UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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MARINUS PHARMACEUTICALS, INC.,
Petitioner

v.

OVID THERAPEUTICS, INC.,
Patent Owner

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Case PGR2023-00020
Patent 11,395,817

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# PETITION FOR POST GRANT REVIEW OF U.S. PATENT NO. 11,395,817

**TABLE OF CONTENTS**

## TABLE OF AUTHORITIES

### Cases



### Statutes

**Other Authorities**



**Rules**

## EXHIBITS

| Petitioner Exhibit Number | Exhibit Description |
|---|---|
| 1001 | U.S. Patent No. 11,395,817 to Ovid Therapeutics, Inc. "the '817" or "the '817 patent" |
| 1002 | Excerpts from the File History of the '817 Patent |
| 1003 | Declaration and Curriculum Vitae of Dr. Michael A. Rogawski ("the Rogawski Declaration") |
| 1004 | Reddy and Kuruba, "Experimental Models of Status Epilepticus and Neuronal Injury for Evaluation of Therapeutic Interventions," *Int. J. Mol. Sci.* 14:18284–318 (2013) ("Reddy" or "Reddy & Kuruba") |
| 1005 | Seinfeld et al., "Status Epilepticus," in Additional Perspectives on Epilepsy: The Biology of a Spectrum Disorder (Cold Spring Harbor Laboratory Press, 2016, ed. Gregory L. Holmes and Jeffrey L Noebels) ("Seinfeld") |
| 1006 | Imtiyaz et al., "The Evolution of the Pilocarpine Animal Model of Status Epilepticus," *Heliyon* 6:e04557 (2020) ("Imtiyaz") |
| 1007 | Turski, et al., "Review: Cholinergic Mechanisms and Epileptogenesis. The Seizures Induced by Pilocarpine: A Novel Experimental Model of Intractable Epilepsy," *Synapse* 3:154–71 (1989) ("Turski") |
| 1008 | Kokate et al., "Neuroactive Steroids Protect Against Pilocarpine- and Kainic Acid-induced Limbic Seizures and Status Epilepticus in Mice," *Neuropharmacology*, 35(8):1049–56 (1996) ("Kokate") |
| 1009 | WIPO Publication No. WO 2016/127170 ("Zhang") |
| 1010 | WIPO Publication No. WO 2007/062266 ("Shaw") |

| | |
|---|---|
| 1011 | 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") |
| 1012 | 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_abstraclistingdigi_v1424 ("AAN Meeting Brochure") |
| 1013 | 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") |
| 1014 | 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") |
| 1015 | Declaration of Michael Saporito |
| 1016 | Saporito, "Ganaxolone Administered IV Blocks Experimental Status Epilepticus," "Data Blitz" Presentation, Aril 20, 2016, at the 2016 AAN Annual Meeting ("Saporito Data Blitz Slides") |
| 1017 | 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") |

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|---|---|
| 1018 | Trinka et al., "A definition and classification of status epilepticus—Report of the ILAE Task Force on Classification of Status Epilepticus." *Epilepsia*, 56(10):1515-1523 (2015) ("Trinka") |
| 1019 | 2016 AAN Annual Report |
| 1020 | 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 6th London-Innsbruck Colloquium on Status Epilepticus and Acute Seizures April 6–8, 2017, Salzburg, Austria ("Tsai") |
| 1021 | Drug Development and Review Definitions, August 20, 2015, Available at: https://www.fda.gov/drugs/investigational-new-drug-ind-application/drug-development-and-review-definitions |
| 1022 | 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-Trial-for-Ganaxolone-IV/default.aspx ("June 22, 2016, Press Release" or "Marinus's Phase I Press Release") |
| 1023 | U.S. Patent No. 10,799,485 |
| 1024 | U.S. Patent No. 10,603,308 |
| 1025 | U.S. Patent No. 10,363,246 |
| 1026 | Excerpts from the File History of US Patent No. 10,603,308 |
| 1027 | Excerpts from the File History of US Patent No. 10,799,485 |
| 1028 | Carter et al., "Characterization of the Anticonvulsant Properties of Ganaxolone (CCD 1042: 3α-Hydroxy-3β-methyl-5α-pregnan-20-one), a Selective, High-Affinity, Steroid Modulator of the γ-Aminobutyric $Acid_A$ Receptor," *The Journal of Pharmacology and Experimental Therapeutics*, 280(3):1284–95 (1997 |

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| 1029 | Saporito et al., Intravenous Administration of Ganaxolone Attenuates Electroencephalographic Seizures in a Diazepam Resistant Model of Status Epilepticus, *Neurobiology*, 86 (16 supplement), Abstract, published April 4, 2016 ("Saporito A2") |
| 1030 | Saporito et al., Ganaxolone Administered Intravenously Prevents Behavioral Seizures and Promotes Survival in the Rat Lithium-Pilocarpine Model of Status Epilepticus, *Neurology* 86 (16 Supplement), Abstract, published April 4, 2016 ("Saporito A1") |
| 1031 | Chez, "Ganaxolone Therapy Improves Interictal EEG and Seizure Control in Lennox Gastaut Syndrome in Patients with PCDH19 and CDKL5," *Annals of Neurol*. 80 (suppl 20), S326 published October 26, 2016. |

## TABLE OF ABBREVIATIONS

| Abbreviation | Term |
|---|---|
| "Petitioner" or "Marinus" | Marinus Pharmaceuticals, Inc. |
| "Patent Owner" or "PO" or "Ovid" | Ovid Therapeutics, Inc. |
| "PGR" | Post Grant Review |
| "the Challenged Claims" | Claims 1–31 of the '817 Patent |
| "AAN" | American Academy of Neurology |
| "CDD" | CDKL5 Deficiency Disorder |
| "CNS" | Central Nervous System |
| "CSE" | Convulsive Status Epilepticus |
| "EEG" | Electroencephalogram |
| "FDA" | U.S. Food and Drug Administration |
| "IDS" | Information Disclosure Statement |
| "IV" | Intravenous |
| "POSA" | Person of Ordinary Skill in the Art |
| "SE" | Status Epilepticus |

## I. INTRODUCTION

Marinus and Ovid are both companies involved in the research and development of treatments for various epileptic disorders. Whereas Marinus has focused its research and clinical studies on a drug called ganaxolone, Ovid has focused its clinical work on other drugs. Ovid began prosecuting its provisional applications with disclosure and claims related to ***gaboxadol*** for use in any epileptic disorder under the sun. Then, through continuations and claim amendments, Ovid was able to capture claims covering a different drug—ganaxolone—for a specific indication—status epilepticus ("SE"). The problem for Ovid is that Marinus had long been studying and publishing on ganaxolone and its use to treat SE.

Prior to Ovid's earliest claimed priority date, Marinus had done much with ganaxolone. Two of Marinus's own patent applications related to its ganaxolone program, including for the use of ganaxolone in the treatment of SE, had published: the first, WO 2007/062266 A2 ("Shaw"), in 2007 and the second, WO 2016/127170 Al ("Zhang"), on August 11, 2016, the same day Ovid's first provisional application was filed. Marinus had also received orphan drug designation for ganaxolone for the treatment of SE, and had begun its Phase I clinical trial. In a series of publications and presentations (again, before Ovid's earliest priority date), Marinus disclosed pre-clinical data demonstrating

ganaxolone activity in a rat lithium-pilocarpine model of SE, including in two posters presented at the 2016 American Academy of Neurology ("AAN") Annual Meeting ("Saporito P1" and "Saporito P2").

Ovid, for its part, has not carried out any clinical trials of ganaxolone for SE or for any other disorder. What Ovid did do was, after seeing Marinus's success with ganaxolone, start targeting claims to Marinus's invention.

As a result of Ovid's maneuverings, and the limited prosecution related to the later ganaxolone for SE-directed claims, Ovid was able to obtain claims in the '817 patent that, for the reasons described in this petition, are either, on the one hand, *prima facie* anticipated and/or obvious over the prior art, or, on the other hand, enabled only by what ***Marinus*** (the company actually working on ganaxolone) disclosed and claimed first.

Ovid's filings are too little, too late. Marinus's numerous publications render the Challenged Claims anticipated and/or obvious. As demonstrated in this petition, in line with constitutional principles and statutory requirements, if anyone is entitled to the Challenged Claims it is Marinus. Not Ovid.

Marinus respectfully submits that PGR should be instituted, and that the Challenged Claims should be canceled as unpatentable.

## II. REQUIREMENTS FOR PGR (37 C.F.R. § 42.204)

### A. Grounds for Standing and PGR Eligibility (37 C.F.R. § 42.204(a))

Marinus certifies that the '817 Patent is available for PGR. This petition is being filed within nine months of July 26, 2022, the date of issuance of the '817 patent. Marinus has not filed a civil action challenging the validity of any claim of the '817 patent and is not barred or estopped from requesting review of the Challenged Claims on the identified grounds. Marinus has not yet been served with any complaint for infringement of the '817 Patent.

### B. Challenge (37 C.F.R. § 42.204(b)) and Relief Requested

Marinus requests PGR of the Challenged Claims on the grounds in the table below and requests that each of the Challenged Claims be found unpatentable. An explanation of how the Challenged Claims are unpatentable under the statutory grounds identified below is provided in the form of a detailed description that follows, showing where each element can be found in the cited prior art, and the relevance of that prior art. Additional explanations and support for each ground is set forth in Ex. 1003, the Declaration of Dr. Michael A, Rogawski, M.D., Ph.D., a practicing neurologist with substantial experience in researching anti-seizure medicines.[1]

[1] Ex. 1003, ¶¶ 1–15.

| Ground | Claims | Basis for Rejection |
|---|---|---|
| **1** | **1–3, 10–17, and 19–31** | Anticipation under 35 U.S.C. § 102 by Zhang (Ex. 1009) |
| **2** | **1–3, 10–17, and 19–31** | Obviousness under 35 U.S.C. § 103 over Zhang |
| **3** | **1–3, 10–17, and 19–31** | Obviousness under 35 U.S.C. § 103 over Zhang and Saporito P1 (Ex. 1013) and/or Saporito P2 (Ex. 1014) |
| **4** | **1–3, 10–17, and 19–31** | Obviousness under 35 U.S.C. § 103 over Zhang, Marinus's Orphan Drug Press Release (Ex. 1011), and Marinus's Phase I Press Release (Ex. 1022) |
| **5** | **4–9 and 18** | Obviousness under 35 U.S.C. § 103 over Zhang and Shaw (Ex. 1010) |
| **6** | **4–9 and 18** | Obviousness under 35 U.S.C. § 103 over Zhang, Shaw, Marinus's Orphan Drug Press Release (Ex. 1011), and Marinus's Phase I Press Release (Ex. 1022) |
| **7** | **1–3, 10–17, and 19–31** | Lack of enablement under 35 U.S.C. § 112 |
| **8** | **4–9 and 18** | Lack of enablement under 35 U.S.C. § 112 |

Zhang (Ex. 1009, a Marinus patent publication discussed in detail in Section VIII.A) is prior art under 35 U.S.C. § 102(a)(2). Zhang is a printed publication of a patent application that was effectively filed at least by February 8, 2016 (its

international filing date), and that published under 35 U.S.C. § 122(b) on August 11, 2016.

Shaw (Ex. 1010, a Marinus patent publication discussed in detail in Section VIII.E) is prior art under 35 U.S.C. §§ 102(a)(1) and 102(a)(2). Shaw is a printed publication of a patent application that was effectively filed at least by November 28, 2006 (its international filing date), and that published under 35 U.S.C. § 122(b) on May 31, 2007.

Saporito P1 (Ex. 1013) and Saporito P2 (Ex. 1014) are both prior art under 35 U.S.C. § 102(a)(1). Saporito P1 and Saporito P2 are posters that were presented publicly in April, 2016, at the American Academy of Neurology ("AAN") Annual Meeting.[2] The AAN Annual Meeting is an annual gathering of thousands of clinicians and researchers interested in potential new treatments for neurological disorders such as SE (including many who fit the description of a POSA, below).[3] One of Marinus's scientists supporting this Petition, Dr. Michael Saporito, presented Saporito P1 and Saporito P2.[4] As Dr. Saporito explains, Saporito P1 was displayed for over nine hours on April 17, and Saporito P2 was displayed for over

[2] Ex. 1015, ¶¶ 4–15.

[3] Ex. 1015, ¶¶ 5–6.

[4] Ex. 1015, ¶¶ 1–3, 9–15.

ten hours on April 19.[5] Attendees were free to view the posters, as well as take pictures and notes while they were on display.[6] Dr. Saporito was personally available to answer questions about the posters during portions of that time, during which he interacted with many meeting attendees who asked questions about the studies described in the posters, took pictures of the posters, and took notes as they were viewing the posters.[7]

In addition to the poster sessions themselves, Dr. Saporito also presented data from the studies described on the posters as part of a "data blitz" during a well-attended Integrated Neuroscience Session on April 20.[8] Following that presentation, as part of the same Session, Saporito Poster 1 was again on display as part of a highly selective "Guided Poster Round" from 3pm to 3:30pm, during which only six other posters were on display.[9] Dr. Saporito discussed the poster

[5] Ex. 1015, ¶¶ 9, 14.

[6] Ex. 1015, ¶¶ 8–15.

[7] Ex. 1015, ¶¶ 8–15,

[8] Ex. 1015, ¶¶ 16–18; *see also* Ex. 1016 (the slides Dr. Saporito presented during this session).

[9] Ex. 1015, ¶ 19–21.

with attendees at that session, which was also well attended.[10]

Because Saporito P1 and Saporito P2 were publicly accessible before the '817's earliest possible priority date of August 11, 2016, they are each printed publications and/or were "otherwise available to the public under 35 U.S.C. § 102(a)(1)." *See In re Klopfenstein*, 380 F.3d 1345, 1348 (Fed. Cir. 2004) ("[t]he statutory phrase 'printed publication' has been interpreted to mean that before the critical date the reference must have been sufficiently accessible to the public interested in the art.").

Marinus's April 15, 2016, Press Release (Orphan Drug Press Release, Ex. 1011) and Marinus's June 22, 2016, Press Release (Phase I Press Release, Ex. 1022) are both prior art under 35 U.S.C. § 102(a)(1). These Press Releases were distributed via GlobeNewswire (https://www.globenewswire.com/) on April 15, 2016, and June 22, 2016, respectively, and also published on Marinus's own website. Like Saporito P1 and P2, Marinus's April 15, 2016 Orphan Drug Press Release and June 22, 2016, Phase I Press Release are printed publications and/or were "otherwise available to the public under 35 U.S.C. § 102(a)(1)."

None of the Grounds require the Board to reach any potential issues related to the priority date for the claims.

[10] Ex. 1015, ¶ 19–21.

## III. BACKGROUND OF THE TECHNOLOGY

### A. Status Epilepticus ("SE")

Seizures are a potentially serious medical condition that afflict millions of people worldwide.[11] A seizure is defined as an abnormal electrical discharge in the brain that causes alteration in consciousness, sensation, and behavior.[12] One of the most common seizure disorders is epilepsy, which is a chronic condition in which patients experience recurrent, unprovoked seizures.[13]

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.[14] Historical definitions of SE were based on seizures being "long enough" to cause damage, which was originally considered to be a seizure episode lasting 30 or 60 minutes.[15]

Before the 2016–2017 timeframe, however, seizures, and in particular, convulsive seizures (seizures that involve repeated, rapid and rhythmic contraction

[11] Ex. 1004 at 18287; Ex. 1003, ¶ 16.

[12] *Id.*

[13] *Id.*

[14] Ex. 1004 at 18287; Ex. 1003, ¶ 17.

[15] Ex. 1005 at 1; Ex. 1003, ¶ 17

of the muscles in the extremities or trunk), that last for five minutes or longer are likely to be prolonged and not resolve on their own.[16] Therefore, intervention at the five minute mark is appropriate.[17]

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.[18] Often, however, the cause is unknown, making the condition even more complicated.[19]

While people with epilepsy may experience SE, SE is not a form of epilepsy.[20] SE is distinct from epileptic conditions such as CDKL5 and PCDH19, which are rare types of genetically based epilepsies.[21] Furthermore, while

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[16] Ex. 1005, 1–2; Ex. 1003, ¶ 18.

[17] *Id.*; *see also* Ex. 1009, ¶ [0001] ("Status epilepticus (SE) is a serious seizure disorder in which the epileptic patient experiences a seizure lasting more than five minutes, or more than one seizure in a five minute period without recovering between seizures.").

[18] Ex. 1006 at 1; Ex. 1005 at 2; Ex. 1003, ¶ 19.

[19] Ex. 1005 at 2; Ex. 1003, ¶ 19.

[20] Ex. 1003, ¶ 20.

[21] *Id.*

treatments for most epilepsies (including CDKL5 and PCDH19) are intended to *prevent* the occurrence of seizures, treatments for SE are intended to *stop (terminate)* the prolonged or repeated seizure condition that the patient is experiencing.[22] While some epilepsy patients (e.g., CDKL5 or PCDH19 epilepsy patients) may also experience SE, they then would require additional treatment to stop the SE, as is the case generally for SE.[23]

SE is considered a life-threatening medical emergency and, as such, it is generally treated in a hospital.[24] The prolonged seizures that are characteristic of SE can cause substantial damage to the brain and lead to a high rate of mortality ranging from 7–39%, depending on the age and other medical conditions of the patient.[25]

SE can be characterized by behavioral manifestations and/or electrophysiological correlates.[26] The behavioral manifestations evolve over

[22] *Id.*

[23] *Id.*

[24] Ex. 1003, ¶ 21.

[25] Ex. 1005 at 7; Ex. 1003, ¶ 21..

[26] Ex. 1003, ¶ 22; *see also* Ex. 1017, Ex. 1018.

time.[27] In the case of convulsive SE, this includes generalized tonic-clonic movements of the extremities and impaired mental status.[28] The electrophysiological correlates are detectable on an electroencephalogram (EEG) recording.[29]

Even where not fatal, SE can cause significant damage to the brain, which may be associated with cognitive and other neurological impairments.[30] Currently, first-line therapies for SE include benzodiazepines such as lorazepam and diazepam.[31] 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.[32] Second-line therapies, including phenytoin, fosphenytoin, levetiracetam, or valproic acid, can be administered if the first-line therapies fail.[33] Unfortunately, the second-line therapies may not work

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[27] *Id.*

[28] *Id.*

[29] *Id.*

[30] Ex. 1004 at 18284; Ex. 1003, ¶ 23.

[31] Ex. 1004 at 18287; Ex. 1003, ¶ 23.

[32] *Id.*

[33] *Id.*

either, which puts patients in significant danger of worse outcomes, including death.[34] Indeed, up to 40% of SE is resistant to many standard treatments, referred to as "refractory" SE.[35] Because of the serious risks associated with treatment failures, the development of new treatments that can address SE is critical.[36]

### B. The Use of Animal Models for SE

Developing potential treatments for SE, in some cases, relies on the use of animal models that can serve as a basis for predicting the results in humans.[37] When a potential treatment is identified, it may be advanced to human clinical trials, which are required for regulatory approval.[38] In the selection of an animal model to identify treatments for SE, researchers consider the extent to which the model mimics the various clinical features of SE in humans.[39] One desirable characteristic is that the model exhibits seizures that last longer than 5 minutes, so

[34] *Id.*

[35] Ex. 1004 at 18287; Ex. 1003, ¶ 24.

[36] Ex. 1006 at 1; Ex. 1003, ¶ 24.

[37] Ex. 1006 at 1; Ex. 1003, ¶ 25.

[38] Ex. 1006 at 1–2; Ex. 1003, ¶ 26.

[39] *Id.*

that the seizures satisfy the definition of SE.[40] An additional desirable characteristic is that the model should reproduce the neuropathological injuries that are observed in specific brain regions of patients who have experienced SE.[41] Finally, if the intent is to identify treatments for refractory SE, the model should simulate the pharmacoresistance to certain antiseizure medications that is characteristic of refractory SE.[42]

The rat pilocarpine model, originally developed in the 1980s, is an animal model for SE that is commonly understood to meet those criteria.[43] As explained in the literature, "the pilocarpine model of status epilepticus is a well-established, clinically translatable model that satisfies all the criteria for an animal model of status epilepticus."[44]

In the rat pilocarpine model, rats are typically administered a high dose of pilocarpine by injection, which induces convulsive SE.[45] Within about 30 minutes

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[40] *Id.*

[41] *Id.*

[42] *Id.*

[43] Ex. 1007; Ex. 1006 at 1; Ex. 1004 at 18291–2; Ex. 1003, ¶¶ 27–33.

[44] Ex. 1006 at 1; Ex. 1004 at 18291–2; Ex. 1003, ¶ 27.

[45] Ex. 1004 at 18292; Ex. 1007 at 154; Ex. 1003, ¶ 28.

of dosing, pilocarpine induces convulsive seizures, and those seizures persist over time so that the animals are in a state of SE.[46]

To allow for continuous EEG recording to assess the presence or absence of SE, the rats being evaluated in the pilocarpine model may implanted with electrodes before they are dosed with pilocarpine.[47]

After its initial development, the rat pilocarpine model underwent further refinements to improve its usefulness, and one of those improvements involved the addition of a dose of lithium, resulting in the rat lithium-pilocarpine model.[48] In this iteration of the model, rats are pre-dosed with lithium chloride before the administration of pilocarpine, which allows for the use of a lower dose of pilocarpine that will still induce SE.[49] It may also reduce the time to SE onset and/or increase the frequency of occurrence of SE.[50] The rat lithium-pilocarpine

[46] *Id.*; *see also* Ex. 1006 at 2–3.

[47] Ex. 1004 at 18293; Ex. 1003, ¶ 29.

[48] Ex. 1006 at 3; Ex. 1003, ¶ 30.

[49] *Id.*

[50] *Id.*

model generates the same behavioral and electrographic SE as the pilocarpine model without lithium.[51]

It is well recognized in the field that the rat pilocarpine model, including the rat lithium-pilocarpine model, are translationally relevant model for identifying treatments for SE.[52] This is in part because "studies have found similar electrophysiological and morphological abnormalities in the rat hippocampus of the pilocarpine model of SE … and human SE."[53]

A common use of the model includes administration of test substances at certain time intervals after the onset of SE (e.g., 15 min, 30 min, or 60 min), while monitoring the behavior of the animal and the EEG power in various frequency bands.[54] A statistically significant reduction in the EEG power in the frequency bands in relation to vehicle indicates that a test substance, at the dose administered, is effective in treating SE.[55] Alternatively, if the test substance protects, prevents,

[51] *Id.*

[52] Ex. 1006 at 2; Ex. 1003, ¶ 31.

[53] *Id.*

[54] Ex. 1003 ¶ 32.

[55] *Id.*

halts, or blocks convulsive behavioral seizures, it is considered effective in treating SE.[56]

### C. The Development of Ganaxolone as a Treatment for SE

Ganaxolone is a compound that is currently under development by Marinus for the treatment of SE.[57] Ganaxolone is a synthetic neurosteroid compound that is a CNS-selective $GABA_A$ modulator.[58]

Early on, Marinus had evaluated various dosage forms of ganaxolone, including oral dosage forms, for the treatment of epilepsy.[59] As described in Shaw (Ex. 1010), for example, Marinus measured the blood levels of ganaxolone, administered to six healthy subjects as an oral suspension.[60] Marinus found that it resulted in a "$C_{max}$ of 37 ± 25 ng/ml and an $AUC_{(0\text{-}24)}$ of 184 ± 104 ng*h/ml."[61]

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[56] *Id.*

[57] Ex 1009, ¶¶ [0026]–[0027]; Ex. 1022; Ex. 1003, ¶ 34.

[58] *Id.*

[59] Ex. 1010, ¶¶ [0002], [0174]; Ex. 1003, ¶ 35.

[60] Ex. 1010, ¶ [00546]; Ex. 1003, ¶ 35.

[61] *Id.*

Marinus also sought to develop ganaxolone specifically for treatment of SE.[62] Patients with SE are frequently unconscious and unable to swallow, and, therefore, oral administration may be difficult or impossible.[63] As a result, oral dosage forms are not typically used in the treatment of SE.[64] Rather, the most common route of administration of drugs used in the treatment of SE is intravenous (IV).[65] Accordingly, in Marinus's research on ganaxolone to treat SE, ganaxolone was administered intravenously.[66]

By 2016, Marinus did substantial work using the rat-lithium pilocarpine model to predict the efficacy of IV-administered ganaxolone for SE in humans, had published patent applications, and presented the results of its research at various times, including in the Zhang publication, as well as at the 2016 AAN Annual Meeting.[67]

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[62] Ex. 1011; Ex. 1003, ¶ 36.

[63] Ex. 1003, ¶ 36.

[64] *Id.*

[65] *Id.*

[66] *Id.*

[67] Ex. 1009; Ex. 1010, Ex. 1012, Ex. 1013; Ex. 1014; Ex. 1003, ¶ 34.

The American Academy of Neurology (AAN) is a professional organization, which, at year end in 2016, had 26,000 US members, including 14,000 neurologists and 910 researchers.[68] The 2016 annual meeting where Marinus's posters were presented was held at the Vancouver Convention Center in Vancouver, B.C. and had 11,670 attendees who were able to study the 2,700 poster presentations available for public viewing at the meeting.[69] The Saporito posters were among those on public display and freely available to all 11,670 attendees.[70]

Marinus's research examined the impact of IV-administered ganaxolone on both the electrical (EEG) and behavioral effects of SE.[71] 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.[72] As to the behavioral effects, the research found that IV-administered ganaxolone "halted CSE [convulsive status epilepticus] and produced a dose-dependent reduction in

[68] Ex. 1019 at 19; Ex. 1003, ¶ 37.

[69] Ex. 1019 at 12; Ex. 1003, ¶ 37.

[70] Ex. 1003, ¶ 37.

[71] Ex. 1014; Ex. 1003, ¶ 38.

[72] *Id.*

seizures associated with CSE when administered at 3 different doses over four separate time points after the first observed convulsive seizure."[73] It also promoted survival, measured 24 hours after CSE onset.[74]

Seeing these results in the rat pilocarpine model, persons skilled in the art would have reasonably believed that ganaxolone would show efficacy in treating human SE as well, for the reasons discussed above.[75]

With these animal results in hand, Marinus turned to confirming that ganaxolone is safe and effective for treatment of SE in humans. The FDA had already granted Marinus Orphan Drug Designation for ganaxolone to treat SE on April 15, 2016.[76] In June 2016, Marinus reported that it had dosed the first human patients, healthy volunteers, in a Phase 1 clinical trial for ganaxolone IV.[77] In 2017, Marinus reported results from that Phase I trial, which showed 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

[73] Ex. 1013; Ex. 1003, ¶ 39.

[74] *Id.*

[75] Ex. 1003, ¶ 40.

[76] Ex. 1011; Ex. 1003, ¶ 41.

[77] Ex. 1022; Ex. 1003, ¶ 41.

limit getting to a potentially efficacious plasma concentration in a short period of time."[78] In short, by 2016, Marinus had established and published that ganaxolone shows efficacy in the rat lithium-pilocarpine model for SE, and had gone on to start clinical trials of IV-administered ganaxolone in humans, after FDA granted orphan status to Marinus for ganaxolone as a treatment for SE.

## IV. THE '817 PATENT AND ITS PROSECUTION HISTORY

### A. The '817 U.S. Patent Family

Ovid's '817 patent issued on July 26, 2022, from U.S. Patent Application Serial No. 17/024,127 (the '127 application). The '127 application was filed September 17, 2020, and was examined by Examiner Rei-tsang Shiao.[79] The '817 patent claims priority to provisional applications 62/490,293 and 62/373,589, filed on April 26, 2017, and August 11, 2016, respectively, as well as a number of non-provisional US applications, including: 16/789,709, filed Feb. 13, 2020 (issued on October 13, 2020, as 10,799,485[80]), and 16/447,300, filed June 20, 2019 (issued on

[78] Ex. 1020; Ex. 1003, ¶ 41.

[79] Ex. 1001, cover page.

[80] Examined by Examiner Shiao, with issued claims directed to methods "of treating **PCDH19 related epilepsy** comprising administering to a patient in need

March 31, 2020 as 10,603,308[81]).[82]

### B. The '817 Patent Specification

The '817 patent relates to "[u]se of allosteric modulators and/or gaboxadol for the treatment of epileptic disorders in a subject in need thereof."[83] Among the allosteric modulators are neurosteroids (e.g., ganaxolone, allopregnanolone), benzodiazepines (e.g., midazolam, clobazam, clonazepam, diazepam, lorazepam, flurazepam) and potassium channel openers (e.g., retigabine or flupirtine)."[84] Among the many epileptic disorders disclosed, is SE.[85]

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thereof a pharmaceutical composition comprising **ganaxolone** or a pharmaceutically acceptable salt thereof." Ex. 1023, cover page, 38:33–39:24.

[81] Examined by Examiner Shiao, with issued claims directed to methods "of treating **CDKL5 deficiency disorder** comprising administering to a patient in need thereof a pharmaceutical composition comprising **ganaxolone** or a pharmaceutically acceptable salt thereof wherein the patient is administered up to 1,800 mg of ganaxolone per day." Ex. 1024, cover page, 38:45–39:8.

[82] Ex. 1001, cover page; Ex. 1003, ¶ 42.

[83] Ex. 1001, 2:13–35; *see also* Ex. 1003, ¶ 43.

[84] Ex. 1001, 6:22-66; Ex. 1003, ¶ 44.

[85] Ex. 1001, 2:13–35, 2:45–3:36; Ex. 1003, ¶ 43.

The ’817 patent contains four Examples. The first relates to gaboxadol (not ganaxolone) plasma concentration profiles.[86] The second relates to the assessment of residual effects resulting from gaboxadol (not ganaxolone) administration.[87] The third describes the evaluation of allopregnanolone, ganaxolone, and gaboxadol “for acute anticonvulsive efficacy when administered with escalating doses at 30 min after the onset of status epilepticus” to block benzodiazepine-resistant SE in a rat lithium-pilocarpine model of SE.[88] The fourth is a purely prophetic example describing future studies that could be carried out to “assess the potential for synergistic activity of gaboxadol with either allopregnanolone, ganaxolone, or [lorazepam] against benzodiazepine-resistant status epilepticus in the [rat lithium-pilocarpine model].”[89]

Table 2 and FIGs. 3, 4, 5, 6A, and 6B contain data on ganaxolone for the treatment of SE (administered intraperitoneally in the rat model).[90] For these experiments, rats were administered ganaxolone intraperitoneally 30 minutes after

[86] Ex. 1001, 33:25–34:52; Ex. 1003, ¶ 45.

[87] Ex. 1001, 34:53–35:29; *see also* Ex. 1003, ¶ 45.

[88] Ex. 1001, 35:31–37:15; Ex. 1003, ¶¶ 45–47.

[89] Ex. 1001, 37:17–38:40, Ex. 1003, ¶ 45.

[90] Ex. 1001, 35:31–37:15; Ex. 1003, ¶ 46.

the first observed convulsive seizure.[91] The rats were then observed and scored for seizure severity for two hours post drug administration.[92] Only a single data point, showing that 4 out of 13 rats administered the very highest dose of ganaxolone (20 mg/kg) were protected against further convulsive seizure after 10 min of drug administration, suggest any efficacy for treating SE.[93] At lower doses there was either no protection (0.5, 2, and 5 mg/kg), or the level of protection was not statistically significant (10 mg/kg).[94] The remainder of the data in Example 3 relate to either 24-hour survival (Table 2, Figure 4) or the number of post-treatment seizures (Figure 5).[95]

### C. Prosecution History of the '817 Patent Family

The '817 Patent Family consists of ten published US Patent Applications, of which only four have been issued as patents. Of those four issued patents, one is directed to gaboxadol (10,363,246, Ex. 1025), while three are directed to ganaxolone. The three directed to ganaxolone (the '817 patent, its parent (the '485

[91] *Id.*

[92] *Id.*

[93] Ex. 1001, 36:4–24, Table 2, FIG. 3; Ex. 1003, ¶ 46.

[94] Ex. 1001, Table 2, FIG. 3; Ex. 1003, ¶ 46.

[95] Ex. 1001, Table 2, FIG. 4, FIG. 5; Ex. 1003, ¶ 47.

patent, Ex. 1023), and its grandparent (the '308 patent, Ex. 1024)) are the only three that were examined by Examiner Shiao.

### 1. The Grandparent (the '308)

The '308 patent (Ex. 1024) is the first in the '817 family that Examiner Shiao examined. Upon substantive examination, the claims recited methods "of treating **CDKL5 disorder** comprising administering to a patient in need thereof a pharmaceutical composition comprising **ganaxolone** or a pharmaceutically acceptable salt thereof wherein the patient is administered up to 1,800 mg of ganaxolone per day."[96]

In that application, Examiner Shiao issued both an obviousness rejection and an enablement rejection, in addition to double patenting rejections over Ovid's '246 patent (methods for treating **essential tremor** by administering ***gaboxadol***), '500 application (**ganaxolone**, **CDKL5 disorder**), and '074 application (**ganaxolone**, **CDKL5 disorder**).[97]

With respect to the obviousness rejection, the Examiner indicated that "[t]he difference between instant claims and [the prior art] is that the instant claims are

[96] Ex. 1026, pages 50–56 (June 20, 2019, Preliminary Amendment at 2–3)

[97] Ex. 1026, pages 33–49 (October 8, 2019, Office Action)

silent on the scope of CDKL5 disorders."[98] According to the Examiner, that prior art teaches: 1) "ganaxolone [] used for treating epileptic seizure, infantile spasms," using a dose "from 200 mg to 500 mg by oral administration composition," which "can be formulated as tablet or capsule"; 2) "ganaxolone [] used for treating epileptic seizure, and the dose is from 2 mg to 160 mg in a pediatric subject," where the "composition can be formulated as tablet or capsule;" 3) "a number of disorders or diseases including seizure, epilepsy, regression, or autonomic feature disorder, which are associated with CDKL5 mutation;" and 4) "that CDKL5 mutation cause infantile spasm, early onset seizure and severe mental retardation in patients."[99]

The Examiner indicated that the enablement rejection could "be overcome by incorporation of named diseases or disorders supported by the specification (i.e., see claim 18) into claim 6."[100]

Ovid then amended the claims to recite "CDKL5 deficiency disorder," and also presented Marinus's post-filing clinical data that describe Marinus's clinical trial of ganaxolone for CDKL5 deficiency disorder as evidence of enablement and

[98] Ex. 1026, 42 (October 8, 2019, Office Action at 9)

[99] *Id.*

[100] Ex. 1026, 40 (October 8, 2019, Office Action at 7).

unexpected results.[101]

Based on the amendment and arguments, Examiner Shiao withdrew the enablement and obviousness rejections.[102] Once Ovid pointed out to Examiner Shiao that the '246 is directed to unrelated drugs (gaboxadol, not ganaxolone) and different indications,[103] the double patenting rejection over it was withdrawn.[104] Ovid expressly abandoned the '500 and '074 applications to overcome the remaining double patenting rejections.[105]

### 2. The Parent (the '485)

The '485 patent (Ex. 1023), upon substantive examination, recited methods "of treating **PCDH19 related epilepsy** comprising administering to a patient in need thereof a pharmaceutical composition comprising **ganaxolone** or a pharmaceutically acceptable salt thereof."[106] That application was filed on February 13, 2020, and, on April 17, 2020, Examiner Shiao issued an Office

[101] Ex. 1026, pages 24–32 (October 24, 2019, Response, at 4–5).

[102] Ex. 1026, pages 18–23 (January 2, 2020, Office Action at 2).

[103] Ex. 1026, pages 10–17 (January 10, 2020, Response at 4–5).

[104] Ex. 1026, pages 1–9 (Notice of Allowance at 2).

[105] Ex. 1026, 17 (January 10, 2020, Response at 6).

[106] Ex. 1027, pages 23–31 (February 13, 2020, Preliminary Amendment at 3–5).

Action rejecting the claims for obviousness-type double patenting over Ovid's '246 (methods for treating **essential tremor** by administering ***gaboxadol***) and '308 patents (methods for treating **CDKL5 deficiency disorder** by administering **ganaxolone**).[107] The Examiner did not make any other rejections.[108]

On April 20, 2020, Ovid replied by filing a terminal disclaimer in connection with the '308 patent, but traversed the rejection over the '246 patent for the same reason as in the grandparent application (because the '246 claims recite *gaboxadol*, not ganaxolone).[109]

A notice of allowance was mailed on June 12, 2020, in which the Examiner indicated that the claims were "neither anticipated nor rendered obvious over the art of record, and therefore are allowable," and that "[a] suggestion for modification of a reference to obtain the instant methods of use has not been found."[110] The patent issued on October 13, 2020.[111]

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[107] Ex. 1027, pages 16–22 (April 17, 2020, Office Action at 2–4).

[108] *See* Ex. 1027, generally.

[109] Ex. 1027, pages 9–15 (April 20, 2020, Response at 5).

[110] Ex. 1027, pages 1–8 (Notice of Allowance at 3).

[111] Ex. 1023, cover page.

### 3. The ’817

The ’127 application was filed with twenty claims: one independent claim (claim 1) reciting “a method of treating status epilepticus comprising administering to a patient in need thereof a pharmaceutical composition comprising ganaxolone or a pharmaceutically acceptable salt thereof,” as well as 19 dependent claims reciting administration routes (oral suspension(s) and capsule(s), claims 5, 6, 7, 8, 9, and 18) and dosing timing/amounts/concentrations (claims 2–4, and 7–18), and treatment outcomes (claims 19 and 20).[112] These claims were nearly identical to the claims issued in the parent (10,799,485) except that they recite “status epilepticus” rather than “PCDH19 related epilepsy.”[113] None of these claims were directed to an intravenous dosing format.

On January 6, 2021, before substantive prosecution began, Applicant filed

[112] Ex. 1002, pages 1–6. These claims were not amended during prosecution and issued as claims 1–20 of the ’187 patent (with some numbering changes). *Compare* Ex. 1002, pages 1–6 *to* Ex. 1001 38:48–40:8.

[113] *Compare* Ex. 1001, pages 1–6 to Ex. 1023, 38:33–39:26. In the ’485 patent, all dependent claims depend upon claim 1. In the ’127 application / ’817 patent claims, one of the dependent claims depends from claim 4 as issued.

an IDS citing, among other references, WO2016/127170 to Marinus ("Zhang").[114] On February 8, 2021, third party observations were submitted, citing Zhang, along with seven other publications and a detailed description of how they demonstrated that, well before the earliest possible effective filing date of the '127 application, it was known in the art that ganaxolone can effectively treat SE.[115]

The first and only Office Action, mailed April 4, 2022, included just two rejections—for obviousness type double patenting over the two other Ovid patents that Examiner Shiao had examined (the '308 patent and the '485 patent).[116] Examiner Shiao also returned initialized forms—the five IDSs submitted by the Applicant and the two forms PTO/SB/429 submitted with the third party observations—indicating that all references had been considered as of April 4, 2022.[117]

The Applicant filed terminal disclaimers to obviate the double patenting rejections on April 19, 2022[118], and then, on May 11, 2022, filed a supplemental

[114] Ex. 1002, pages 7–24; *see* Foreign Patent Documents Cite No 1.

[115] Ex. 1002, pages 33–61.

[116] Ex. 1002, pages 86–94.

[117] Ex. 1002, pages 95–124.

[118] Ex. 1002, pages 129–141.

response to introduce new claims 21–31: one independent claim (claim 21) reciting a "method of treating status epilepticus comprising administering to a patient in need thereof a pharmaceutical composition comprising ganaxolone or a pharmaceutically acceptable salt thereof **wherein the pharmaceutical composition is administered intravenously**," as well as 10 dependent claims reciting dosing amounts/concentrations (claims 23–31) and treatment outcomes (claim 22).[119]

A notice of allowance was mailed on June 13, 2022, indicating that claims 1–31 were allowed.[120] The Examiner indicated in the notice of allowance, that "[c]laims 1-31 [of the '127 application] are neither anticipated nor rendered obvious over the record" and that "[a] suggestion for modification of a reference to obtain the instant methods of use has not been found."[121] Ovid made no comments on the Examiner's statement of reasons for allowance.

On June 21, 2022, after the issue fee had been paid, Examiner Shiao

[119] Ex. 1002, pages 142–150. These claims were not amended during prosecution and issued as claims 21–31 of the '187 patent. *Compare* Ex. 1002 pages 148–149 *to* Ex. 1001 40:9–33.

[120] Ex. 1002, pages 160–178.

[121] Ex. 1002, page 165.

returned a new initialed form—the form PTO/SB/429, originally submitted with the third party observations, that listed all eight publications.[122] **The Examiner struck through the previous date of consideration (February 18, 2022), along with references 1 and 4–7, indicating that references 1 and 4–7 had not, in fact, been considered**.[123]

On June 24, 2022, another notice of allowance was mailed, indicating that **claims 1–20** were allowed.[124]

On June 28, updated issue information was mailed,[125] and on June 29, 2022, yet another notice of allowance was mailed, indicating that **claims 1–31** were allowed.[126]

## V. LEGAL STANDARDS

### A. Anticipation

A patent claim is anticipated under 35 U.S.C. § 102 by a prior art reference that discloses every limitation of the claimed invention, either explicitly or

[122] Ex. 1002, pages 179–182, 183–185.

[123] Ex. 1002, page 184; *see also* Section IX.A.

[124] Ex. 1002, pages 186–197.

[125] Ex. 1002, page 198.

[126] Ex. 1002, pages 199–209.

inherently. *In re Gleave*, 560 F.3d 1331, 1334 (Fed. Cir. 2009).

So long as the prior art reference "discloses all of the claim limitations and enables 'the subject matter that falls within the scope of the claims at issue,' the reference anticipates." *Id.* (quoting *Schering Corp. v. Geneva Pharms., Inc.* 339 F.3d 1373, 1380–81 (Fed. Cir. 2003)). The burden to establish the anticipating references as non-enabling rests with Ovid. *C.f. Amgen Inc. v. Hoechst Marion Roussel*, 314 F.3d 1313, 1355 (Fed. Cir. 2003). ("[A] court cannot ignore an asserted prior art patent in evaluating a defense of invalidity for anticipation, just because the accused infringer has not proven it enabled. Like the application in *ex parte* prosecution, however, the patentee may argue that the relevant claimed or unclaimed disclosures of a prior art patent are not enabled and therefore are not pertinent prior art.").

**B. Obviousness**

35 U.S.C. § 103 "forbids issuance of a patent when 'the differences between the subject matter sought to be patented and the prior art are such that the subject matter would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." *KSR Int'l Co. v. Teleflex Inc.,* 550 U.S. 398, 406 (2007). The question of obviousness requires analyzing (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of skill in the art;

and (4) objective evidence of nonobviousness. *Id.*

A reference, even if not an enabling prior art reference for the purposes of anticipation, "can still qualify as prior art in determining obviousness." *In re Antor Media Corp.*, 689 F.3d 1282, 1292 (Fed. Cir. 2012). Thus, a reference that "suggest[s] the possibility of using" the claimed subject matter, "merely without adequate explanation within the reference itself," is enough to render the claimed subject matter obvious. *Allergan, Inc. v. Apotex Inc.,* 754 F.3d 952, 963–4 (Fed. Cir. 2014). Moreover, a "motivation to combine may be implicit in the prior art—silence does not imply teaching away. *Id.* at 964.

### C. Enablement

Unlike a prior art publication, which needs only enable an embodiment or species *encompassed* by Challenged Claims in order to be an enabling anticipatory reference, the Challenged Claims themselves must be enabled across their full scope, without undue experimentation. *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1365 (Fed. Cir. 2008); *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1998).

## VI. LEVEL OF ORDINARY SKILL IN THE ART

A hypothetical person of ordinary skill in the art ("POSA") of the '817 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.

## VII. CLAIM CONSTRUCTION (37 C.F.R. §§ 42.204(B)(3))

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). Claim terms are construed only to the extent necessary to resolve a controversy. *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3D 795, 803 (Fed. Cir. 1999).

For the purposes of this proceeding only, Marinus submits a construction for the term "patient." All remaining terms should be given their plain meaning.

The '817 defines "patient" (used interchangeably with "subject") as "includ[ing], but not limited to, primates such as humans, canines, porcine, ungulates, rodents, poultry, and avian."[127] One such patient within the scope of the

[127] Ex. 1001, 32:65–67; *See also* Ex. 1003, ¶ 67.

Challenged Claims is, therefore, a rat.[128] Another is a human.[129]

## VIII. THE CHALLENGED CLAIMS ARE UNPATENTABLE

For at least the reasons set forth in this petition, the Challenged Claims are unpatentable.[130]

### A. GROUND 1: Zhang Anticipates Claims 1–3, 10–17, and 19–31

Zhang (Ex. 1009) is a Marinus patent publication titled "Intravenous Ganaxolone Formulations and Their Use in Treating Status Epilepticus and Other Seizure Disorders."

Because "[g]anaxolone is very poorly soluble in water," it is "difficult to formulate as an aqueous injectable."[131] Thus, Zhang provides ganaxolone "formulated as an aqueous injectable by complexing [it] with a substituted β-cyclodextrin, such as [CAPTISOL®, also referred to as sulfobutyl ether β-cyclodextrin[132]]."[133]

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[128] Ex. 1003, ¶ 62.

[129] *Id.*

[130] *See also* Ex. 1003, ¶¶ 48–160.

[131] Ex. 1009, ¶ [0031]; Ex. 1003, ¶ 64.

[132] Ex. 1009, ¶ [0005]; Ex. 1003, ¶ 64.

[133] Ex. 1009, ¶ [0031]; Ex. 1003, ¶ 64.

Zhang teaches a POSA how to make its ganaxolone formulations throughout the specification (including by way of working examples),[134] and also teaches a POSA how to *use* its ganaxolone formulations to treat SE, in particular, by including working examples demonstrating the efficacy of ganaxolone for the treatment of SE in the rat lithium-pilocarpine model.[135]

Example 7 of Zhang discloses plasma concentration profiles of ganaxolone over time in rats infused with IV-administered ganaxolone-CAPTISOL®,[136] and Example 8 of Zhang describes the effects of ganaxolone in rats with lithium pilocarpine-induced SE.[137]

The rats of Example 8 were administered a CAPTISOL®-ganaxolone formulation intravenously at 12 and 15 mg/kg, administered either 15 or 60 minutes after onset of SE.[138] Therapeutic activity of ganaxolone in the treatment of SE was assessed by determining changes in EEG power for five hours after onset

[134] Ex. 1009, ¶¶ [0104]–[0115] (Examples 1–6); Ex. 1003, ¶ 64.

[135] Ex. 1009, ¶¶ [0116]–[0136]; Ex. 1003, ¶ 65.

[136] Ex. 1009, ¶ [0116], FIG. 2; Ex. 1003, ¶ 65.

[137] Ex. 1009, ¶¶ [0117]–[0136]; Ex. 1003, ¶ 65.

[138] Ex. 1009, ¶ [0117]; Ex. 1003, ¶ 66.

of SE.[139] Ganaxolone at both 12 and 15 mg/kg "produced a very strong reduction in SE amplitude overall."[140]

In particular, when dosed 15 minutes after the onset of SE, ganaxolone reduced EEG power across all frequency ranges tested to baseline levels or lower for up to 5 hours.[141] Even when dosed 60 minutes after SE onset, when many other drugs have no effect, ganaxolone also strongly reduced EEG power (not below baseline for up to 70 Hz, but dropping below baseline for 70-96 Hz).[142] This reduction in EEG power indicates to a POSA that ganaxolone is an effective method for treating SE.[143] Tables 6 and 7, as well as Figures 3 and 4, present details of these results.[144]

In sum, Zhang not only discloses an actual reduction to practice of "a method of treating status epilepticus comprising administering to a patient in need thereof a pharmaceutical composition comprising ganaxolone or a

[139] Ex. 1009, ¶ [0118]; Ex. 1003, ¶ 66.

[140] Ex. 1009, ¶ [0134]; Ex. 1003, ¶ 66.

[141] Ex. 1009, ¶ [0135]; Ex. 1003, ¶ 67.

[142] Ex. 1009, ¶ [0136]; Ex. 1003, ¶ 67.

[143] Ex. 1003, ¶ 67.

[144] *Id.*

pharmaceutically acceptable salt thereof" in a rat with SE, but seeing those results, a person skilled in the art would have reasonably believed that ganaxolone would show efficacy in treatment of SE in human patients as well.[145]

As described below, Zhang discloses each and every limitation of claims 1–3, 10–17, and 19–31 of the '817 patent, and, therefore, anticipates these claims.[146]

While Zhang was purportedly considered by the Examiner (*see* Section IX.A), it was not cited in any art-based rejections or discussed in any manner. Indeed, given the anticipatory disclosure of Zhang, it is difficult to contemplate any explanation other than the Examiner overlooked it.

**1. Claim 1**

Claim 1 recites "A method of treating status epilepticus comprising administering to a patient in need thereof a pharmaceutical composition comprising ganaxolone or a pharmaceutically acceptable salt thereof."[147]

As described above, Zhang anticipates claim 1 (as well as claims 2, 3, 10–17, 19, and 20, each of which depend from claim 1).[148] And while Zhang

[145] Ex. 1003, ¶¶ 68–69.

[146] *See also* Ex. 1003, ¶¶ 60–105.

[147] Ex. 1001, 32:65–67; Ex. 1003, ¶ 61.

[148] Section VIII.A; *See also* Ex. 1003, ¶¶ 60–69.

anticipates claim 1 as it relates to a human patient, as noted above, the patients of claim 1 encompass not only human patients, but also rat patients, including rats with chemically induced status epilepticus.[149] Therefore, Zhang discloses an *actual reduction to practice* in its Example 8.

**2. Claims 2 and 3**

Claims 2 and 3, which depend upon claim 1, recite "wherein the patient is administered ganaxolone or a pharmaceutically acceptable salt thereof" either "twice daily" (claim 2) or "three times daily" (claim 3).[150]

Zhang discloses that "seizure disorders that may be treated with the substituted β-cyclodextrin-ganaxolone injectable formulation include status epilepticus . . ." and that "treating a patient suffering from seizures . . . include administering multiple injections of the substituted β-cyclodextrin-ganaxolone injectable formulation over a period of 1 to 10 days."[151] In particular, the injections "may be given at intervals of 1 to 24 hours" and "[d]osing schedules in which the substituted β-cyclodextrin-ganaxolone injectable formulation is injected every 1 hr, 2 hrs, 4 hrs, 6 hrs, 8 hrs [i.e., three times daily], 12 hrs [i.e., twice

[149] VIII.A.1; *see also* Ex. 1003, ¶ 62.

[150] Ex. 1001, 38:52–57, Ex. 1003, ¶ 70.

[151] Ex. 1009, ¶¶ [0070], [0074]; Ex. 1003, ¶ 71.

daily], or 24 hrs" are described.[152]

Therefore, Zhang anticipates claims 2 and 3.[153]

### 3. Claims 10–17

Claims 10–17, each of which depends on claim 1, recite "wherein the patient is administered [X] mg ganaxolone or a pharmaceutically acceptable salt thereof," where "X" is 600 mg (claims 10 and 11), 50 mg (claim 12), 100 mg (claim 13), 200 mg (claim 14), 300 mg (claim 15), 400 mg (claim 16), or 500 mg (claim 17). Claims 10 and 12–17 do not specify how or over what timeframe the recited amount is administered. Claim 11 specifies that the patient is administered the 600 mg "three times daily."[154]

Zhang discloses "embodiments in which multiple bolus doses of the ganaxolone/ sulfobutyl ether-β-cyclodextrin formulation are administered to the patient."[155] "In certain embodiments the multiple bolus doses are given over 1 to 10 days at intervals of 1 to 24 hours."[156] And, "[i]n certain embodiments each

[152] Ex. 1009, ¶ [0074]; Ex. 1003, ¶ 71.

[153] Ex. 1003, ¶ 72.

[154] Ex. 1001, 39:10–34; Ex. 1003, ¶ 73.

[155] Ex. 1009, ¶ [0085], Ex. 1003, ¶ 76.

[156] *Id.*

bolus dose comprises about 1 mg/kg to about 20 mg/kg ganaxolone."[157] As described by Dr. Rogawski, based on Zhang's descriptions, one could calculate the total dose in mg for an average human patient, weighing in at 70 kg, as shown in the table below.[158]

| **Claim(s)** | **Amount Administered (total mg)** | **Amount Administered to a 70 kg patient (in mg/kg)** |
|---|---|---|
| 10, 11 | 600 | 8.57 |
| 12 | 50 | 0.71 |
| 13 | 100 | 1.43 |
| 14 | 200 | 2.86 |
| 15 | 300 | 4.29 |
| 16 | 400 | 5.71 |
| 17 | 500 | 7.14 |

As Dr. Rogawski explains, and as is readily apparent from this table, Zhang's bolus doses of 1 mg/kg to 20 mg/kg, for a 70 kg patient, encompass each of the amounts recited in claims 10–17, with the exception of 50 mg (claim 12).[159] However, a person of skill in the art would immediately understand that, for example, for a patient weighing 50 kg (a human child, perhaps), when

[157] *Id.*

[158] Ex. 1003, ¶¶ 74–77.

[159] Ex. 1003, ¶ 78.

administered a 1 mg/kg dose would be administered a total of 50 mg (as recited in claim 12). [160]

With respect to claim 11, which adds that the 600 milligrams is administered three times daily, Zhang teaches that multiple bolus doses (such as a 8.57 mg/kg dose administered to a 70 kg patient, can be administered every 8 hours (i.e., three times a day). [161]

Therefore, Zhang anticipates claims 10–17.[162]

#### 4. Claims 19 and 20

Claims 19 and 20, which each depend on claim 1, recite patient outcomes: "wherein the pharmaceutical composition provides reduction in the frequency of seizures" (claim 19) and "where in the pharmaceutical composition provides reduction in the frequency of seizures, the severity of seizures, or a combination thereof" (claim 20).[163]

Zhang discloses "methods of treating status epilepticus . . . comprising administering an effective amount of the substituted β-cyclodextrin-ganaxolone

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[160] *Id.*

[161] Ex. 1003, ¶ 79.

[162] Ex. 1003, ¶ 80.

[163] Ex. 1001, 40:4–8; Ex. 1003, ¶ 81.

injectable formulation to a patient suffering from [the same]."[164] Zhang teaches that "treatment" (in the context of its disclosure) includes "relieving a condition caused by the disease or disorder, or reducing the symptoms of the disease or disorder"[165] and, as noted above, that SE is a "serious seizure disorder."[166]

As described above, Example 8 in Zhang shows that ganaxolone (at both the 12 and 15 mg/kg doses) "produced a very strong reduction in SE amplitude overall" in the rat lithium-pilocarpine model.[167]

As described by Dr. Rogawski, the data in Example 8 would be understood by a person skilled in the art as demonstrating that ganaxolone terminated (i.e., stopped) SE.[168]

Therefore, Zhang anticipates claims 19 and 20.[169]

**5. Claim 21**

Claim 21 recites a "method of treating status epilepticus comprising

[164] Ex. 1009, ¶ [0069]; Ex. 1003, ¶ 82.

[165] Ex. 1009, ¶ [0025]; Ex. 1003, ¶ 83.

[166] Ex. 1009, ¶ [0001]; Ex. 1003, ¶ 82.

[167] Ex. 1009, ¶ [0134]; Ex. 1003, ¶ 84.

[168] Ex. 1003, ¶¶ 84–87.

[169] Ex. 1003, ¶ 88.

administering to a patient in need thereof a pharmaceutical composition comprising ganaxolone or a pharmaceutically acceptable salt thereof wherein the pharmaceutical composition is administered intravenously. Claim 21 differs from claim 1 only in that it specifies that the pharmaceutical composition is administered intravenously.[170]

Zhang teaches that its ganaxolone formulations "include parenteral formulations suitable for intravenous infusion," and teaches a POSA how to use ganaxolone (intravenously) to treat a patient with SE (whether human or rat). [171]

Furthermore, as noted above, in Example 8, Zhang discloses an actual reduction to practice of treating SE by administering ganaxolone (intravenously) to a rat with chemically induced SE.[172]

Therefore, Zhang anticipates claim 21.[173]

**6. Claim 22**

Claim 22 recites "wherein the pharmaceutical composition provides

[170] Ex. 1001, 38:48–51, 40:8–12; Ex. 1003, ¶¶ 89–90.

[171] Ex. 1009, ¶ [0029]; Ex. 1003, ¶ 90.

[172] Ex. 1009, ¶¶ [0017]-[0136]; Ex. 1003, ¶ 90.

[173] Ex. 1003, ¶ 91.

improvement to the patient after administration for more than 8 hours."[174] While Zhang does not expressly disclose that its ganaxolone formulations provide "improvement to the patient after administration for more than 8 hours," this would be the natural result of administering them to a patient with SE, as taught by Zhang.[175] As such, Zhang inherently teaches the limitation of claim 22.

Moreover, Zhang states: "Methods of treatment also include administering multiple injections of the β-cyclodextrin-ganaxolone injectable formulation over a period of 1 to 10 days. The injections may be given at intervals of 1 to 24 hours."[176] A skilled artisan would immediately recognize that if a single bolus treatment for SE suppresses seizures for up to 2 hours as ganaxolone is clearly shown to do in Tables 6 and 7, then the treatment could be repeated at intervals of 2 hours to provide sustained treatment for more than 8 hours.

Therefore, Zhang anticipates claim 22.[177]

**7. Claim 23**

Claim 23, which depends on claim 21, recites "wherein the pharmaceutical

[174] Ex. 1001, 40:13–15; Ex. 1003, ¶ 92.

[175] Ex. 1003, ¶ 93.

[176] Ex. 1009, ¶ [0074]; Ex. 1003, ¶ 96.

[177] Ex. 1003, ¶ 95.

composition comprises about 30 mg ganaxolone."[178] Claim 23 does not recite what volume of the pharmaceutical composition comprises about 30 mg ganaxolone.[179] To the extent that claim 23 is not indefinite, however, it is anticipated by Zhang, as at the upper end of the concentration range taught in Zhang (i.e., 15 mg/mL), 2 mL of the composition would comprise about 30 mg ganaxolone.[180]

Therefore, Zhang anticipates claim 23.[181]

**8. Claims 24–31**

Claims 24–31, each of which depends on claim 21, recite "wherein the patient is administered about [X1] mg to [X2] mg/day ganaxolone," where "X1" and "X2" are low and high amounts of a range, respectively. Claims 24–31 do not specify how the recited amount is administered.[182]

Zhang discloses "embodiments in which multiple bolus doses of the ganaxolone/ sulfobutyl ether-β-cyclodextrin formulation are administered to the

[178] Ex. 1001, 4016–17; Ex. 1003, ¶ 101.

[179] Ex. 1003, ¶ 97.

[180] *Id.*

[181] Ex. 1003, ¶ 98.

[182] Ex. 1001, 40:19–33; Ex. 1003, ¶ 99.

patient."[183] "In certain embodiments the multiple bolus doses are given over 1 to 10 days at intervals of 1 to 24 hours."[184] And, "[i]n certain embodiments each bolus dose comprises about 1 mg/kg to about 20 mg/kg ganaxolone."[185]

As described by Dr. Rogawski, a person of skill in the art would readily be able to calculate the total daily dose in mg.[186] For example, based on Zhang's descriptions, one could calculate the total dose in mg for an average human patient, weighing in at 70 kg, as shown in the table below. [187]

| Claim(s) | Amount Administered Per Day (range in mg) | Amount Administered to a 70 kg Patient Per Day (range in mg/kg) |
|---|---|---|
| 24 | 150–1000 | 2.14–14.29 |
| 25 | 500–1000 | 7.14–14.29 |
| 26 | 625–650 | 8.93–9.29 |
| 27 | 650–675 | 9.29–9.64 |
| 28 | 675–700 | 9.64–10 |
| 29 | 625–700 | 8.93–10 |
| 30 | 700–725 | 10–10.36 |

[183] Ex. 1009, ¶ [0085]; Ex. 1003, ¶ 102.

[184] *Id.*

[185] *Id.*

[186] Ex. 1003, ¶¶ 100–103.

[187] Ex. 1003, ¶ 103.

| Claim(s) | Amount Administered Per Day (range in mg) | Amount Administered to a 70 kg Patient Per Day (range in mg/kg) |
|---|---|---|
| 31 | 1025–1050 | 14.64–15 |

As described by Dr. Rogawski, and as is readily apparent from this table, Zhang's bolus doses of 1 mg/kg to 20 mg/kg, for a 70 kg patient, encompass each of the amounts recited in claims 24–31.[188]

Therefore, Zhang anticipates claims 24–31.[189]

### B. GROUND 2: Claims 1–3, 10–17, and 19–31 Would Have Been Obvious over Zhang

Claims 1–3, 10–17, and 19–31 are anticipated by Zhang, as described above, because Zhang teaches each and every limitation of claims 1–3, 10–17, and 19–31. To the extent that Zhang does not anticipate claims 1–3, 10–17, and 19–31, however, they are obvious over Zhang, at least because Zhang suggests the subject matter of claims 1–3, 10–17, and 19–31, as described below. A POSA would have, based on common knowledge, supplied any limitations that Zhang does not teach directly, and a POSA would have arrived at the recited claims with a reasonable expectation of success.[190] For example, as Dr. Rogawski explains, the

[188] Ex. 1003, ¶ 104.

[189] Ex. 1003, ¶ 105.

[190] Ex. 1003, ¶¶ 106–109.

rat lithium-pilocarpine model was, and is, considered to be a widely accepted model to identify potential treatments for SE.[191] Example 8 of Zhang teaches that the IV-administered ganaxolone formulations terminates SE in the model. [192]

If Zhang's teachings, as described in Section VIII.A, do not teach the limitations of claim 1–3, 10–17, and 19–31, they suggest them.[193] And, based on Zhang's teachings, including, for example, the results described in Example 8, a POSA would have had a reasonable expectation of success at arriving at the claimed methods of treating SE with ganaxolone—whether in a rat patient or a human patient.[194] Ovid did not point to any objective evidence otherwise.

Therefore, claims 1–3, 10–17, and 19–31 would have been obvious over Zhang.[195]

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[191] Ex. 1003, ¶ 108.

[192] *Id*.

[193] *See* Section VIII.A.1 re Claim 1, Section VIII.A.2 re Claims 2 and 3, Section VIII.A.3 re Claims 10–17, Section VIII.A.4 re claims 19 and 20, Section VIII.A.5 re claim 21, Section VIII.A.6 re claim 22, Section VIII.A.7 re claim 23, and Section VIII.A.8 re claims 24–31, in particular; *see also* Ex. 1003, ¶¶ 106–109.

[194] Ex. 1003, ¶ 109.

[195] *Id*.

### C. GROUND 3: Claims 1–3, 10–17, and 19–31 Would Have Been Obvious over Zhang and Saporito P1 and/or Saporito P2

Zhang is described above in Section VIII.A.

Saporito P1 (Ex. 1013), titled "Ganaxolone Administered Intravenously Prevents Behavioral Seizures and Promotes Survival in the Rat-Lithium Pilocarpine Model of Status Epilepticus," reports on a study conducted by Marinus to investigate the effects of IV-administered ganaxolone in the rat lithium-pilocarpine model.[196] In the study described on the poster, rats were administered lithium chloride (127 mg/kg) and pilocarpine (50 mg/kg) to induce convulsive SE (CSE), a type of SE in which the seizures experienced by the subject are convulsions.[197] Rats were then administered ganaxolone (formulated at a concentration of 2.5 mg/mL in 30% CAPTISOL®) at a dose of 6, 9, or 12 mg/kg at the time of seizure onset (time zero) and 15, 30, and 60 minutes after seizure onset.[198]

The data on the poster shows that the IV administered ganaxolone "halted CSE and produced a dose-dependent reduction in seizures associated with CSE

[196] Ex. 1013; Ex. 1003, ¶ 112.

[197] *Id.*

[198] *Id.*

when administered at 3 different doses over four separate time points after the first observed convulsive seizure."[199] That data is presented in Figure 2, which shows the percentage of rats that were protected from seizure with the vehicle, the three different doses of ganaxolone, and the one dose of allopregnanolone tested, administered at time zero, 15 minutes, 30 minutes, and 60 minutes.[200] After the administration of each agent, animals were monitored for 2 hours.[201] Animals that did not exhibit a convulsive seizure during that time period were categorized as protected.[202]

The poster also shows that the IV administered ganaxolone promotes survival, measured 24 hours after the onset of CSE.[203] That data is presented in Figure 3.[204]

As discussed above, those of skill in the art understood, and still understand, the rat lithium-pilocarpine model to be a widely accepted model to identify

[199] Ex. 1013; Ex. 1003, ¶ 113.

[200] *Id.*

[201] *Id.*

[202] *Id.*

[203] Ex. 1013; Ex. 1003, ¶ 114.

[204] *Id.*

potential treatments for SE.[205] Thus, Saporito P1 teaches a method of treating SE by administering to a patient in need thereof a pharmaceutical composition of ganaxolone (including a human patient).[206]

Saporito P2 (Ex. 1014), titled "Intravenous Administration of Ganaxolone Attenuates Electroencephalographic Seizures in a Diazepam Resistant Model of Status Epilepticus," like Saporito P1, shows that rats were administered lithium chloride followed by pilocarpine to induce SE.[207] The poster explains that "[s]tatus epilepticus can be modeled in experimental animals by administration of lithium and pilocarpine."[208] In this study, the rats had been pre-implanted with cortical electrodes to measure electrical activity consistent with seizures.[209] Ganaxolone was administered via IV bolus injection 15 or 60 minutes after the detection of SE onset.[210]

The results of the study showed that the IV administration of ganaxolone

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[205] Section III.B; Ex. 1003, ¶ 115.

[206] Ex. 1003, ¶ 115.

[207] Ex. 1014, Ex. 1003, ¶ 117.

[208] *Id.*

[209] *Id.*

[210] *Id.*

elicited a sustained block of SE when it was administered either 15 or 60 minutes after onset of SE.[211] In other words, it showed that the administration of ganaxolone treated SE, by terminating or stopping SE.[212] The data is shown in Figures 3 and 4.[213]

Thus, Saporito P2 teaches a method of treating SE by administering to a patient in need thereof a pharmaceutical composition of ganaxolone (including a human patient).[214]

As described in Section IX.A, neither of these references were considered by the Examiner during prosecution.

**1. Claim 1**

As discussed in Section VIII.A, Zhang discloses "methods of treating status epilepticus . . . comprising administering an effective amount of the substituted β-cyclodextrin-ganaxolone injectable formulation to a patient suffering from [the same]."[215] Zhang also includes data demonstrating that ganaxolone [administered

[211] Ex. 1014, Ex. 1003, ¶ 118.

[212] Ex. 1003, ¶ 118.

[213] Ex. 1014; Ex. 1003, ¶ 118.

[214] Ex. 1003, ¶ 119.

[215] Ex. 1009, ¶ [0069]; Ex. 1003, ¶ 123.

intravenously] at both 12 and 15 mg/kg "produced a very strong reduction in SE amplitude overall" in a rat pilocarpine model of SE.[216]

Saporito P1 and Saporito P2, as described above each provide additional experimental evidence supporting a method of treating SE by administering to a patient in need thereof a pharmaceutical composition of ganaxolone (including a human patient).[217]

A POSA would have readily combined these references—as they both describe the same drug, the same disease, and the same animal model.[218] And, for at least the reasons described in Section VIII.B, it would have been with a reasonable expectation of success, with the posters providing additional data demonstrating the success of ganaxolone at treating SE.[219]

Therefore, claim 1 would have been obvious over Zhang in combination with Saporito P1 and/or Saporito P2.[220]

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[216] Ex. 1009, ¶ [0117]–[0136]; Ex. 1003, ¶ 123.

[217] Ex. 1003, ¶¶ 111–120.

[218] *Id.*

[219] *See also* Ex. 1003, ¶¶ 110–121.

[220] Ex. 1003, ¶ 121.

### 2. Claims 2 and 3

For at least the same reasons set forth for claim 1, a POSA would have combined Zhang's teachings (e.g., as described in Section VIII.A.2) with Saporito P1 and/or P2's teachings, as described above. And, for at least the reasons described in Section VIII.B, it would have been with a reasonable expectation of success. Therefore, claims 2 and 3 would have been obvious.[221]

### 3. Claims 10–17

For at least the same reasons set forth for claim 1, a POSA would have combined Zhang's teachings (e.g., as described in Section VIII.A.3) with Saporito P1 and/or P2's teachings, as described above. And, for at least the reasons described in Section VIII.B, it would have been with a reasonable expectation of success. Therefore, claims 10–17 would have been obvious.

### 4. Claims 19 and 20

For at least the same reasons set forth for claim 1, a POSA would have combined Zhang's teachings (e.g., as described in Section VIII.A.4) with Saporito P1 and/or P2's teachings, as described above. And, for at least the reasons described in Section VIII.B, it would have been with a reasonable expectation of

[221] *Id.*

success. Therefore, claims 19 and 20 would have been obvious.[222]

### 5. Claim 21

For at least the same reasons set forth for claim 1, a POSA would have combined Zhang's teachings (e.g., as described in Section VIII.A.5) with Saporito P1 and/or P2's teachings, as described above. And, for at least the reasons described in Section VIII.B, it would have been with a reasonable expectation of success. Therefore, claim 21 would have been obvious.[223]

### 6. Claim 22

For at least the same reasons set forth for claim 1, a POSA would have combined Zhang's teachings (e.g., as described in Section VIII.A.6) with Saporito P1 and/or P2's teachings, as described above. In addition, Saporito P1 shows that ganaxolone promoted survival in the rats, measured 24 hours after the onset of CSE, suggesting improvement after 8 hours.[224] And, for at least the reasons described in Section VIII.B, it would have been with a reasonable expectation of success. Therefore, claim 22 would have been obvious.[225]

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[222] *Id.*

[223] *Id.*

[224] Ex. 1013 at Figure 3.

[225] *Id.*

#### 7. Claim 23

For at least the same reasons set forth for claim 1, a POSA would have combined Zhang's teachings (e.g., as described in Section VIII.A.7) with Saporito P1 and/or P2's teachings, as described above. And, for at least the reasons described in Section VIII.B, it would have been with a reasonable expectation of success. Therefore, claim 23 would have been obvious.[226]

#### 8. Claims 24–31

For at least the same reasons set forth for claim 1, a POSA would have combined Zhang's teachings (e.g., as described in Section VIII.A.8) with Saporito P1 and/or P2's teachings, as described above. And, for at least the reasons described in Section VIII.B, it would have been with a reasonable expectation of success. Therefore, claims 24–31 would have been obvious.[227]

### D. GROUND 4: Claims 1–3, 10–17, and 19–31 Would Have Been Obvious over Zhang and Marinus's Orphan Drug Press Release and/or Marinus's Phase I Press Release

Zhang (Ex. 1009) is described above in Section VIII.A.

Marinus's Orphan Drug Press Release (Ex. 1011) is titled "Marinus Pharmaceuticals Receives FDA Orphan Drug Designation for Ganaxolone IV to

[226] *Id.*

[227] *Id.*

Treat Status Epilepticus." It discloses 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]."[228] It also discloses 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."[229]

Marinus's Phase I Press Release (Ex. 1022) is titled "Marinus Pharmaceuticals Doses First Subject in Phase 1 Clinical Trial for Ganaxolone IV." It discloses that Marinus had "dosed the first subject in its Phase 1 clinical trial of ganaxolone IV, an intravenous (IV) formulation" for the treatment of SE."[230] It also discloses that the study would "include a dose escalation of a bolus dosage of ganaxolone IV and a bolus dose of ganaxolone IV, followed by a continuous infusion."[231]

As described in Section IX.A, neither of these references was considered by the Examiner during prosecution.

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[228] Ex. 1011; Ex. 1003, ¶ 125.

[229] *Id.*

[230] Ex. 1022; Ex. 1003, ¶ 126.

[231] *Id.*

As Dr. Rogawski describes, a POSA would know that in order to obtain Orphan Drug Designation, the FDA would have required the submission of significant data supporting the rationale for the use of ganaxolone for SE.[232] And, the FDA would have had to refuse to grant the designation if "[t]here is insufficient information about the drug, or the disease or condition for which it is intended, to establish a medically plausible basis for expecting the drug to be effective in the prevention, diagnosis, or treatment of that disease or condition."[233]

A POSA would have recognized that as sufficient evidence that Marinus had established a medically plausible basis for ganaxolone to be effective for treating SE.[234]

Furthermore, as Dr. Rogawski describes, a POSA would have recognized that in order for the FDA to permit a clinical study such as the one described in Marinus's Phase I Press Release to be undertaken under an IND, those of skill in the art understand that the sponsor must provide evidence that "the compound

[232] Ex. 1003, ¶ 125.

[233] *Id.*; 21 C.F.R. § 316.20(b)(4); 21 C.F.R. § 316.25.

[234] Ex. 1003, ¶ 125.

exhibits pharmacological activity that justifies commercial development."[235] Since the purpose of Marinus's trial was to advance commercial development of ganaxolone for the treatment of SE, a person of skill in the art would have recognized that the FDA had determined that IV ganaxolone was reasonably likely to be successful in the treatment of SE in humans.[236]

A POSA reading Zhang would have readily combined Zhang with Marinus's Orphan Drug Press Release and/or Phase I Press Release.[237] And, for at least the reasons described above, it would have been with a reasonable expectation of success.[238]

**1. Claim 1**

As discussed in Section VIII.A, Zhang discloses "methods of treating status epilepticus . . . comprising administering an effective amount of the substituted β-cyclodextrin-ganaxolone injectable formulation to a patient suffering from [the

[235] Ex. 1003, ¶ 126; https://www.fda.gov/drugs/investigational-new-drug-ind-application/drug-development-and-review-definitions (Ex. 1021).

[236] Ex. 1003, ¶ 126.

[237] Ex. 1003, ¶ 124.

[238] Ex. 1003, ¶¶ 122–128.

same].”[239] Zhang also includes data demonstrating that Ganaxolone [administered intravenously] at both 12 and 15 mg/kg “produced a very strong reduction in SE amplitude overall” in a rat pilocarpine model of SE, demonstrating that ganaxolone is useful in the treatment of SE.[240]

A POSA would have recognized, based on Marinus’s Orphan Drug Press Release and Phase I Press Release, that the FDA had determined that IV ganaxolone was reasonably likely to be successful in the treatment of SE in humans.[241]

Therefore, claim 1 would have been obvious over Zhang in combination with Marinus’s Orphan Drug Press Release and/or Marinus’s Phase I Press Release.[242]

**2. Claims 2 and 3**

For at least the same reasons set forth for claim 1, a POSA would have combined Zhang’s teachings (e.g., as described in Section VIII.A.2) with the teachings of Marinus’s Orphan Drug and Phase I Press Releases, as described

[239] Ex. 1009, ¶ [0069]; Ex. 1003, ¶ 123.

[240] Ex. 1009 ¶ [0017]–[0136]; Ex. 1003, ¶ 123.

[241] Ex. 1003, ¶¶ 124–126.

[242] Ex. 1003, ¶¶ 122–128.

above. And, for at least the reasons described in Section VIII.B, it would have been with a reasonable expectation of success, with the Press Releases providing additional evidence supporting that a POSA would have expected ganaxolone to be successful in treating SE. Therefore, claims 2 and 3 would have been obvious over Zhang and Marinus's Orphan Drug Press Release and/or Marinus's Phase I Press Release.[243]

### 3. Claims 10–17

For at least the same reasons set forth for claim 1, a POSA would have combined Zhang's teachings (e.g., as described in Section VIII.A.3) with the teachings of Marinus's Orphan Drug and Phase I Press Releases, as described above. And, for at least the reasons described in Section VIII.B, it would have been with a reasonable expectation of success. Therefore, claims 10–17 would have been obvious over Zhang and Marinus's Orphan Drug Press Release and/or Marinus's Phase I Press Release.[244]

### 4. Claims 19 and 20

For at least the same reasons set forth for claim 1, a POSA would have combined Zhang's teachings (e.g., as described in Section VIII.A.4) with the

[243] Ex. 1003, ¶ 128.

[244] *Id.*

teachings of Marinus's Orphan Drug and Phase I Press Releases, as described above. And, for at least the reasons described in Section VIII.B, it would have been with a reasonable expectation of success. Therefore, claims 19 and 20 would have been obvious over Zhang and Marinus's Orphan Drug Press Release and/or Marinus's Phase I Press Release.[245]

**5. Claim 21**

For at least the same reasons set forth for claim 1, a POSA would have combined Zhang's teachings (e.g., as described in Section VIII.A.5) with the teachings of Marinus's Orphan Drug and Phase I Press Releases, as described above. And, for at least the reasons described in Section VIII.B, it would have been with a reasonable expectation of success. Therefore, claim 21 would have been obvious over Zhang and Marinus's Orphan Drug Press Release and/or Marinus's Phase I Press Release.[246]

**6. Claim 22**

For at least the same reasons set forth for claim 1, a POSA would have combined Zhang's teachings (e.g., as described in Section VIII.A.6) with the teachings of Marinus's Orphan Drug and Phase I Press Releases, as described

[245] *Id.*

[246] *Id.*

above. And, for at least the reasons described in Section VIII.B, it would have been with a reasonable expectation of success. Therefore, claim 22 would have been obvious over Zhang and Marinus's Orphan Drug Press Release and/or Marinus's Phase I Press Release.[247]

### 7. Claim 23

For at least the same reasons set forth for claim 1, a POSA would have combined Zhang's teachings (e.g., as described in Section VIII.A.7) with the teachings of Marinus's Orphan Drug and Phase I Press Releases, as described above. And, for at least the reasons described in Section VIII.B, it would have been with a reasonable expectation of success. Therefore, claim 23 would have been obvious over Zhang and Marinus's Orphan Drug Press Release and/or Marinus's Phase I Press Release.[248]

### 8. Claims 24–31

For at least the same reasons set forth for claim 1, a POSA would have combined Zhang's teachings (e.g., as described in Section VIII.A.8) with the teachings of Marinus's Orphan Drug and Phase I Press Releases, as described above. And, for at least the reasons described in Section VIII.B, it would have

[247] *Id.*

[248] *Id.*

been with a reasonable expectation of success. Therefore, claims 24–31 would have been obvious over Zhang and Marinus's Orphan Drug Press Release and/or Marinus's Phase I Press Release.[249]

### E. GROUND 5: Claims 4–9 and 18 Would Have Been Obvious Over Zhang and Shaw

Shaw (Ex. 1010) is a Marinus patent publication titled "Ganaxolone Formulations and Methods for the Making and Using Thereof."[250]

While Shaw, like Zhang, was purportedly considered by the Examiner (*see* Section IX.A), it was not cited in any art-based rejections or discussed in any manner. Indeed, given the teachings of Shaw, it is difficult to contemplate any explanation other than the Examiner overlooked it.

Shaw describes "ganaxolone formulations . . . as well as methods of making ganaxolone formulations and their use in the treatment of epilepsy-related and other central nervous system disorders."[251] Shaw teaches a POSA how to make and use its ganaxolone formulations throughout the specification.[252]

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[249] *Id.*

[250] Ex. 1010, cover page; Ex. 1003, ¶ 130.

[251] Ex. 1010, ¶ [0002]; Ex. 1003, ¶ 131.

[252] Ex. 1010, ¶ [00426]; Ex. 1003, ¶ 131.

Shaw also shows that ganaxolone, administered to 6 healthy subjects, as an oral suspension, resulted in a "Cmax of 37 ± 25 ng/ml and an $AUC_{(0-24)}$ of 184 ± 104 ng*h/ml."[253]

Zhang (Ex. 1009), described in Section VIII.A above, discloses, among other things, "methods of treating status epilepticus . . . comprising administering an effective amount of the substituted β-cyclodextrin-ganaxolone injectable formulation to a patient suffering from [the same]."[254]

As noted above in Section VIII.A, Zhang not only teaches a POSA how to use ganaxolone to treat a patient with SE (whether human or rat), it also discloses an actual reduction to practice of treating SE by administering ganaxolone to a rat, intravenously, with chemically induced SE.[255]

A person of skill in the art would have been motivated to combine Shaw and Zhang—at least because they are two studies authored by the same group, to study the same drug, for treatment of seizure conditions.[256] And, they would have done so with a reasonable expectation of success at arriving at the claimed methods (i.e.,

[253] Ex. 1010, ¶ [00546]; Ex. 1003, ¶ 132.

[254] Ex. 1009, ¶ [0069]; Ex. 1003, ¶ 133.

[255] Ex. 100, ¶¶ [0117]–[0136]; *see also* Ex. 1003, ¶ 141.

[256] Ex. 1003, ¶ 134.

methods of treating status epilepticus using ganaxolone), with Zhang providing data to show the success of using ganaxolone to treat SE, and Shaw providing evidence of blood levels of ganaxolone after administration to healthy patients and the use of oral dosage forms.[257]

### 1. Claims 4 and 5

Claim 1 recites "A method of treating status epilepticus comprising administering to a patient in need thereof a pharmaceutical composition comprising ganaxolone or a pharmaceutically acceptable salt thereof." Claims 4 and 5, each of which depend on claim 1, recite particular dosage forms. In particular, wherein the pharmaceutical composition is an "oral suspension" (claim 4) or an "oral capsule" (claim 5).[258]

Shaw teaches that its "pharmaceutical ganaxolone compositions . . . can be formulated into any suitable dosage form, including but not limited to . . . aqueous oral suspensions" and "solid dosage forms including oral solid dosage forms" such as "capsules."[259]

Relevant to the oral dosing requirements for claims 4 and 5, Zhang teaches

[257] *See* Ex. 1003, ¶¶ 130–134.

[258] Ex. 1001; Ex. 1003, ¶ 135.

[259] Ex. 1010, ¶ [00174]; Ex. 1003, ¶ 136.

that "[g]anaxolone has a relatively long half-life – approximately 20 hours in human plasma following *oral administration*," [emphasis added] and that it "has a short $T_{max}$, which means that therapeutic blood levels are reached quickly."[260] Thus, Zhang suggests to those of skill in the art that oral administration is appropriate for ganaxolone.[261]

Combined with Shaw and Zhang's teachings described above, a POSA would have arrived at claims 4 and 5 with a reasonable expectation of success.[262] Therefore, claims 4 and 5 would have been obvious over Shaw and Zhang.[263]

**2. Claim 6**

Claim 6, which depends on claim 4 ("oral suspension") recites that the ganaxolone or pharmaceutically acceptable salt thereof is administered in an amount of up to 1,800 mg/day.[264]

Shaw teaches that "[in one] aspect, the invention is directed to a liquid pharmaceutical oral suspension comprising ganaxolone . . . based on a dose of 200

[260] Ex. 1009, ¶ [0027]; Ex. 1003, ¶ 137.

[261] Ex. 1003, ¶ 137.

[262] Ex. 1003, ¶ 138.

[263] *Id.*

[264] Ex. 1001; Ex. 1003, ¶ 139.

mg ganaxolone."[265] And Shaw also discloses that its ganaxolone formulations can be administered "once-a-day, twice-a-day (b.i.d), or three times a day (t.i.d.)."[266] 200 mg administered one, two, or three times a day is within the range of "up to 1,800 mg/day."[267]

Combined with Shaw and Zhang's teachings described above, a POSA would have arrived at claim 6 with a reasonable expectation of success. Therefore, claim 6 would have been obvious over Shaw and Zhang.[268]

### 3. Claims 7–9

Claims 7–9, each of which depends on claim 1, recite various doses and administration schedules of an "oral suspension" comprising ganaxolone or a pharmaceutically acceptable salt thereof.[269]

Shaw discloses that "[i]n one embodiment, a ganaxolone formulation is administered as an aqueous oral suspension at a concentration of about 25 mg/ml to about 100 mg/ml final concentration," and that these suspensions "can be

[265] Ex. 1010, ¶ [0068]; Ex. 1003, ¶ 140.

[266] Ex. 1010, ¶ [00174]; Ex. 1003, ¶ 140.

[267] Ex. 1003, ¶ 140.

[268] Ex. 1003, ¶ 141.

[269] Ex. 1001; Ex. 1003, ¶ 142.

administered both as a single dose per day or given multiple times within a 24 hour period," including "three times a day."[270] In one case, Shaw teaches administering 4 ml of a 50 mg/ml suspension.[271] When administered three times daily, this 4 ml of a 50 mg/ml suspension totals 600 mg a day.[272]

Thus, Shaw's disclosure encompasses 50 mg/ml (claim 7), 50 mg/ml three times daily (claim 8) and, when administered in 4 ml volume three times daily, 50 mg/ml three times daily, in an amount of up to 1,800 mg/day (claim 9).[273]

Combined with Shaw and Zhang's teachings described above, a POSA would have arrived at claims 7–9 with a reasonable expectation of success.[274] Therefore, claims 7–9 would have been obvious over Shaw and Zhang.[275]

#### 4. Claim 18

Claim 18 recites a particular dose and format of the ganaxolone or

[270] Ex. 1010, ¶ [00289]; Ex. 1003, ¶ 143.

[271] Ex. 1010, ¶ [00546]; Ex. 1003, ¶ 143.

[272] Ex. 1003, ¶ 143.

[273] Ex. 1003, ¶ 144.

[274] *Id.*

[275] *Id.*

pharmaceutically acceptable salt thereof (200–600 mg as an oral capsule).[276]

Shaw teaches that "[i]n various other embodiments of the present invention, the amount of ganaxolone administered to a subject via a solid dosage form to achieve a therapeutically effective concentration ganaxolone is typically in the range of 50 mg to about 800 mg."[277] Shaw's "solid dosage forms include oral solid dosage forms" such as "capsules."[278] Furthermore, Shaw's formulations can be administered "three times a day."[279]

Combined with Shaw and Zhang's teachings described above, a POSA would have arrived at claim 18 with a reasonable expectation of success.[280] Therefore, claim 18 would have been obvious over Shaw and Zhang.[281]

### F. GROUND 6: Claims 4–9 and 18 Would Have Been Obvious over Zhang, Shaw, and Marinus's Orphan Drug Press Release and/or Marinus's Phase I Press Release

Shaw (Ex. 1010) is described in above, in Section VIII.E.

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[276] Ex. 1001; Ex. 1003, ¶ 145.

[277] Ex. 1010, ¶ [00288]; Ex. 1003, ¶ 146.

[278] Ex. 1010, ¶ [00174]; Ex. 1003, ¶ 146.

[279] *Id.*

[280] Ex. 1003, ¶ 147.

[281] *Id.*

Zhang (Ex. 1009) is described above, in Section VIII.A

Marinus's Orphan Drug Press Release and Marinus's Phase I Press Release are described above, in Section VIII.D.

A person of skill in the art would have been motivated to combine Shaw, Zhang, and Marinus's Orphan Drug Press Release and/or Marinus's Phase I Press Release—at least because they are studies authored by the same group, to study the same drug, for treatment of the same disease.[282] And, they would have done so with a reasonable expectation of success at arriving at the claimed methods (i.e., methods of treating status epilepticus using ganaxolone), with the Press Releases providing additional evidence supporting that a POSA would have expected ganaxolone to be successful in treating SE.[283]

**1. Claims 4 and 5**

For at least the reasons described in Section VIII.E.1, a POSA would have combined Shaw and Zhang to arrive at the claimed invention. And, a POSA would have been further motivated and had a further expectation of success based on the teachings of Marinus's Orphan Drug Press Release and Marinus's Phase I Press Release, noted above. Therefore, claims 4 and 5 would have been obvious over

[282] Ex. 1003, ¶ 146.

[283] Ex. 1003, ¶ 150.

Shaw, Zhang, and Marinus's Orphan Drug Press Release and/or Marinus's Phase I Press Release.[284]

### 2. Claim 6

For at least the reasons described in Section VIII.E.2, a POSA would have combined Shaw and Zhang to arrive at the claimed invention. And, a POSA would have been further motivated and had a further expectation of success based on the teachings of Marinus's Orphan Drug Press Release and Marinus's Phase I Press Release, noted above. Therefore, claim 6 would have been obvious over Shaw, Zhang, and Marinus's Orphan Drug Press Release and/or Marinus's Phase I Press Release.[285]

### 3. Claims 7–9

For at least the reasons described in Section VIII.E.3, a POSA would have combined Shaw and Zhang to arrive at the claimed invention. And, a POSA would have been further motivated and had a further expectation of success based on the teachings of Marinus's Orphan Drug Press Release and Marinus's Phase I Press Release, noted above. Therefore, claims 7–9 would have been obvious over Shaw, Zhang, and Marinus's Orphan Drug Press Release and/or Marinus's Phase I Press

[284] Ex. 1003, ¶¶ 148–151.

[285] *Id.*

Release.[286]

#### 4. Claim 18

For at least the reasons described in Section VIII.E.4, a POSA would have combined Shaw and Zhang to arrive at the claimed invention. And, a POSA would have been further motivated and had a further expectation of success based on the teachings of Marinus's Orphan Drug Press Release and Marinus's Phase I Press Release, noted above. Therefore, claim 18 would have been obvious over Shaw, Zhang, and Marinus's Orphan Drug Press Release and/or Marinus's Phase I Press Release.

### G. GROUND 7: Claims 1–3, 10–17, and 19–31 Are Not Enabled

As noted above, in Section IV.B, the '817 patent specification contains very little data to support its claims related to treating SE with ganaxolone. If Ovid takes the position that the references applied to Challenged Claims 1–3, 10–17, and 19–31, above—which contain as much and, in fact, *more* data to support treating SE with ganaxolone—do not anticipate and/or render them obvious by arguing that the references are not enabling, then the claims of the '817 cannot be enabled.[287]

Claim 1, and claims 2, 3, 10–17, 19, and 20 (which depend upon claim 1)

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[286] *Id.*

[287] Ex. 1003, ¶ 152.

recite "treating status epilepticus" by "administering to a patient in need thereof a pharmaceutical composition comprising ganaxolone or a pharmaceutically acceptable salt thereof."[288]

As described in Section VIII.A, and further explained by Dr. Rogawski, Zhang not only teaches each and every limitation of claims 1–3, 10–17, 19, and 20, it also provides more experimental evidence—both in quantity and quality—to enable "treating status epilepticus" by "administering to a patient in need thereof a pharmaceutical composition comprising ganaxolone or a pharmaceutically acceptable salt thereof."[289]

**1. Claim 1**

For the reasons noted above, the full scope of claim 1, if not anticipated and/or obvious, is not enabled by the disclosure of the '817.

**2. Claims 2 and 3**

Claims 2 and 3 recite administration either "twice daily" (claim 2) or "three times daily" (claim 3).[290] A person of skill in the art would have arrived at these

[288] Ex. 1001.

[289] Ex. 1003, ¶¶ 152–160.

[290] Ex. 1001.

administration schedules based on Marinus's publications.[291] If not, however, a person of skill in the art would certainly not have arrived at them based on the only dose (20 mg/kg) for which data is presented the '817 patent (Example 3) that could possibly suggest efficacy for treating SE in a rat.[292] Therefore, to the extent that Marinus's publications do not render these doses and administration schedules anticipated or obvious, the '817 patent does not enable them.[293]

### 3. Claims 10–17

Claims 10–17 recite dosing amounts.[294] A person of skill in the art would have arrived at these dosing amounts based on Marinus's publications.[295] If not, however, a person of skill in the art would certainly not have arrived at them based on the only dose (20 mg/kg) for which data is presented the '817 patent (Example 3) that could possibly suggest efficacy for treating SE in a rat.[296] Therefore, to the extent that Marinus's publications do not render these doses and administration

[291] Ex. 1003, ¶ 159.

[292] *Id.*

[293] *Id.*

[294] Ex. 1001; Ex. 1003, ¶ 159.

[295] Ex. 1003, ¶ 159.

[296] *Id.*

schedules anticipated or obvious, the '817 patent does not enable them.[297]

#### 4. Claims 19 and 20

Claims 19 and 20 recite patient outcomes: "wherein the pharmaceutical composition provides reduction in the frequency of seizures" (claim 19) and "where in the pharmaceutical composition provides reduction in the frequency of seizures, the severity of seizures, or a combination thereof" (claim 20).[298] Again, the disclosure in the '817 patent is not more compelling than that in the Marinus publications.[299] Therefore, to the extent that Marinus's publications do not render these outcomes anticipated or obvious, the '817 patent does not enable them.[300]

#### 5. Claims 21–31

Claims 21–31 recite a particular dosage form (intravenous), and in some cases, particular concentrations, dosing amounts, or patient outcomes.[301] The '817 patent (unlike Marinus's publications), does not contain any working examples of

[297] *Id.*

[298] Ex. 1001; Ex. 1003, ¶ 159.

[299] *Id.*

[300] *Id.*

[301] Ex. 1001.

treating SE (in a rat model or otherwise) using an intravenous dose form.[302] In the '817 patent's Example 3, the rats were administered ganaxolone intraperitoneally.[303] And, as noted above, a POSA would have arrived at the concentrations, dosing amounts and/or patient outcomes based on Marinus's publications.[304] If not, however, a person of skill in the art would certainly not have arrived at them based on the only dose (20 mg/kg) for which data is presented the '817 patent (Example 3) that could possibly suggest efficacy for treating SE in a rat.[305] Therefore, to the extent that Marinus's publications do not render claims 21–31 anticipated or obvious, the '817 patent does not enable them.[306]

### H. GROUND 8: Claims 4–9, and 18 Are Not Enabled

As noted above, in Section IV.B, the '817 patent specification contains very little data to support its claims related to treating SE with ganaxolone. If Ovid takes the position that the references applied to Challenged Claims 4–9 and 18, above, do not anticipate and/or render them obvious, then the claims of the '817

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[302] Ex. 1003, ¶ 158.

[303] *Id.*

[304] Ex. 1003, ¶¶ 158–160.

[305] *Id.*

[306] *Id.*

cannot be enabled.[307]

Claim 1, and claims 4–9 and 18 (which depend upon claim 1), recite "treating status epilepticus" by "administering to a patient in need thereof a pharmaceutical composition comprising ganaxolone or a pharmaceutically acceptable salt thereof."[308]

As described in Section VIII.A and further explained by Dr. Rogawski, Zhang not only teaches each and every limitation of claims 4–9 and 18, it also provides more experimental evidence—both in quantity and quality—to enable "treating status epilepticus" by "administering to a patient in need thereof a pharmaceutical composition comprising ganaxolone or a pharmaceutically acceptable salt thereof."[309]

Claims 4–9, and 18, which depend on claim 1, recite particular oral dosage forms: oral suspensions (claims 4 and 6–9) and oral capsules (claims 5 and 18).[310] The '817 patent (unlike Marinus's publications), does not contain any working

[307] Ex. 1003, ¶¶ 152–160.

[308] Ex. 1001.

[309] Ex. 1003, ¶¶ 152–160.

[310] Ex. 1001; Ex. 1003, ¶ 158.

examples of treating SE (in a rat model or otherwise) using an oral dose form.[311] In the '817 patent's Example 3, the rats were administered ganaxolone intraperitoneally.[312] And, as noted above, a POSA would have arrived at these concentrations, dosing amounts and/or administration schedules based on Marinus's publications.[313] If not, however, a person of skill in the art would certainly not have arrived at them based on the only dose (20 mg/kg) for which data is presented the '817 patent (Example 3) that could possibly suggest efficacy for treating SE in a rat.[314] Therefore, to the extent that Marinus's publications do not render these doses and administration schedules anticipated or obvious, the '817 patent does not enable them.[315]

## IX. DISCRETIONARY DENIAL IS NOT WARRANTED

To determine whether to deny our petition, the Board will consider "whether the same or substantially the same" art or arguments were "previously presented to the Office" and, if so, will then consider whether we have "demonstrated that the

[311] Ex. 1003, ¶ 158.

[312] *Id.*

[313] Ex. 1003, ¶ 159.

[314] *Id.*

[315] *Id.*

Office erred in a manner material to the patentability of the challenged claims." *Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH*, IPR20109-01469, Paper 6 at 8 (PTAB Feb. 13, 2020) (precedential).

In the second part of the test, i.e., whether the petitioner has demonstrated material error, the Board considers several factors, including "the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection;" "whether the petitioner has pointed out sufficiently how the examiner erred in its evaluation of the asserted prior art;" and "the extent to which additional evidence and facts presented in the petition warrant reconsideration of the prior art or arguments." *Id.*, 9 n.10 (citing *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 at 17-18 (PTAB Dec. 15, 2017).

The art and arguments presented in this petition are not the same or substantially the same as those previously presented to the Office. And, even to the extent that they are, the Examiner plainly erred in a manner material to the patentability of the challenged claims. Therefore, discretionary denial is not warranted.

### A. The Art and Arguments Presented are Not the Same or Substantially the Same as those Previously Presented to the Office

Neither the art nor the arguments presented in this petition are the same or

substantially the same as those previously presented to the Office.

While, as described above in Section IV.C, third party submissions were made to the Office during prosecution, it is clear from the prosecution history that neither the art nor the arguments presented were properly considered, or, in some cases, even considered at all.

In particular, as summarized in the Table below, the Examiner explicitly *did not consider* some of the highly probative publications presented in the third party observations. Nor did the Examiner make a single anticipation or obviousness rejection during prosecution—over these or any other prior art publication(s).

| **Publication #** | **Reference** | **Applicant IDS[316]** | **April 4, 2022 1449s[317]** | **June 22, 2022 1449[318]** | **Face of the '187 Patent** |
|---|---|---|---|---|---|
| 1 | Carter (Ex. 1028) | **-** | Considered | **Not Considered** | - |
| 2 | Marinus WO2016/127170 ("Zhang", Ex. 1009) | Jan. 6, 2021[319] | Considered | Considered | Page 1 |
| 3 | Marinus WO2007/062266 | - | Considered | Considered | Page 1 |

[316] Ex. 1002, pages 7–32, 62–85, 151–159.

[317] Ex. 1002, page 96.

[318] Ex. 1002, page 184.

[319] Ex. 1002 page 19.

| | | | | | |
|---|---|---|---|---|---|
| | ("Shaw", Ex. 1010) | | | | |
| 4 | Saporito 2016A ("Saporito A2", Ex. 1029) | July 30, 2021[320] | Considered | **Not Considered** | Page 2 |
| 5 | Saporito 2016B ("Saporito A1", Ex. 1030) | - | Considered | **Not Considered** | - |
| 6 | June 22, 2016 Press Release (Ex. 1022) | - | Considered | **Not Considered** | - |
| 7 | April 15, 2016 Press Release (1011) | - | Considered | **Not Considered** | - |
| 8 | Chez (Ex. 1031) | - | Considered | Considered | Page 3 |

Marinus relies on several prior art publications in this petition which are not the same or substantially the same as those previously presented and/or are relied upon in ways that do not overlap with previously presented arguments.

Although the April 15, 2016 Orphan Drug Press Release (Ex. 1011) and the June 22, 2016 Phase I Press Release (Ex. 1022) were each cited in the third party observations, the Examiner expressly marked them as "not considered" and they do not appear on the face of the '817 patent. These press releases build on the data present in Zhang and Shaw by reflecting views from FDA that there was a reasonable basis for expecting ganaxolone to be safe and effective development for

[320] Ex. 1002, page 75.

SE.[321]

Saporito Poster 1 (Ex. 1013) and Saporito Poster 2 (Ex. 1014) were not previously presented to the Office. As Dr. Saporito explains, the meeting brochure for the AAN Annual Meeting[322] was available online before the meeting, and is still available online today, and the two posters were publicly presented at that meeting.[323] Saporito A1 (Ex. 1030) and Saporito A2 (Ex. 1029), abstracts related to the posters, were presented to the Office by way of third party submission, but as described above, were expressly not considered by the Office and do not appear on the face of the '817 patent. Moreover, the data contained in the posters is more complete than the data included in the abstracts, including figures to fully illustrate the results.

The Saporito Posters provide additional data demonstrating protection against seizures in a rat pilocarpine model of SE, and survival after the onset of CSE that does not appear in Zhang and/or Shaw.[324]

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[321] Ex. 1003, ¶¶ 124–126; 21 C.F.R. §§ 316.20(b)(4), 316.25.

[322] Ex. 1012, which lists Saporito P1 and Saporito P2 at pages 46 and 97, respectively.

[323] Ex. 1015, ¶ 4.

[324] *See* Section VIII.C.

Except for the third party observations, which, as described herein, the Examiner did not properly consider, the Office was not presented with any arguments with respect to novelty or non-obviousness over any of the prior art relied on by Marinus because the Examiner made *no* rejections over any of that art. Indeed, the Examiner made no Section 102 or 103 rejections over *any* art. The only rejections made in prosecution were double patenting rejections over other Ovid patents.

Furthermore, there were no arguments presented during prosecution regarding the requirements for patentability set forth in 35 U.S.C. § 112.

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

During prosecution, the Examiner failed to properly consider evidence highly probative to the (un)patentability of the challenged claims. These errors, along with the additional evidence and facts presented in this petition, warrant full consideration of the prior art and arguments.

First, the Examiner erred with respect to claim interpretation, which led to material error. No construction of any of the claim terms was provided on the record. And, the Examiner did not, on the record, recognize that the claims

encompass treating a rat with chemically induced status epilepticus.[325] Given that the Examiner purportedly considered Zhang, which demonstrates an actual reduction to practice of this embodiment of claim 1,[326] but did not make any anticipation or obviousness rejection over Zhang, either the Examiner overlooked Zhang's teachings, or made an error of law.

Second, the Examiner erred in the double patenting rejections that were made, which contributed to material error. As noted above, in the first and only office action mailed during prosecution of the '817, Examiner Shiao rejected the pending claims for obviousness-type double patenting over claims of Ovid's parent and grandparent applications (U.S. Patent No. 10,799,485 and U.S. Patent No. 10,603,308). [327]

An obviousness-type double patenting rejection is "'analogous to [a failure to meet] the nonobviousness requirement of 35 U.S.C. § 103' except that the patent disclosure principally underlying the double patenting rejection is not considered prior art" (though it may be used to interpret the claims). *See* MPEP 804(II)(B)(3), quoting *In re Braithwaite*, 379 F.2d 549, 154 USPQ 29 (CCPA 1967). A proper

[325] *See* Section VII.

[326] *See* Section VIII.A.

[327] *See* Section IV.C.

obviousness rejection requires that the Examiner: 1) identify the differences between the claims(s) and the prior art reference(s); and 2) provide specific supporting rationale for combining reference(s) in a manner that would render the claim(s) obvious. *KSR Int'l Co. v. Teleflex Inc.,* 550 U.S. 398, 406, 418 (2007).

Examiner Shiao correctly noted that the pending claims were directed to a method of treating ***status epilepticus*** by administering ganaxolone, whereas the claims of the '485 and '308 were directed to treating ***PCDH19 related epilepsy*** and ***CDKL5 deficiency disorder***, respectively.[328] Yet, in making the rejection the Examiner did not consider those differences and stated only that "[t]he difference between instant claims and [those of the '485 and '308] is that the instant claims are silent on the scope of dose of ganaxolone."[329] Thus, the Examiner overlooked material teachings—that the claims differ in the disorder that they recite (*see* Section III, above), and not simply the dose of ganaxolone—which led to a misapplication of the law.

Had this meaningful factual difference been recognized and acknowledged, the Office would—according to the requirements of a proper obviousness rejection—have had to identify additional art that a POSA would have combined

[328] Ex. 1002, 89–90.

[329] Ex. 1002, 90.

with the ’485 and/or ’308 in order to render the treatment of ***status epilepticus*** obvious. There was plenty of such art in the record (*see, e.g.*, Ex. 1009, Ex. 1010, Ex. 1011, Ex. 1022, Ex. 1028, Ex. 1029, Ex. 1030, and Ex. 1031).

A closer examination of that art would necessarily have revealed the deficiencies of the claims with respect to novelty and non-obviousness over that prior art.[330] Furthermore, had the scope and relevance of the prior art been fully comprehended, it would have been unreasonable to merely conclude that “[c]laims 1–31 [of the ’127 application] are neither anticipated nor rendered obvious over the record” and that “[a] suggestion for modification of a reference to obtain the instant methods of use has not been found.”[331]

Moreover, even for the difference that was identified (the scope of dose), the Examiner did not explicitly identify any additional reference or specific rationale for a POSA to have arrived at the claimed dose ranges, stating only that: “[o]ne having ordinary skill in the art would find the claims 1-20 prima facie obvious because one would be motivated to employ the methods of use of During’s ’485 and ’308” and that “[t]he motivation to make the claimed methods of use derived from the known methods of use of During’s ’485 and ’308 would possess same

[330] *See, e.g.,* Sections VIII.A, VIII.B, VIII.D, VIII.E, and VIII.F.

[331] Ex. 1002, 201.

yields to that which is claimed in the reference."[332] Had the legal requirement to provide specific rationale been addressed, here, again, the Examiner would have had to identify additional art that a POSA would have combined with the '485 and/or '308 in order to render the particular scope of dose obvious—another missed opportunity for properly considering the scope and contents of the prior art.

Had the Examiner not simply rubber stamped these claims without proper substantive examination, the claims could not have been allowed—at least for the reasons set forth in this Petition.

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

Finally, this Petition relies on additional evidence that was not available to the Examiner in prosecution in the form of the declaration of Dr. Rogawski (Ex. 1003). Dr. Rogawski's declaration explains what the data presented in the prior art would have meant to a person skilled in the art and to show how the art renders the claims of the '817 patent anticipated or obvious. During prosecution, the Examiner did not have the benefit of the explanations provided in Dr. Rogawski's declaration. That additional evidence presented here with the Petition is another reason why discretionary denial is not appropriate here. *See, e.g.*, *Adv. Energy*

[332] Ex. 1002, 90.

*Indus. v. Reno Techs.*, IPR2021-01397, Paper 7, 7-9 (PTAB Feb. 16, 2022) (rejecting discretionary denial argument and relying in part on additional evidence submitted in the form of an expert declaration).

### D. Conclusion

For at least these reasons, Marinus submits that discretionary denial is not appropriate in this case.

## X. CONCLUSION

Petitioner respectfully requests institution of the PGR and requests that the Board ultimately find the Challenged Claims unpatentable.

## XI. PAYMENT OF FEES

Marinus authorizes charge of fees to Deposit Account 06-1050.

## XII. MANDATORY NOTICES UNDER 37 C.F.R § 42.8 (A)(1)

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

Marinus Pharmaceuticals, Inc. is the real party-in-interest.

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

Petitioner is not aware of any disclaimers, reexamination certificates, other than the PGR petition.

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

Marinus provides the following designation of counsel.

| Lead Counsel | Backup Counsel |
|---|---|
| Martina Tyreus Hufnal, Reg. No. 58,916<br>Fish & Richardson P.C.<br>60 South Sixth Street, Suite 3200<br>Minneapolis, MN 55402<br>Tel: 858-678-5070<br>Fax: 877-769-7945<br>Email: PGR50689-0016PS1@fr.com | Deanna Reichel, *Pro Hac Vice* Forthcoming<br>Anita L. Meiklejohn, Reg. No. 35,283<br>Katie E. Hyma, Reg. No. 75,037<br>Fish & Richardson P.C.<br>60 South Sixth Street, Suite 3200<br>Minneapolis, MN 55402<br>Tel: 858-678-5070<br>Fax: 877-769-7945<br>PGR50689-0016PS1@fr.com |

### D. Service Information

Please address all correspondence and service to the address listed above. Marinus consents to electronic service by email at PGR50689-0016PS1@fr.com (referencing Attorney Docket No. 50689-0016PS1).

Respectfully submitted,

Dated __3/15/2023_____

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**CERTIFICATION UNDER 37 C.F.R. § 42.24**

Under the provisions of 37 C.F.R. § 42.24(d), the undersigned hereby certifies that the word count for the foregoing Petition for Post Grant Review totals 16,370 words, which is less than the 18,700 allowed under 37 C.F.R. § 42.24.

Dated 3/15/2023

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**CERTIFICATE OF SERVICE**

Pursuant to 37 C.F.R. §§ 42.6(e)(4)(i) *et seq.* and 42.105(b), the undersigned certifies that on March 15, 2023, a complete and entire copy of this Petition for Post Grant Review and all supporting exhibits were provided via Federal Express, to the Patent Owner by serving the correspondence address of record as follows:

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