d)	25 mg	Not allowed	80 mg/h for 2 h 40 mg/h for 6 h 18 mg/h for 16 h	29 mg/h for 24 h	25% rate decrease every 6 h
Medium (650 mg/d)	25 mg	Allowed ^c	35 mg/h for 12 h 25 mg/h for 4 h 13 mg/h for 8 h	25 mg/h for 24 h	
Low (500 mg/d)	30 mg	Not allowed	85 mg/h for 2 h 40 mg/h for 2 h 20 mg/h for 2 h 10 mg/h for 18 h	20 mg/h for 24 h	

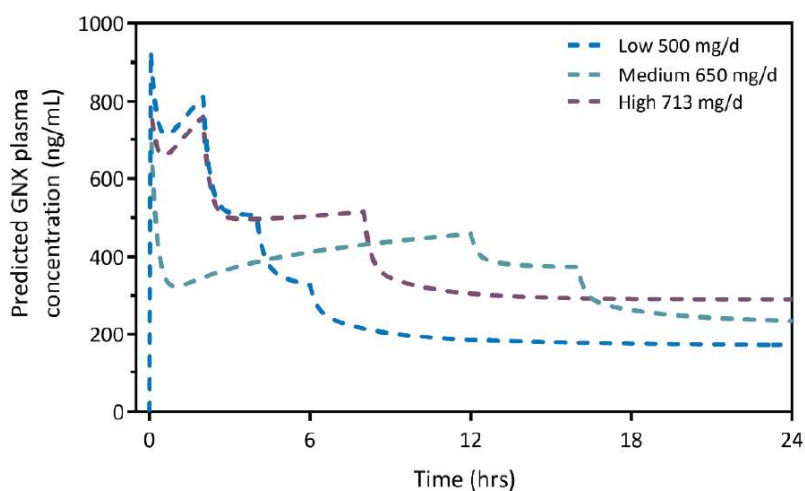
^aInitial bolus was delivered over 3 min.

^bTaper was initiated at the end of continuous infusion (i.e., Day 2, Day 4, or Early Discontinuation for those subjects who did not progress to 3rd line IV anesthesia for SE treatment). Ganaxolone infusion was stopped without taper in subjects who progressed to 3rd line anesthesia for SE treatment.

^cAdditional as-needed boluses were allowed in the Medium Cohort in the maximum total daily dose of up to 65 mg on Day 1 and up to 114 mg on Days 2-4 to manage seizures. It was recommended that a single dose of bolus was not to exceed 25 mg.

The three dosing cohorts in the trial were referred to as the “Low” “Medium,” and “High” cohorts, all of which included a bolus for the “rapid loading of ganaxolone (plasma concentration ~ 900 ng/ml) designed to abort SE” followed by continuous infusion to administer “maintenance doses aimed at sustaining seizure control.” Ex. 2011, ¶ 33; Ex. 1016, 3. The *Epilepsia* paper

provides modeling of ganaxolone plasma concentrations for each of the three dosing cohorts (Ex. 2011, ¶ 33; Ex. 1016, 4):



The study's primary end point was "the number of patients not requiring escalation to IV anesthetic treatment within 24 h of ganaxolone initiation," and none of the 17 patients in the study required such escalation. Ex. 2011, ¶ 34; Ex. 1016, 3-5. Marinus reported that "no patient required escalation to third-line IV anesthetics during the 24-h period following ganaxolone initiation." *Id.* The study also measured and reported the number of patients who were "[s]tatus-free" and/or required "no escalation to additional IV ASMs or to third-line IV anesthetics for status relapse" "during 24 h following infusion completion." Ex. 2011, ¶ 34; Ex. 1016, 6 (Table 2). No patient in the high-dose cohort required such escalation. *Id.*

In the Phase 2 study, Marinus surprisingly found that "[s]ustained clinical response was associated with maintaining ganaxolone plasma concentrations ≥ 500

ng/ml.” Ex. 2011, ¶ 35; Ex. 1016, 6. The *Epilepsia* paper explains that “[g]anaxolone plasma levels ≥ 500 ng/ml were achieved only briefly during the initial bolus for patients in the medium-dose cohort, whereas those in the low- and high-dose cohorts maintained such levels for 4 h and 8 h, respectively.” *Id.* The paper highlights the results for the high-dose cohort, noting that “[t]he greatest decrease in seizure burden was seen when ganaxolone concentrations were maintained at ≥ 500 ng/ml for at least 8 h.” *Id.*

The discussion section of the paper continues to focus on the high-dose cohort and explains that the “data support that the ganaxolone regimen administered in the high-dose cohort (713 mg/day) may reduce or prevent escalation of care to third-line IV anesthetics,” a result that would be “clinically significant” due to the risks of IV anesthesia. Ex. 2011, ¶ 36; Ex. 1016, 8. The paper also emphasizes the importance of maintaining the plasma concentration of ganaxolone above 500 mg/ml, as the high-dose cohort did: “Patients in the high-dose cohort maintained ganaxolone plasma concentrations ≥ 500 ng/ml for 8 h following treatment initiation and demonstrated the most durable reductions in seizure burden.” *Id.* The figure showing modeled plasma concentrations for the three dosing cohorts also points out that “[h]igh-dose [ganaxolone] achieves and maintains target plasma levels (≥ 500 ng/ml) for ~8 h, designed to sustain SE cessation.” Ex. 2011, ¶ 36; Ex. 1016, 4. Seeing the benefits that resulted from

maintaining plasma concentrations of ≥ 500 ng/ml for 8 hours, the *Epilepsia* paper notes that maintaining that plasma concentration for an even longer period “may offer additional benefit.” Ex. 2011, ¶ 36; Ex. 1016, 8.

III. OVERVIEW OF THE '100 PATENT

The '100 patent was filed as U.S. Patent Application No. 17/186,569 (the “'569 Application”) on February 26, 2021. Ex. 1001, cover page; Ex. 2011, ¶ 37. It is a continuation of PCT/US2020/044843, filed on August 4, 2020, and claims priority to provisional application No. 62/882,648, filed on August 5, 2019. *Id.* The '648 provisional was filed based on and includes information learned early in the Phase 2 study. *See, e.g.*, Ex. 2018, 81-90 (Example 2); *see also* Section VII.A.

A. Specification

The '100 patent “relates to a method for treating SE.” Ex. 1001, 2:61; Ex. 2011, ¶ 38. “[T]he inventors believed that ganaxolone could provide effective therapy for SE,” but, “given the complexity and difficulties in treating SE, and failure of prior studies to show efficacy, the inventors expected that a high drug exposure for at least 4 days, followed by a maintenance dose for at least 1 day, would be required for the effective treatment of SE.” *Id.*, 3:4-10. But, as described in the '100 specification, “[c]ontrary to these expectations, the inventors surprisingly discovered that administering ganaxolone as a bolus plus continuous infusion to maintain plasma concentration of ganaxolone at a much lower than

expected serum level for at least 8 hours (or possibly at least about 4 hours in some subjects) results in rapid and continued suppression of SE.” *Id.*, 3:10-16. The specification also “describe[s] and exemplifie[s] [that] continued suppression of SE was achieved when the continuous infusion maintains a plasma concentration of ganaxolone of about 500 ng/ml or higher for a target concentration period of at least about 8 hours or at least about 12 hours (although in some patients 4 hours can be sufficient), in the patients that were studied.” *Id.*, 3:16-22.

The inventors found that when these plasma concentrations are reached, “[s]urprisingly, SE continues to be suppressed by the continuous intravenous infusion even [when] the amount of [ganaxolone] administered during the continuous intravenous infusion is decreased during the treatment period.” *Id.*, 16:63-67; Ex. 2011, ¶ 39. “As a result, the method[s] provide enhanced safety and efficacy with lower exposure to ganaxolone than was expected.” *Id.*, 16:67-17:2.

“Accordingly, [the ’100 patent] relates to a method for effectively treating SE that provides rapid suppression of SE, sustained efficacy (i.e., prevents SE-relapse and provides for continued suppression of SE), and improved safety.” *Id.*, 3:23-26; Ex. 2011, ¶ 40.

These surprising results are shown, for example, in Example 2, titled “Preliminary Clinical Evidence of Efficacy in Subject with Status Epilepticus,” which describes the work that led to the United States Food and Drug

Administration to allow an increase in daily exposure limits of Captisol® to “allow[] for [ganaxolone] exposure to be maintained at >500 ng/ml for approximately 8 hours,” (Ex. 1001, 53:43-50) and confirmed in Example 3, titled “Phase 2 Open-Label Dose Range Study,” which shows that “[a]cute maintenance of [ganaxolone] plasma concentrations >500 ng/mL was associated with improved seizure control on EEG” (Ex. 1001, 56:63-65). Ex. 1001, 47:47-54:50, 54:52-57:7; Ex. 2011, ¶ 41; *see also* Section VII.A

B. Claims

The ’100 patent has 21 claims (the “Challenged Claims”), of which claim 1 is independent. Ex. 1001, 57:9-58:41; Ex. 2011, ¶ 42-43. Petitioner asserts that all 21 claims are unpatentable under 35 U.S.C. § 103. Claim 1 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 hours to about 12 hours.

Dependent claims recite specific bolus and continuous infusion amounts (in milligrams and milligrams per hour, respectively), specific durations (in hours), and specific conditions (refractory SE). *Id.*

C. Prosecution History

At the time that substantive examination began, claim 55 (which would ultimately issue as claim 1) recited 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,” where the effective amount “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.” Ex. 1029, 137. Claim 65 recited “wherein the intravenous bolus produces a ganaxolone plasma concentration in the subject of at least about 500 ng/ml to about 1000 ng/ml.” *Id.*, 139. Claim 66 recited “wherein the continuous intravenous infusion produces a ganaxolone plasma concentration in the subject of at least about 500 ng/ml to about 1000 ng/ml for at least about 8 hours.” *Id.* Claim 71 recited “wherein the intravenous bolus plus continuous infusion produces and maintains a ganaxolone plasma concentration of at least about 500 ng/ml for at least about 8 hours to about 12 hours.” *Id.*, 140.

In an Office Action dated April 20, 2021, the Examiner rejected claims 55-64 and 67-74 for lack of enablement and claims 55-74 as being obvious over US 2016/0228454 (“Zhang US,” Ex. 2019), which is equivalent to WO 2016/127170A1 (“Zhang,” Ex. 2012). *Id.*, 187-192. In a subsequent Examiner Interview, the Examiner indicated, with respect to enablement, that “[t]he range of

serum ganaxolone of at least 500 ng/mL runs into the anesthetic effect which [paragraph [0012] of the '569 application] teaches should be avoided when levels are above 1000 ng/mL.” *Id.* 203. The Examiner also noted that “the administration of ganaxolone for at least 8 hrs led to the rejection under 35 USC 103 over [Zhang] since it is an open ended timeframe.” *Id.*

Following this interview, Applicant amended claim 55 (which would become claim 1 of the '100 patent) to incorporate limitations of claims 65, 66, and 71, so that claim 55 recited a method of treating 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 “is administered as an intravenous bolus plus continuous infusion to produce and maintain a ganaxolone plasma concentration of ~~at least about 500 ng/ml~~ to about 1000 ng/ml for ~~at least about 8 hours~~ to about 12 hours.” *Id.*, 206.

Applicant also submitted the declaration of Dr. Hulihan (pages 216-219 of Ex. 1029), describing how Marinus “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. In particular, Dr. Hulihan explained that “it 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,” and that “[i]n

fact, it was completely contrary to [the inventors'] expectations.” *Id.* Dr. Hulihan also explained that Marinus’s work “surprisingly revealed that targeting a transient ganaxolone plasma concentration of about 500 ng/ml to about 1000 ng/ml was not enough to result in persistent suppression of SE,” but that “it is important to maintain that ganaxolone plasma concentration for about 8 to about 12 hours to achieve persistent suppression, i.e., to break SE.” *Id.* This “surprising and unexpected discovery” provided “significant clinical advantages,” including “enhanced safety for patients by limiting the duration of exposure to high drug levels” and “lessen[ed] risk of unwanted adverse effects.” *Id.*

The Examiner allowed the claims with that amendment and declaration, stating that “[t]he prior art neither teaches, nor fairly suggests the instantly claimed method of treating status epilepticus (SE),” noting specifically that “the prior art treating takes longer, and the instantly claimed method reaches cessation of SE activity by achieving . . . the claimed Cmax within about 8 to about 12 hours at the specified dosage by a bolus followed by continuous infusion.” *Id.*, 248-250.

IV. LEVEL OF ORDINARY SKILL IN THE ART

A hypothetical person of ordinary skill in the art (“POSA”) of the ’100 patent at the time of its filing would have had a medical degree, or a Ph.D. in pharmacology or other field related to the development of pharmaceuticals, or equivalent degree, and several years of experience as a practicing neurologist

treating patients who suffer from seizure disorders including status epilepticus and/or several years of experience in researching treatments for such seizure disorders. Ex. 2011, ¶ 44.

V. CLAIM CONSTRUCTION

Petitioner asks the Board to commit legal error and read explicit limitations out of the claims. Claim 1 recites 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 hours to about 12 hours.” Ex, 1001, 57:9-15. Petitioner asks the Board to construe “[t]he term ‘to produce and maintain a ganaxolone plasma concentration of about 500 ng/ml to about 1000 ng/ml’ of independent claim 1 . . . as nonlimiting.” Pet., 18. This ask is not supported by the claim language, the intrinsic evidence, or precedent. Claims are construed using the *Phillips* standard and in accordance with “the ordinary and customary meaning of [each] claim as understood by one of ordinary skill in the art and the prosecution history pertaining to the patent.” 37 C.F.R. § 42.200; *see also Phillips v. AWH Corp.*, 415 F.3d 1303, 1312–14 (Fed. Cir. 2005) (en banc). The “determination of whether a ‘wherein’ clause imposes a limitation in a claim must be determined on a case-by-case

basis.” *MPHJ Tech. Invs. LLC v. Ricoh Americas Corp.*, 847 F.3d 1363, 1379 (Fed. Cir. 2017) (citing *Griffin v. Bertina*, 285 F.3d 1029, 1033–34 (Fed. Cir. 2002)).

In this case, the entirety of the “wherein” clause where the disputed phrase appears must be read as limiting for two main reasons. First, because the “‘wherein’ clause states a condition that is material to patentability, it cannot be ignored in order to change the substance of the invention.” *Allergan Sales, LLC v. Sandoz, Inc.* 935 F.3d 1370, 1376 (Fed. Cir. 2019) (quoting *Hoffer v. Microsoft Corp.*, 405 F.3d 1326, 1329 (Fed. Cir. 2005)). Second, the pharmacokinetic (PK) parameters of the “wherein” clause are limiting because they relate back to “effective amount” required by claim 1 and gives “meaning and purpose to the manipulative steps.” *Griffin*, 285 F.3d at 1033.

As to the first point, the Patent Owner and the Examiner expressly relied on the language in the “wherein” clause to distinguish over prior art cited in prosecution. Just as in *Allergan*, which found efficacy results contained in a “wherein” clause to be limiting, Patent Owner argued that the improved efficacy of the claimed methods were “unexpected results,” and “the Examiner explicitly relied on the ‘wherein’ clause[] in explaining why the claims of the [’100 patent] were” patentable over the prior art. *See* Section III.C; *Allergan*, 935 F.3d at 1375–76. Specifically, Marinus submitted a declaration from Dr. Hulihan discussing the

unexpected nature of maintaining the recited plasma concentrations for more than 8 hours to support patentability, and the Examiner noted in the “Reasons for Allowance” that “the instantly claimed method [was] allowable over the prior art” **because** “cessation of SE activity ... is achieved by the claimed Cmax within about 8 to about 12 hours at the specified dosage by a bolus followed by continuous infusion.” Ex. 1029, 249-250.

Petitioner’s reliance on *In re Copaxone Consol. Cases*, 906 F.3d 1013 (Fed. Cir. 2018) and *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368 (Fed. Cir. 2001) is misplaced. In those cases, the claim terms were either not “necessary or relevant to the examiner’s approval” (*In re Copaxone*) or were “voluntarily made after the examiner had already indicated . . . the claims were allowable” and such “unsolicited assertions of patentability made during prosecution do not create a material claim limitation.” *Allergan*, 906 F.3d at 1376 (quoting *In re Copaxone*, 906 F.3d at 1024 and *Bristol-Myers Squibb*, 246 F.3d at 1375). Here, by contrast, the PK parameters that Petitioner would like read out of the wherein clause were explicitly relied on by both Applicant and the Examiner to distinguish over the prior art and thus support patentability over the prior art.

As to the second, point, it is evident from the claim language itself that the PK parameters recited in the “wherein” clause give “meaning and purpose to the manipulative steps” because it relates back to how the “effective amount” must be

administered and what it must do. *Griffin*, 285 F.3d at 1033. Specifically, the “effective amount” required by claim 1 must be “effective” to *both* “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.” Ganaxolone dosing regimens that do not achieve those results are not encompassed by claim 1.

Petitioner’s argument that “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” is also incorrect. As described in the specification, “an effective amount of ganaxolone to suppress SE” is not coextensive with “produc[ing] and maintain[ing] 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.*, Ex. 1001, 3:23-26; 47:47-57:7 (Examples 2 and 3); *see also* Ex. 1016. While all the dosing regimens (“low,” “medium,” and “high” dose cohorts) described in Example 3 were able to suppress SE for a period of time, only the “high” dose cohort resulted in the claimed plasma concentrations (≥ 500 ng/ml for about 8 hours). Ex. 1001, Fig. 15; *see also* Ex. 1016, Fig. 2. And it was only this high dose cohort that provided the sustained suppression (e.g., through 24 hours after ganaxolone discontinuation and during the 4-wk follow up period). Ex. 1001, Example 3, Tables 4, 5, and 6; *see also* Ex. 1016, Fig. 2, Fig. 3, Table 2.

Moreover, it was this high dose cohort that provided the unexpected results as described in the declaration by Dr. Hulihan. Ex. 1029, 216-219.

Given all of the above, the entire “wherein” clause is limiting and should be given its plain and ordinary meaning. The Board should reject Petitioner’s attempt to read express limitations out of the claims.

**VI. INSTITUTION SHOULD BE DENIED ON ALL GROUNDS
BECAUSE PETITIONER’S ARGUMENTS DEPEND ON AN
INCORRECT CLAIM CONSTRUCTION**

Each of Petitioner’s obviousness grounds rely on their faulty claim construction that reads the PK parameters recited in the “wherein” clause out of the claim completely. *See* Section V.¹ Because Petitioner has not addressed obviousness under the correct claim construction—in which “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” is limiting—the Petition should be denied. Indeed, the claimed plasma concentration and claimed duration of the plasma concentration is not found in the prior art.

¹ Pet., 39 (Ground 1, “Motivation to Combine”); 41-42 (Ground 1, “Reasonable Expectation of Success”); 49 (Ground 2, “Motivation to Combine”); 50 (Ground 2, “Reasonable Expectation of Success”); 54 (Ground 3, “Motivation to Combine”); 55-56 (“Reasonable Expectation of Success”).

**VII. INSTITUTION ON THE BASIS OF GROUND 3 SHOULD BE
DENIED BECAUSE PETITIONER'S CITED REFERENCES
ARE NOT AVAILABLE AS PRIOR ART**

Regarding Ground 3, the Petitioner relies on references that are not prior art, so Petitioner's argument should be rejected. Petitioner cites four different references related to Marinus's Phase 2 Clinical Trial Results (Ex. 1010, Ex. 1008, Ex. 1011, Ex. 1009; *see* Pet., ii) for allegedly disclosing administering 713 mg/day ganaxolone to achieve a plasma concentration of >500 ng/ml for about 8 hours and suppressing SE. Pet., 53-58. Petitioner alleges that these disclosures, combined with During (Ex. 1003) render the Challenged Claims obvious. *Id.* But this challenge fails because the four Phase 2 Clinical Trial references are not prior art to the Challenged Claims.

First, the Challenged Claims are entitled to priority to that application because it provides written description and enablement support for those claims. Because all four references published after the '648 provisional application filing date, they are not prior art.

Second, these references are all Marinus's own work, specifically, the inventors' own work, and the 102(b) exceptions apply. "In an IPR proceeding based on prior art," Petitioner's burden under 35 U.S.C. § 316(e) "necessarily includes the burden to establish that the references relied upon qualify as prior art." *Google LLC v. IPA Techs. Inc.*, IPR2019-00731, Paper 73 at 14. As described

below, Petitioner has failed to discharge that burden.

A. The Challenged Claims Are Entitled to Priority to the Provisional Application

The Challenged Claims of the '100 patent are entitled to the August 5, 2019 priority date of the '648 provisional application. For claims to be entitled to the filing date of a provisional application,² the provisional must disclose the claimed invention “in the manner provided by § 112(a) (other than the requirement to disclose the best mode).” 35 U.S.C. § 119(e), 120. In other words, the '648 provisional must meet the written description and enablement requirements for the Challenged Claims. It plainly meets both.

To meet the written description requirement of §112, the provisional must “demonstrate possession” of the claimed invention but does not need to provide

² Patent Owner notes that Petitioner did not provide, and Dr. Sankar did not opine on, the full specification of the '648 provisional application for their arguments on lack of priority. Exhibit 1031 does not include the figures, claims, or abstract that were filed as part of the provisional application. *Compare* Ex. 1031 to Ex. 2018. Patent Owner thus submits Exhibit 2018, which is a complete version of the '648 provisional application's file history that includes important information omitted from Petitioner's exhibit (including the Figures associated with Example 2).

“examples or an actual reduction to practice” or an *in haec verba* description.

Ariad Pharms., Inc. v. Eli Lilly & Co., 598 F.3d 1336, 1352 (Fed. Cir. 2010). “It is not necessary that the application describe the claim limitations exactly, . . . but only so clearly that persons of ordinary skill in the art will recognize from the disclosure that [the inventors] invented processes including those limitations.” *In re Wertheim*, 541 F.2d 257, 262 (C.C.P.A. 1976).

To meet the enablement requirement of §112, the specification must “contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same.” 35 U.S.C. § 112. “To prove that a claim is invalid for lack of enablement, a challenger must show by clear and convincing evidence that a person of ordinary skill in the art would not be able to practice the claimed invention without ‘undue experimentation.’” *Alcon Rsch. Ltd. v. Barr Labs., Inc.*, 745 F.3d 1180, 1188 (quoting *In re Wands*, 858 F.2d 731, 736-37 (Fed. Cir. 1988)).

The entirety of Petitioner’s priority attack is directed to the limitation in Claim 1 requiring that the ganaxolone is administered in a manner “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.” Pet., 21-26. The provisional

application directly highlights the importance of both the claimed plasma concentration range and claimed timeframe for which it must be maintained.

The provisional specification includes initial data from the results of its Phase 2 clinical trial that support the specifically claimed ranges. Ex. 2011, ¶ 50; Ex. 2018, 81-90 (Example 2). For the Phase 2 study, the daily exposure limit for Captisol®, a solubilizing agent used in the ganaxolone formulation, was initially 35 mg/day according to FDA requirements. Ex. 2011, ¶ 51; Ex. 2018, 84-85, 90 at ¶¶ [0188], [0208]. Under the 35 g/day Captisol® protocol, patients received a bolus and continuous infusion of ganaxolone, but the total daily dose of ganaxolone was limited to 500 mg/day due to the Captisol® limit. Ex. 2011, ¶ 52; Ex. 2018, 90 at ¶ [0203].

For the first five patients to receive the 500 mg/day dose, “the initial 3-minute bolus dose of 30 mg [ganaxolone] with concurrent continuous infusion at 85 mg/hr for 2 hours followed by 40 mg/hr for 2 hours . . . resulted in the immediate cessation of seizures.” Ex. 2011, ¶ 53; Ex. 2018, 84-85 at ¶ [0188]. However, due to the daily Captisol® limit, ganaxolone exposure had to be lowered to “20 mg/hr for 2 hours and ending with 10 mg/hr for the remaining 18 hours on Day 1.” *Id.* When the infusion rate was lowered and the plasma level fell below 500 ng/ml, “seizure control could not be maintained” and seizures relapsed. *Id.*

The PK modeling data from the 35 g/day Captisol® patients is shown in

Figure 2 of the '648 provisional application and reproduced below. Ex. 2011, ¶ 54; Ex. 2018, 84-85 at ¶ [0188].

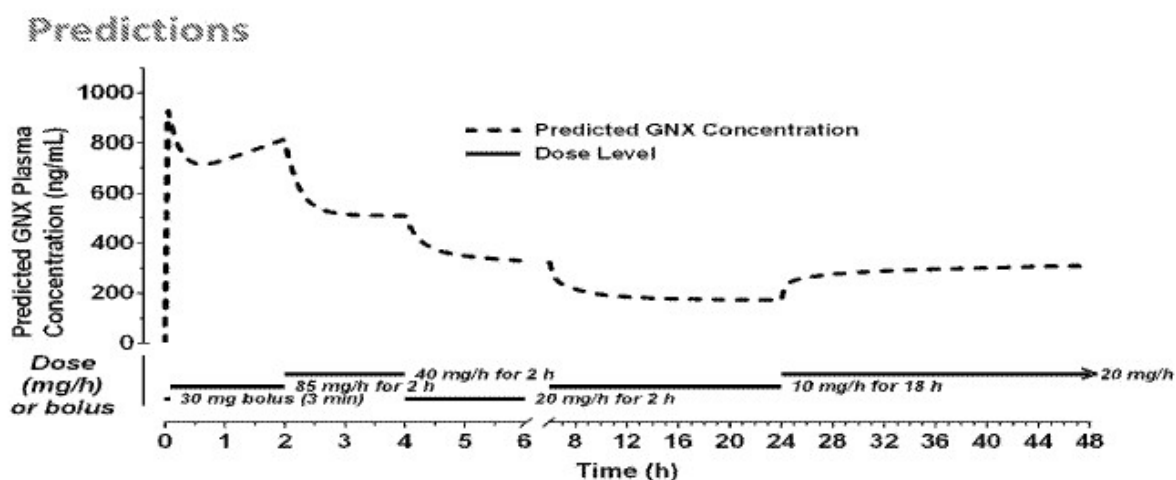


Figure 2

The '648 provisional provides details of the first five patients' measured ganaxolone plasma concentrations and the timing of their relapses. Ex. 2011, ¶¶ 55-57; Ex. 2018, 84-89. The first patient's seizures relapsed at about 5 hours post infusion start, when measured plasma concentration fell below 500 ng/mL. *Id.* The second, third, and fourth patient's seizures all relapsed at about 6 hours post infusion start, when measured plasma concentrations fell below 500 ng/mL. *Id.* The final patient's seizures "did not return during the treatment period. *Id.*

Together, the PK modeling data from those five patients "suggested that exposure levels of [ganaxolone] at approximately 1000 ng/mL were associated with rapid and complete SE suppression," while "lower [ganaxolone] exposures at < 500 ng/mL were associated with seizure relapse." Ex. 2018, 85 at ¶ [0188]-

[0189]. Indeed, “[s]eizure activity *relapsed* when plasma concentrations of [ganaxolone] decreased < 500 ng/mL in 4 out of 5 subjects.” *Id.* (emphasis added). That is, the ’648 provisional demonstrates that the inventors recognized the claimed plasma concentration range of 500 ng/mL to 1000 ng/mL was important and recognized that seizures would return if those concentrations were not maintained for a long enough timeframe. Ex. 2011, ¶ 58.

After receiving this “encouraging data,” Marinus went back to FDA and received permission to “allow[] the daily limit of Captisol[®] exposure to increase to 50 g/day (and the total daily dose of [ganaxolone] to increase from 500 to 715 mg), thereby allowing for [ganaxolone] exposure to be maintained at > 500 ng/ml for approximately 8 hours.” Ex. 2011, ¶ 59; Ex. 2018, 89-90 at ¶¶ [0203], [0208] (emphasis added).

The new dosing regimen, based on the increased 50 g/day Captisol® limit, for patients weighing 40 kg or more is shown in the table on page 57 of the ’648 specification, and reproduced below (Ex. 2011, ¶ 59-60; Ex. 2018, 83-84):

Days	Start Time from Dose Initiation	Dose Level of Study Drug IV (infusion rate)	Duration
Day 1	0 hours: bolus dose via syringe or infusion pump	25 mg	3 minutes
Day 1	0 hours through 2 hours post-dose: continuous infusion, started with bolus	80 mg/hour	2 hours
Day 1	2 hours post-dose through 8 hours post-dose	40 mg/hour	6 hours
Day 1	8 hours post-dose through 24 hours post-dose	18 mg/hour	16 hours
Day 2 or Day 2 through Day 4	24 hours post-dose through 48 hours post dose (Day 2) or 24 hours post-dose through 96 hours post-dose (Day 2-4)	29 mg/hour	24-72 hours (Day 2 or Day 4)
Taper for subjects discontinuing study drug			
Day 3 or Day 5	48 or 96 hours post-dose: 18-hour taper	Reduce infusion rate by 25%	6 hours
		Reduce infusion rate by 25%	6 hours
		Reduce infusion rate by 25%	6 hours

This dosing regimen results in a daily dose of 713 mg of ganaxolone, dosed as a bolus and continuous infusion (as recited in the Challenged Claims). *Id.*

The '648 provisional discloses that one patient had already received ganaxolone under the 50 g/day Captisol® protocol. Ex. 2011, ¶ 61; Ex. 2018, 89 at ¶ [0204]. The provisional states that “[w]ithin 3 minutes after starting the IV [ganaxolone] infusion, the [patient’s SE] ceased and seizure protection was maintained for the remaining 48 hours of [ganaxolone] treatment.” *Id.* In other words, the provisional application not only discloses a specific dosing regimen that

was designed to maintain the patient's plasma level above 500 ng/ml for at least 8 hours, it also discloses that a patient was successfully treated with the dosing regimen such that SE did not recur. Ex. 2011, ¶ 62.

As for the 12-hour upper end of the claimed 8-12 hour range, 12 hours is within the broad ranges for maintaining the plasma levels taught in the '648 provisional (*see, e.g.*, Ex. 2011, ¶ 63; Ex. 2018, 38-39, 45-46 at ¶¶ [0028], [0042]) and would be understood by a POSA to be a reasonable timeframe to maintain plasma concentrations in the required range for more patients, given patient-to-patient variability. Ex. 2011, ¶ 63. And the 12-hour limit was added because the Examiner required that administration duration not be open-ended on the upper end to distinguish the Zhang prior art. Ex. 1029, 203. The Examiner explained that "the administration of ganaxolone for at least 8 hrs led to the rejection under 35 USC 103 over [Zhang] since it is an open-ended time frame." *Id.* In response, Applicant amended the claims to recite "a ganaxolone plasma concentration of ~~at least~~ about 500 ng/ml to about 1000 ng/ml for ~~at least~~ about 8 hours to about 12 hours," moving the 12-hour requirement from dependent claim 71 into the independent claim, after which the Examiner allowed the case. Ex. 1029, 137, 206, 249-250.

The '648 provisional teaches a specific ganaxolone dosing regimen used to achieve the claimed plasma concentrations for the claimed timeframe, so there can

be no undue experimentation involved in practicing the claims. Ex. 2011, ¶ 64; Ex. 2018, 82-84 at ¶¶ [0182]-[0186]. Indeed, the provisional teaches precisely what to do and why. *Id.* Given all the above, the '648 provisional unambiguously shows possession of and teaches how to practice a method that achieves “ganaxolone plasma concentrations of about 500 ng/ml to about 1000 ng/ml for about 8 hours to about 12 hours.” Ex. 2011, ¶ 65.

The additional data in the '100 patent (Example 3 and Figures 12-15) simply **confirm** what was already disclosed in the '648 provisional. Notably, the “high” dose cohort in Example 3 uses the same dosing regimen as described in Example 2 of the '648 for the 50 g/day Captisol® patients. Ex. 2011, ¶ 64; Ex. 2018, Ex. 1001, 55:5-30; Ex. 2018, 82-84 at ¶¶ [0182]-[0186].

Petitioner's arguments for lack of priority rely in large part on pointing out that the '648 provisional application does not include data showing the claimed PK parameters were actually achieved. (Pet., 21, 23-24.) But § 112 does not require such data. *See Eli Lilly & Co. v. Teva Pharms. USA, Inc.*, 619 F.3d 1329, 1334-35, 1343-44 (Fed. Cir. 2010) (rejecting an enablement challenge to patents that were filed while clinical trial results were pending). The specification includes both the target results and a specific dosing regimen designed to achieve them; no more is required.

Petitioner also argues that during prosecution of the '569 application, the

inventors “specifically identified ‘Figure 15’ . . . as support for the alleged unexpected results,” but that “neither Figure 15 nor the experimental data depicted by Figure 15 were disclosed in the ’648 application.” Pet., 22. But Petitioner fails to show that Patent Owner’s argument, made in the context of unexpected results to support non-obviousness during prosecution, leads to a lack of § 112 support for the claims in the provisional application. Given all of the above, Petitioner’s priority attack fails, and Ground 3 can be dismissed on that basis alone.

B. The Phase 2 CTR References are Not Prior Art Because § 102(b)(1) Exceptions Apply

Even if the Board were to find that the Challenged Claims are not entitled to the priority of the provisional application, the Phase 2 CTR References are still not prior art because they represent the inventors’ own work. If the pertinent subject matter A) was obtained directly or indirectly from an inventor of the ’100 patent; or B) had already been publicly disclosed by an inventor (or another who obtained it directly or indirectly from an inventor), then the reference is not prior art. 35 U.S.C. §§ 102(b)(1).

Here, the subject matter of each of the Marinus Phase 2 CTR References that Petitioner relies on (the “pertinent subject matter”) reports the Marinus inventors’ own disclosure of the details and unexpected results of the Phase 2 trial.” Pet., 53-58.

1. Overview of the Phase 2 CTR References

Practical Neurology 2019 (Ex. 1010): Exhibit 1010 is a news post from Practical Neurology dated October 18, 2019, which contains pharmacokinetic results from Marinus’s Phase 2 clinical study. Ex. 2001, ¶¶ 4-10; Ex. 2002, ¶¶ 3-8.

AES 2019 Poster (Ex. 1011) and Abstract (Ex. 1008): Exhibits 1008 and 1011 are an abstract and poster, respectively, from the American Epilepsy Society (AES) Annual Meeting in December 2019. Like Exhibit 1010, they include pharmacokinetic results from Marinus’s Phase 2 clinical study. Ex. 2001, ¶¶ 11-17; Ex. 2002, ¶¶ 9-13.

With respect to Exhibit 1011, the poster itself contains no indication that it was ever made “sufficiently accessible to the public interested in the art,” and Petitioner has not provided any evidence at all that it was. *In re Klopfenstein*, 380 F.3d 1345, 1348 (Fed. Cir. 2004). “[A]t the institution stage, the petition must identify, with particularity, evidence sufficient to establish a reasonable likelihood that the reference was publicly accessible before the critical date of the challenged patent and therefore that there is a reasonable likelihood that it qualifies as a printed publication.” *Hulu, LLC v. Sound View Innovations, LLC*, IPR20108-01039, Paper 29 at 13 (PTAB Dec. 20, 2019) (Precedential). Thus, Petitioner’s Ground 3 argument on Exhibit 1011 falls short for this additional reason.

Husain 2020 (Ex. 1009): Exhibit 1009 is a *Journal of Clinical*

Neurophysiology Publication (Volume 37, Number 4, July 2020), that includes “Poster Abstracts” from the “2020 American Clinical Neurophysiology Society (ACNS) Annual Meeting,” including Poster Abstract F53 titled “Intravenous Ganaxolone Achieves Rapid and Dose-Dependent Sustained Improvement in EEG Seizure Burden in Patients with Refractory Status Epilepticus.” Ex. 2001, ¶¶ 18-21; Ex. 2002, ¶¶ 14-18.

Exhibit 1009 does not include the PK data showing that the 713 mg/day ganaxolone dosing regimen achieves a plasma concentration of 500 ng/mL for ~8 hours. Ex. 2001, ¶ 19; Ex. 2002, ¶ 18.

2. § 102(b)(1)(A) Applies to all the Phase 2 CTR References

Exhibits 1008, 1009, 1010, and 1011 are not prior art under § 102(b)(1)(A) because the non-inventor co-authors (R. Eugene Ramsay, Christa B. Swisher, Aatif M. Husain, Steven Smith, Heather Van Heusen, and Brad Kolls) obtained the pertinent subject matter from the Marinus inventors. Ex. 2001. “[A]uthorship of an article by itself does not raise a presumption of inventorship with respect to the subject matter disclosed in the article.” *In re Katz*, 687 F.2d 450, 455 (Fed. Cir. 1982). “[C]o-authors may not be presumed to be coinventors merely from the fact of coauthorship.” *Id.* Here, Petitioner has improperly made that presumption.

As explained by inventor Maciej Gasior, none of the non-inventor co-

authors on any of these exhibits contributed to the invention of the dosing regimen designed to maintain plasma concentrations above 500 ng/ml for at least 8 hours, or, indeed, of any of the other particulars of any of the dosing regimens used in the Phase 2 trial. Ex. 2001. That subject matter was communicated either directly or indirectly from the inventors to the non-inventor co-authors. Ex. 2001. Dr. Braunstein (quoted in Ex. 1010) is and was Marinus's CEO at the time. *Id.*, ¶¶ 4-5. Drs. Vaitevicius, Swisher, Ramsay, Husain, and Kolls were Study Investigators or their collaborators. *Id.*, ¶ 9. Dr. Steven Smith was a Marinus employee who provided PK modeling at the request, direction, and control of the inventors. *Id.* Dr. Heather Van Heusen was the Director of Clinical Operations at Marinus at the time, responsible for coordination and communication with the Study Investigators, but not for the design of the study. *Id.*

The content of the publications, their nature, and the circumstances of their publication are all consistent with these explanations. Both the "content and nature" of the publication and "the circumstances surrounding its publication" must be considered—"not merely its authorship." *In re Katz*, 687 F.2d at 455. The asserted references are either press coverage of Patent Owner Marinus's previously announced clinical trial results (Ex. 1010), or poster/abstracts authored in pertinent part by Marinus scientists for scientific meetings (Ex. 1011, Ex. 1008, Ex. 1009). Ex. 2001.

Furthermore, though such a showing is not necessary for the Board to conclude that the § 102(b)(1)(A) exception applies, non-inventor co-author Dr. Henrikas Vaitevicius confirms what Dr. Gasior has explained. Ex. 2002. *Katz*, 687 F.2d at 455 (it was “clear error” for the board to hold that “disclaiming affidavits or declarations by the other authors are required”). Only “a reasonable showing supporting the basis for [Patent Owner’s] position” is required (*id.*), and the declarations from Dr. Vaitevicius and Dr. Gasior make such a showing.

3. § 102(b)(1)(B) Applies to all the Phase 2 CTR References

Exhibits 1008, 1009, 1010, and 1011 are not prior art under § 102(b)(1)(B). The pertinent subject matter was first disclosed by Dr. Vaitkevicius (who obtained the pertinent subject matter from the Marinus inventors) at the Neurocritical Care Society 17th Annual Meeting in Vancouver, BC, and then by Marinus in an October 17, 2019, press release (Ex. 2004). Ex. 2002, ¶¶ 3-5; *see also* Ex. 2002, ¶¶ 7-18, Ex. 2003; Ex. 2004; Ex. 2005; Ex. 2006; Ex. 2007; Ex. 2008. Thus, the later published exhibits relied on by Ovid that include the same subject matter (Exhibits 1008, 1009, 1010, and 1011) are not prior art.

VIII. INSTITUTION ON THE BASIS OF GROUND 1 SHOULD BE DENIED

Ovid’s Ground 1 is based on the combination of During (Ex. 1003) and a reference related to Marinus’s Phase 2 Clinical Trial—not the results, but its pre-

initiation announcement on clinicaltrials.gov (NCT03350035, Ex. 1004). The results and specifics of the dosing regimen used are nowhere in the prior art.

A. Petitioner’s Primary Reference—(During, Ex. 1003)

During (Ex. 1003, U.S. Patent No. 11,395,817, or the “’817 Patent”) is a continuation in a series of applications starting with U.S. Patent Application No. 15/673,737, filed on August 10, 2017, titled “Methods and Compositions for Treatment of Epileptic Disorders.” Ex. 1003, cover page. During PCT (WO2018031748 A1, Ex. 2013) contains the same disclosure as During and is one of the five “References Cited” on the face of the ’100 patent. Ex. 1003; Ex. 2013; Ex. 1001, cover page; Pet., 60 n. 1.

In total, Petitioner relies on the following teachings in During’s specification: Ex, 1003, 2:13-22; 4:6-16; 6:51-54; 7:40-8:8; 8:11-34; 8:42-44; 10:28-42; and Example 3 (35:31-37:15). Pet., 37-59. None teach a particular dosing regimen or do anything to suggest the plasma concentrations required by the claims of the ’100 patent.

Column 2, lines 13-22, states that During provides methods “for treatment of epileptic disorders,” of which “status epilepticus” and “refractory status epilepticus” are the 19th and 20th listed disorders. The remaining lines in that paragraph go on to recite even more disorders. Column 4, lines 6-16, recites a similar list. Neither of these passages relate specifically to treatment with

ganaxolone, nor do they recite any routes of administration or dosing regimens.

Column 6, lines 51-54, states that “dosages may include amounts of an allosteric modulator or a pharmaceutically acceptable salt thereof in the range of about, e.g., 1 mg to 30 mg. The remainder of the paragraph goes on to give many, many more possible examples of dosing amounts (all the way through paragraph 7, line 27). This passage does not relate specifically to treatment with ganaxolone, nor to the treatment of any particular disease. The list of allosteric modulators at Column 6, lines 22-26, includes 11 specific drugs and several broad classes of drugs (e.g., neurosteroids, benzodazepines and potassium channel openers). It also does not teach any particular dosing regimen.

Column 7, line 40 to Column 8, line 8, also relate to “[t]ypical[] dosages of an allosteric modulator or pharmaceutically acceptable salts thereof” (7:28-29), but not to ganaxolone specifically, nor to any particular disease. The passage gives a laundry list of embodiments in which a “patient can be administered an allosteric modulator” in mg/day doses ranging from 10 mg to 2000 mg/day. It does not teach any particular dosing regimen.

Column 8, lines 11 to 34, is the only passage cited that references any doses for “status epilepticus” and “ganaxolone” specifically, which are recited as mg/kg doses (lines 16-22) or flat mg doses (lines 16-34) without specifying how often the dose is to be administered. This paragraph also says nothing about the mode of

administration, any particular dosing regimen, or any particular result.

Column 8, lines 42-44, recites that “[i]n embodiments, ganaxolone or a pharmaceutically acceptable salt thereof can be administered parenterally in escalating doses as soon as possible after the onset of seizures.” It does not indicate intravenous administration, specifically, nor does it say anything aside from “escalating doses” about what particular dosing regimen should be used, or what result could or should be achieved.

Column 10, lines 27-42, indicates that “[t]he methods described [in During] may also be effective in subjects experiencing” a variety of different seizures. It also notes that “the subject can have . . . a disorder characterized by status epilepticus,” and that “in embodiments, the disclosed methods are used to treat subjects that would otherwise be resistant to one or more conventional therapies.”

Example 3, titled “Evaluation of the Ability of Allopregnanolone, Ganaxolone, and Gaboxadol to Block Benzodiazepine-Resistant Status Epilepticus,” describes an experiment in which rats experiencing chemically induced SE were dosed with ganaxolone (alongside allopregnanolone and gaboxadol) intraperitoneally, with doses of 0.5, 2, 5, 10, and 20 mg/kg. The results “suggest[ed] dose-dependent efficacy of ganaxolone (i.p)—significant ($p < 0.02$) improvement in protection at 20 mg/kg.” Ex. 1003, 37:8-11. As shown in During’s Figure 3, at the 20 mg/kg dose of ganaxolone, about 30% of rats were

“protected.” Ex. 1003, 36:66-37:1. 100% protection was defined as “no further convulsive seizures after 10 min of drug administration.” Ex. 1003, 36:4-8.

Example 3 contains no pharmacokinetic data or any suggestion of targeting any particular plasma concentrations for any reason. Nor does it contain any guidance as to which doses or dosing regimens might achieve the un-contemplated plasma concentrations.

Nothing in During teaches administering ganaxolone to treat SE using the claimed “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.” In fact, During teaches to keep plasma concentrations *less than* 500 ng/ml, explaining that compositions of the invention “provide[] an in vivo plasma profile having a Cmax less than about 500 ng/ml.” Ex. 1003 at 15:12-28. And Petitioner points to no disclosure in During that teaches an “intravenous bolus plus continuous infusion” of ganaxolone to treat SE at all, which is a requirement of all the Challenged Claims.

Petitioner also relies on During’s claims 24-31, which recite certain doses claimed as mg/day. But those mg/day doses say nothing about how that dose is to be given and thus still does not teach or suggest a bolus plus continuous infusion

dosing regimen or the claimed plasma concentrations and durations.³

B. NCT03350035 (Ex. 1004)

NCT03350035 is Version 1 of the clinicaltrials.gov posting for Marinus's Phase 2 Clinical trial titled "Intravenous Ganaxolone as Adjunctive Therapy to

³ In addition, the During claims Petitioner relies on were not present in the originally filed application and were first introduced during prosecution on May 11, 2022. Ex. 2014. Petitioner cannot rely on these claims as prior art because the recited dose levels lack support in the During applications and are not entitled to a priority date before the Challenged Claims. *Penumbra, Inc. v. Rapidpulse, Inc.*, IPR2021-01466, Paper 34 at 33 (PTAB, March 10, 2023) (Precedential). There are only two passages in During where daily dose ranges are recited at all—column 7, line 28 through column 8, line 10 (a portion of which Petitioner cites), and column 5, lines 31-48. The latter is specifically related to gaboxadol (not ganaxolone), and the former is agnostic as to which of During's many allosteric modulators are being administered (*see, e.g.*, 6:22-26) and for the treatment of which of During's many diseases (*see, eg.*, 4:6-32). The only dosing information Petitioner points to in During's specification that relates to both ganaxolone and SE gives a laundry list of doses in mg/kg amounts or mg amounts, with no daily values recited, and provides no blaze marks to the claimed plasma levels. (*See* Section VIII.A.)

Treat Subjects With Status Epilepticus.” As of its posting date of November 17, 2017, the study was “[n]ot yet recruiting.” Ex. 1004, 2.

The study details indicated that ganaxolone would be administered intravenously to patients in the experimental arm as an “IV loading dose with continuous infusion (maintenance dose) for 2-4 days followed by a 24-hour taper.” *Id.*, 3. It does not contain any details regarding what the loading dose or continuous infusion rates would be, nor whether any plasma concentration levels were being targeted (or for how long they should be sustained). *Id.*

C. Petitioner Has Not Shown a Reasonable Likelihood that the Claims Are Obvious Over During and NCT03350035

As an initial matter, as discussed above, Petitioner relies on an incorrect claim construction that reads the PK parameters of the “wherein” clause out of the claim. *See* Section V. Neither During, NCT03350035, or any combination thereof, teach or suggest “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 hours to about 12 hours.” In fact, During *teaches away* from plasma concentrations above 500 ng/ml, stating that compositions of the invention “provide[] an in vivo plasma profile having a Cmax less than about 500 ng/ml.” Ex. 1003 at 15:12-28. Ground

1 can be summarily dismissed on that ground alone.

Faced with the absence of the claimed plasma level and the claimed timeframe in the prior art, Petitioner is forced to argue that the plasma concentrations and required timeframes are met inherently. Pet at 42 (citing *Persion Pharms. LLC v. Alvogen Malta Operations Ltd.*, 945 F.3d 1184, 1191 (Fed. Cir. 2019) and *Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1354 (Fed. Cir. 2012)). But Petitioner's reliance on inherency fails.

Inherency is “a ‘high standard’ that is ‘carefully circumscribed in the context of obviousness.’” *Persion Pharms. LLC*, 945 F.3d at 1190 (quoting *PAR Pharm., Inc. v. TWi Pharms., Inc.*, 773 F.3d 1186, 1195 (Fed. Cir. 2014)). It “may not be established by probabilities or possibilities” and “renders a claimed limitation obvious only if the limitation is ‘necessarily present’ or is the ‘natural result of the combination of elements explicitly disclosed by the prior art.’” *Id.* (emphasis added). The “inherency of an advantage and its obviousness are entirely different questions Obviousness cannot be predicated on what is unknown.” *PAR Pharm., Inc.* 773 F.3d at 1195 (quoting *Application of Shetty*, 566 F.2d 81, 86 (C.C.P.A. 1977)).

Thus, to show inherency, Petitioner would have to show that the claimed plasma concentrations would *necessarily* be achieved and maintained for the claimed timeframes with the dosing taught by the prior art. *See Allergan, Inc. v.*

Sandoz Inc., 726 F.3d 1286, 1294 n.1 (Fed. Cir. 2013) (rejecting inherency argument where there was no evidence that claimed result would necessarily flow from any administration of the two claimed drugs in any fixed combination). Petitioner comes nowhere near meeting this standard. And in fact, the evidence shows that different dosing regimens lead to *different* plasma concentrations and *different* results, not all of which fall within the claimed plasma concentrations maintained over time. Ex. 1016, *see supra* Section II.B. Modeling done for Marinus's Phase 2 trial showed that patients in the high-dose cohort maintained ganaxolone plasma concentrations ≥ 500 ng/ml for 8 hours following treatment initiation, but patients in the low- and medium-dose cohorts did not. Ex. 1016, 4, 8. And the '100 patent specification itself teaches that different dosing regimens lead to different results. Many of the 35 g/day of Captisol® protocol patients did not maintain plasma levels above 500 ng/ml for 8 hours. And while their SE was suppressed for a time, the seizures recurred once the plasma levels fell below 500 ng/ml. *See supra* Section VII.A. Indeed, in the prior proceeding between Petitioner and Marinus, Dr. Sankar, the same expert Petitioner uses here, admitted that "changing the dosing regimen could change the results" and that the plasma concentrations from the Phase 2 trial would not have been reached but for the specific bolus and continuous infusion regimen. Ex. 2036, 53:24-54:9; 55:1-10; 56:9-15; 65:1-66:10, 67:22-68:12. This is a far cry from his position here that

dosing regimens in the prior art *necessarily* achieve the results recited in the claims.

In the cases that Petitioner relies on, the inherency doctrine was invoked with respect to claimed *formulations*, where the formulations were the same as the prior art and the administration of those formulations necessarily exhibited the claimed parameters. In *Persion Pharms. LLC*, there was “no dispute that the [prior art] formulation, which was identical to the [claimed formulation] necessarily exhibited the claimed parameters” when “an unadjusted dose of the [prior art] formulation” was administered “to hepatically impaired patients.” *Persion Pharms. LLC*, 945 F.3d at 1191. In *Santarus, Inc.*, the claimed PK values were “an inherent property *of the formulation*.” *Santarus, Inc.*, 694 F.3d at 1354 (emphasis added).

Here, Petitioner does not argue that the claimed PK values were an inherent property of a claimed formulation. Rather, Petitioner argues that “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,” without identifying *which* doses or dosing regimens of ganaxolone a POSA would have selected (other than, generically, those “described in the prior art that provide an effective amount of ganaxolone to suppress SE”), or any evidence of *why* the resulting PK values would necessarily

have occurred. Pet., 42. Petitioner's expert, Dr. Sankar, does not identify which doses/dosing regimens or why, either, opining only that "a POSA would have known that the ganaxolone plasma concentration levels recited in claim 1 necessarily flow from the dosing method disclosed by NCT03350035 and at the dosage ranges disclosed in the prior art, including in During." Ex. 1002, ¶ 115. And, as discussed above, that argument is contrary to the evidence, which shows that the plasma concentration levels and durations recited in the claims do not necessarily result from the dose ranges in the art (e.g. the low dose cohort in the Phase 2 trial).

Furthermore, Patent Owner provided (and the Office has considered) evidence of the unexpected results flowing from the claimed methods. *See* Sections III.C and XI. As the Examiner correctly determined, those results are convincing evidence of the non-obviousness of the Challenged Claims, which all include the limiting "wherein" clause. *See* Ex. 1029, 249-250.

IX. INSTITUTION ON THE BASIS OF GROUND 2 SHOULD BE DENIED

Petitioner's Ground 2 relies on During (Ex. 1003) in combination with Tsai 2016 (Ex. 1006), Clinical Leader 2016 (Ex. 1007), and Tsai 2017 (Ex. 1005), each of which relate to Patent Owner's Phase 1 Clinical Trials (collectively, the "Phase 1 CTR References"). Ex. 1005, Ex. 1006, Ex. 1007.

A. The Phase 1 CTR References

1. Tsai 2016 (Ex. 1006)

Tsai 2016 (Ex. 1006) contains “abstract S208 in Volume 80, Supplement 20 of the 2016 Annals of Neurology Journal” (at page 77-78 of Ex. 1006) and has the earliest asserted publication date of the Marinus Phase 1 CTR references (October 14, 2016). Pet., 30.

Petitioner asserts that “Tsai 2016 describes the *results* of a Phase 1 study . . .” (Pet., 31 (emphasis added)), but this is incorrect. Tsai 2016 contains no results at all, only statements about what “will be” done in the study, noting that “[r]esults will be presented at the time of the meeting.” Ex. 1006, 77-78. Tsai 2016 discusses no dose levels or target plasma concentrations, even prophetically. *Id.*

2. Clinical Leader 2016 (Ex. 1007)

Clinical Leader 2016 (Ex. 1007) is a printout of a news article titled “Ganaxolone Phase 1 Data Supports Progressing To Phase 2 In Patients With Status Epilepticus,” subtitled “*Data Presented at the 141st Annual Meeting of the American Neurological Association.*” It states that “[e]very dose regimen of ganaxolone IV administered [to healthy patients], either bolus or continuous infusion, was generally safe and well tolerated and reached targeted dose levels in a short period of time,” that “[g]anaxolone IV plasma concentrations were generally proportional to the administered dose, with potential anti-convulsant

plasma concentrations achievable with a bolus dose,” and that “the continuous infusion of ganaxolone IV achieved the targeted PK levels.” Ex. 1007, 1.

It does not disclose what the doses were, what plasma concentrations were reached, or what plasma concentrations would be efficacious.

3. Tsai 2017 (Ex. 1005)

Tsai 2017 is abstract P72 at pages 74-75 in Ex. 1005, which is titled “the Final Programme of the 6th London-Innsbruck Colloquium on Status Epilepticus and Acute Seizures.” It states that “[ganaxolone] administered as a rapid IV bolus or bolus with continuous infusion was generally safe and well tolerated,” and that “there were no safety issues that limit getting to a potentially efficacious plasma concentration in a short period of time.” Ex. 1005, 75. It also states that “[p]redictable PK from this study enables dosing guidance for [ganaxolone] IV.” *Id.*

Like the other Phase 1 CTRs, it does not disclose what the doses were, what plasma concentrations were reached, or what plasma concentrations would be efficacious.

B. Petitioner Has Not Shown a Reasonable Likelihood that the Claims Are Obvious Over During Plus the Phase 1 CTR References

As an initial matter, Petitioner relies on an incorrect claim construction that reads the PK parameters of the “wherein” clause out of the claim. *See* Section V.

Neither During nor any of the Phase 1 CTR References (or any combination thereof) teach or suggest “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 hours to about 12 hours.” In fact, as noted above in Section VIII.A, During teaches away from any plasma concentrations above 500 ng/ml. *See* Ex. 1003 at 15:12-28. Ground 2 can be summarily dismissed on that ground alone.

Unlike for Ground 1, Petitioner offers no arguments at all under the correct claim construction. To the extent that its inherency arguments from Ground 1 (*see* Section VIII.C) were applied here, however, they would fail for the same reasons.

Petitioner’s Ground 2 thus fails for at least the same reasons that Ground 1 fails—the combination of references does not teach each and every claim of the invention (including the PK language in the “wherein” clause, which is required by all of the challenged claims). Furthermore, Patent Owner provided (and the Office considered) evidence of the unexpected results flowing from the claimed methods. *see* Sections III.C and XI. As the Examiner correctly determined, those results are convincing evidence of the non-obviousness of the Challenged Claims.

Furthermore, Petitioner asserts that Tsai 2017 (Ex. 1005) “was available no later than April 6, 2017,” but provides no evidence to establish that Tsai 2017

qualifies as a printed publication for the purposes of § 102(a)(1) other than simply stating that it does. Pet at 29, 30, 31. Therefore, Petitioner has failed to discharge its burden to establish that Tsai 2017 is a printed publication. *See In re Klopfenstein*, 380 F.3d at 1348; *Hulu, LLC*, IPR2018-01039, Paper 29 at 13.

There is no indication in Tsai 2017 that it was published “no later than April 6, 2017.” At most, Tsai 2017 refers to the dates of the Colloquium itself (“6-8 April 2017”), (Ex. 1005 at 1, 4, 6, 7-12, 80, 83, 84) which is insufficient to prove publication of Ex. 1005. Tsai 2017 does not include, and Petitioner has not provided, for example, any information regarding whether Tsai 2017 was available at or distributed as a standalone article at the Colloquium. Even if it was available, Petitioner has not demonstrated that it was published. Publication turns on whether the reference was disseminated or otherwise made available to persons of ordinary skill in the art exercising reasonable diligence. *In re Klopfenstein*, 380 F.3d at 1348. Petitioner does not even assert that Tsai 2017 was disseminated in any way, let alone provide any evidence that it was, even though author Julia Tsai (*see* Ex. 1005 at 26, 74) is now Petitioner’s own Senior Vice President of Clinical Development. Ex. 2021.

X. DR. SANKAR’S TESTIMONY (EX. 1002) SHOULD BE GIVEN NO WEIGHT

In addition to all the bases for denial of institution discussed above,

Petitioner cannot show a reasonable likelihood that any of the Challenged Claims are obvious because the declaration of its expert should be given no weight. First, all Dr. Sankar's opinions regarding unpatentability are based on an improper construction of the Challenged Claims, which reads out the PK limitations in the "wherein" clause (as described in Section V). Ex. 1002, 21-23 (claim construction), 39-74 (opinions on obviousness). Dr. Sankar's testimony should be disregarded on that basis.

Second, Dr. Sankar's testimony lacks any credibility, given his about-face from PGR2023-00020, where he was defending the validity of Ovid's own patent. In PGR2023-00020, Dr. Sankar's opinions that the claims of During (Ex. 1003), which he uses as his primary reference here, are not invalid conflict with his obviousness opinions here.

Claims 25-31 of During, as described in Section VIII.A, recite treating SE by administering ganaxolone in certain daily doses (in mg/day). They do not recite any particular dosing regimen or any particular efficacy. Previously, Dr. Sankar opined that those claims would not have been obvious over Zhang (Ex. 2012) alone or in combination with other Marinus prior art, including the announcement of Marinus's Phase 2 clinical trial. Ex. 2020, 41-67. Dr. Sankar opined that a POSA would not have expected ganaxolone to "treat SE," to "provide improvement to a patient after administration for more than 8 hours," or to treat SE

“using the dose ranges” recited in During’s claims 25-31. Ex. 2020, ¶¶ 89, 124, 143.

Yet now, Dr. Sankar considers it a matter of “routine optimization” for a POSA to have arrived at the Challenged Claims that are much more specific about plasma levels and duration than the claims of During that he previously defended. The Challenged Claims require “an intravenous bolus plus continuous infusion” even under Petitioner and Dr. Sankar’s improper claim construction. And, as described in Section V, the Challenged Claims also require that the effective amount *both* 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.” The claims of the ’817 patent (During, Ex. 1003) require at most a total daily amount of ganaxolone, but do not specify any particular dosing regimen or plasma concentrations.

Strikingly, he draws his conclusions as to the obviousness of the Challenged Claims starting from During (Ex. 1003)—prior art that teaches far less than Zhang (Ex. 2012), the prior art he criticized in his earlier opinion. *See* VIII.A. The additional references in Grounds 1 and 2 add nothing to the prior art to have made it any more “routine” for a POSA to have arrived at the Challenged Claims. *Compare* Ex. 1002, 39-65 to Ex. 2020, 55-60. It is unclear why, then, Dr. Sankar’s opinion has reversed.

Dr. Sankar even reverses his position on the very same “unexpected results” that he opined on in PGR2023-00020. There, he viewed Marinus’s Phase 2 trial results as demonstrating “unexpected results” of During’s claims 22 and 25-31 over Zhang (alone or in combination). Ex. 2020, 41-46. Again, During’s claims are very broad (reciting either no dose amount at all, or simply a total daily dose without any further requirement as to dosing regimen). Yet, now Dr. Sankar views the very same Phase 2 trial results—the unexpectedness of which is tied to Marinus’s specific bolus plus continuous infusion dosing regimens that are not described or claimed in During—as being entirely expected “in view of During’s disclosure of similar doses of ganaxolone to treat SE . . . that would *inherently* reach the same ganaxolone plasma concentration that [Marinus] describe[d] as unexpected.” Ex. 1002, ¶¶ 191-193. But Dr. Sankar himself admitted that these plasma concentrations would not have been reached but for the bolus and continuous infusion regimen that Marinus described and claimed (but that During does not). Ex. 2036, 53:24-54:9; 55:1-10; 56:9-15; 65:1-66:10. He provides no explanation here as to why his current testimony conflicts with his previous testimony.

In sum, Dr. Sankar does not provide any underlying facts or data to support this wholesale change in opinion. His testimony is entirely void of credibility and the Board should not credit it at all. *See, e.g., Xerox Corp., v. Bytemark*, IPR2022-

00624, Paper 9 at 15-16 (August 24, 2022) (Precedential). As in *Xerox*, Dr.

Sankar's unsupported testimony is "particularly problematic" here, because it is provided "not simply to provide a motivation to combine prior-art teachings, but rather to supply a limitation missing from the prior art." *Id.* at 16.

XI. DISCRETIONARY DENIAL IS WARRANTED

The Board has the authority to decline to institute post grant review when "the same or substantially the same prior art or arguments previously were presented to the Office." 35 U.S.C. § 325(d). In evaluating whether to exercise its discretion to deny institution under § 325(d), the Board employs a two-part framework: (1) whether the same or substantially the same art or arguments were presented to the patent office; and (2) whether the petitioner has shown that the Office erred in a manner material to the patentability of challenged claims.

Advanced Bionics, LLC v. Med-El Elektromedizinische Geräte GmbH, IPR2019-01469, Paper 6, 8 (PTAB Feb. 13, 2020) (Precedential).

A. Ovid Presents Substantially The Same Art or Arguments That The Office Already Considered

Petitioner's primary reference, During (Ex. 1003), discussed in Section VIII.A above, is completely cumulative of the more fulsome Zhang reference, art that the Office not only considered, but also issued an obviousness rejection over.

The During PCT, which has the same specification as During, was before

the office during prosecution of the '569 Application (which issued as the '100 patent. While, as Ovid noted, the Examiner did not make a rejection over the During PCT during examination, the Examiner *did* make a rejection over US 2016/0228454 (“Zhang US” (Ex. 2019), Patent Owner Marinus’s own prior patent application). Ex. 1029, 190-191. Zhang US (Ex. 2019) is the equivalent of Zhang (Ex. 2012). Zhang was cited by Marinus (as Petitioner) in PGR20023-00020 as rendering During’s claims anticipated and/or obvious. *See* Ex. 2017, 4.

As described in Section VIII.A, aside from claims 24-31 (which are not prior art, as discussed above, and which Zhang anticipates, as described in PGR2023-00020, *see* Ex. 2017, 57-59), Petitioner relies on just a handful of passages from During to make its obviousness case: three that contain laundry lists of diseases (2:13-22, 4:6-16, 10:27-42); two that either contain laundry lists of doses of “allosteric modulator[s]” untethered to either ganaxolone or SE (6:51-54 and 7:40-8:8); and one that recites administering ganaxolone “parenterally in escalating doses as soon as possible after the onset of seizures” (8:42-44). Only column 8, lines 11 to 34, references any doses for “status epilepticus” and “ganaxolone” specifically, but only in terms of mg/kg or flat doses—not any specific dosing regimen. Petitioner also relies on During’s Example 3, which shows results of administering ganaxolone intraperitoneally to a rat experiencing chemically induced SE.

None of these passages teach a bolus and continuous infusion for dosing, let alone the claimed plasma concentrations. A comparison of these passages with the teachings of Zhang (in particular, Zhang’s “Methods of Treatment” section at paragraphs [0069]-[0089] and Example 8 at paragraphs [0117]-[0136]) confirms that During is completely cumulative of (and even less relevant) than what the Examiner already considered:

Passage in During	Exemplary Teachings in Zhang (emphasis added)
2:13–22 “Methods are provided for treatment of . . . epileptic disorders including . . . status epilepticus . . .”	[0069] “The disclosure includes methods of treating <i>status epilepticus</i> , refractory status epilepticus, super-refractory status epilepticus, PCDH19 female pediatric epilepsy, and other seizure disorders comprising <i>administering</i> an effective amount of the substituted β -cyclodextrin- <i>ganaxolone injectable formulation to a patient suffering from any of these seizure disorders.</i> ”
4:6-16 “Described herein are methods of treating epileptic disorders including . . . status epilepticus . . . “	
10:27-42 “The methods described herein may also be effective in subjects experiencing . . . status epilepticus. Accordingly, in embodiments, the disclosed methods are used to treat subjects that would otherwise be resistant to one or more conventional therapies.”	
6:51-54 “For example, dosages may include amounts of an allosteric modulator or a pharmaceutically acceptable salt	[0074] “Methods of treatment include treating a patient suffering from seizures . . . by administering a single injection (bolus

thereof in the range of about, e.g., 1 mg to 30 mg,”	dose) of a substituted β -cyclodextrin-ganaxolone injectable formulation.
7:40-8:8 “In embodiments, a patient can be administered an allosteric modulator in an amount of, e.g., [a laundry list of mg/day ranges from 10 mg to 25 mg/day on the low end to 1975 mg to 2000 mg/day on the high end], ”	The single injection may be administered intramuscularly or intravenously. The dose of the single injection may be from about 1 mg/kg to about 20 mg/kg . . . Methods of treatment also include administering multiple injections . . . over a period of 1 to 10 days . . . at intervals of 1 to 24 hours . . . Dosing schedules [include injecting] every 1 hr, 2 hrs, 4 hrs, 6 hrs, 8 hrs, 12 hrs, or 24 hrs . . . Dosing schedules [include injecting] for 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 days”
8:11-34 “In embodiments, 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. Ganaxolone or a pharmaceutically acceptable salt thereof can be administered in doses ranging from 10 mg/kg to 40 mg/kg, e.g., [laundry list within that range]. In embodiments, ganaxolone doses can be, e.g., [flat doses from 50 mg to 2000 mg].	[0075] “Methods of treatment include treating a patient suffering from seizures . . . by administering one or more bolus doses of 1 to 10 days as described in the preceding paragraph . . . followed by an intravenous infusion of [the formulation] . . . “
8:42-44 “In embodiments, ganaxolone or a pharmaceutically acceptable salt thereof can be administered parenterally in escalating doses as soon as possible after the onset of seizures.”	[0080] “In certain embodiments the ganaxolone . . . formulation is administered intramuscularly or intravenously.”
Example 3 (35:31-38:45) “Evaluation of the Ability of Allopregnanolone, Ganaxolone, and Gaboxadol to Block Benzodiazepine-	Example 8 (¶¶ [0117]-[0136]) “Ganaxolone Effect on Pilocarpine-Induced Status Epilepticus in Rats”

Resistant Status Epilepticus.”	
Claims 24-31 (40:18-33)	Not prior art and anticipated by Zhang (<i>see, e.g.</i> , Ex. 2017, 57-59; Ex. 2012, ¶¶ [0074], [0084], [0085]).

Patent Owner (then Applicant) overcame the 103 rejection over Zhang by amending claim 1 to recite “wherein the effective amount “is administered as an intravenous bolus plus continuous infusion to produce and maintain a ganaxolone plasma concentration of ~~at least~~ about 500 ng/ml to about 1000 ng/ml for ~~at least~~ about 8 hours to about 12 hours.” Ex. 1029, 206. Along with that amendment, Applicant argued that “[t]he claimed method differs from the disclosure of the Prior Art by requiring the ganaxolone plasma concentration to be maintained at about 500 ng/ml to about 1000 ng/ml for a short period of time of about 8 hours to about 12 hours,” and provided evidence that the claimed method “unexpectedly ‘breaks’ SE with exposure to ganaxolone for a period of time that was much lower than expected,” which “beneficially results in reduced drug exposure and improved safety.” Ex. 1029, 206, 213-214; *see also* Section III.C.

Petitioner does not rely on During (or any of the Ground 1 or 2 references) for teaching “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 hours to about 12 hours.*”

Rather, Petitioner attempts to fill in that gap by arguing for a claim construction that reads out the PK parameters of the “wherein” clause (so that the prior art need only teach or suggest a method to “suppress SE”), which, as discussed above in Section V, is an incorrect claim construction, and arguing “inherency” and “routine optimization.” Pet., 37-53.

The only alleged “additional evidence” that the Office did not consider are the “disclosure[s] of the Phase 1 or Phase 2 study protocols and data” (i.e., the additional references cited in Grounds 1–3) and “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.” Pet., 61-62. But nothing in any of the Ground 1 or Ground 2 references adds anything beyond what the Examiner already considered to be material to the Challenged Claims (and, as discussed in Section VII above, the additional Ground 3 references are not prior art).

In Ground 1, Petitioner relies on NCT03350035 (Ex. 1004) as “describ[ing] 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.’” Pet., 38. Ex. 1004 does not include any plasma concentration levels, or any results at all. NCT03350035 does not teach the limitations of the

Challenged Claims missing from both Zhang and During. There is nothing new and material to consider here over what the Office already has.

In Ground 2, Petitioner relies on Tsai 2016 (Ex. 1006), Clinical Leader 2016 (Ex. 1007), and Tsai 2017 (Ex. 1005). Tsai 2016 and Tsai 2017 are cited as “describ[ing] 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.” Pet., 48. From Tsai 2017 (Ex. 1005), Petitioner cites “the Phase 1 pharmacokinetic results as showing that ganaxolone plasma concentrations were generally proportional to the administered dose,” the conclusion that “[ganaxolone] 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 [ganaxolone] IV.” *Id.* Petitioner cites “[s]imilar results” as were presented in Tsai 2017. *Id.* But these references are in healthy volunteers and do not speak to effective amounts of ganaxolone and what plasma levels and durations would be effective to treat SE. Thus, they also do not teach the limitations of the Challenged Claims missing from both Zhang and During and there is nothing new and material to consider here over what the Office already had.

The only references that Petitioner asserts as teaching *any* portion of the claim limitations that are missing from the prior art the Office already considered are the Phase 2 CTR references cited in Ground 3 (Exhibits 1010, 1011, 1008, and

1009). Pet. 54 (alleging that “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.”). But, as described in Section VII, those references are not prior art.

B. Ovid Fails to Show Material Error

The only alleged “error” that Petitioner asserts is that the Examiner “failed to recognize that the ganaxolone plasma concentration limitations recited in the ’100 patent are non-limiting.” Pet., 61. But this was no error, as the ganaxolone plasma concentrations recited in the Challenged Claims are plainly limiting. *See* Section V, above. Furthermore, the Examiner properly concluded that the claims were not obvious over the prior art, at least because of the evidence of the unexpected safety and efficacy of the claimed methods (e.g., as noted above and described in Sections III.A and III.C).

Discretionary denial under § 325(d) is thus appropriate for Grounds 1 and 2. To institute would be a waste of the Board’s time and resources. *See SAS Inst., Inc. v. Iancu*, 584 U.S. 357, 365 (2018); *Chevron Oronite Co. LLC, v. Infineum USA L.P.*, IPR2018-00923, Paper 9 at 10-11 (Nov. 7, 2018) (Informative); *Deeper, UAB v. Vexilar, Inc.*, IPR2018-01310, Paper 7 at 42-43 (Jan. 24, 2019).

XII. CONCLUSION

In sum, Ovid has not demonstrated that it is more likely than not that the

Challenged Claims would have been obvious. Institution should be denied.

Respectfully submitted,

Dated: June 26, 2024

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CERTIFICATION UNDER 37 C.F.R. § 42.24

Under the provisions of 37 CFR § 42.24(d), the undersigned hereby certifies that the word count for the foregoing Patent Owner's Preliminary Response totals 13,858, which is less than the 14,000 allowed under 37 CFR § 42.24(b)(1).

Dated: June 26, 2024

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e)(4), the undersigned certifies that on June 26, 2024 a complete and entire copy of this Patent Owner's Preliminary Response and its supporting exhibits were provided via email, to the Petitioner by serving the email correspondence addresses of record as follows:

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