

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MARINUS PHARMACEUTICALS, INC.,
Petitioner

v.

OVID THERAPEUTICS, INC.,
Patent Owner

Case PGR2023-00020
Patent 11,395,817

PETITIONER'S REPLY TO PATENT OWNER RESPONSE

TABLE OF CONTENTS

I.	INTRODUCTION	1
II.	Remaining Grounds	2
III.	The Parties’ Expert Declarations	3
IV.	Claim Construction	5
	A. “A method of treating status epilepticus comprising administering to a patient in need thereof” (claims 22 and 25-31)	5
	B. “wherein the pharmaceutical composition provides improvement to the patient after administration for more than 8 hours” (claim 22)	7
V.	Ground I: Zhang Anticipates The Challenged Claims	8
VI.	GROUND 2-4: Obviousness	12
	A. The Challenged Claims are Obvious	12
	B. Ovid Cannot Rely on Marinus’s Clinical Trial Results as “Unexpected Results”	18
	C. Secondary Indicia Do Not Support Nonobviousness	30
VII.	GROUND 7: The Challenged Claims Are Not Enabled	31
VIII.	CONCLUSION	32

TABLE OF AUTHORITIES

Cases

<i>Allergan, Inc. v. Apotex Inc.</i> , 754 F.3d 952 (Fed. Cir. 2014)	20
<i>Bristol-Myers Squibb Co. v. Ben Venue Labs, Inc.</i> , 246 F.3d 1368 (Fed. Cir. 2001)	11
<i>Cubist Pharms., Inc. v. Hospira, Inc.</i> , 805 F.3d 1112 (Fed. Cir. 2015)	
<i>Ex parte Sylvie Beljanski and John Hall</i> , Appeal 2015-001712 (PTAB Mar. 17, 2017)	13
<i>Grünenthal GmbH v. Antecip Bioventures II LLC</i> , PGR2019-00028 (PTAB Aug. 20, 2019)	6
<i>Hoffmann-La Roche Inc. v. Apotex Inc.</i> , 748 F.3d 1326 (Fed. Cir. 2014)	13
<i>In re Brana</i> , 51 F.3d 1560 (Fed. Cir. 1995)	
<i>In re Klopfenstein</i> , 380 F.3d 1345 (Fed. Cir. 2004)	16
<i>Jockmus v. Leviton</i> , 28 F.2d 812 (2d Cir. 1928)	
<i>Par Pharm., Inc. v. TWi Pharms., Inc.</i> , 773 F.3d 1186 (Fed. Cir. 2014)	13
<i>Pharmastem Therapeutics, Inc. v. Viacell, Inc.</i> , 491 F.3d 1342 (Fed. Cir. 2007)	
<i>Rasmusson v. SmithKline Beecham Corp.</i> , 413 F.3d 1318 (Fed. Cir. 2005)	9
<i>Vanda Pharms., Inc. v. Teva Pharms., Inc.</i> , 2023-1247, 2023 U.S. App. LEXIS 11416 (Fed. Cir. May 10, 2023)	18

PETITIONER’S LIST OF EXHIBITS

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” or “First Rogawski Declaration”)
1004	Reddy and Kuruba, “Experimental Models of Status Epilepticus and Neuronal Injury for Evaluation of Therapeutic Interventions,” <i>Int. J. Mol. Sci.</i> 14:18284-318 (2013) (“Reddy” or “Reddy & Kuruba”)
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,” <i>Heliyon</i> 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,” <i>Synapse</i> 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,” <i>Neuropharmacology</i> , 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_abstractlistingdigi_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, April 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”)

1018	Trinka et al., “A definition and classification of status epilepticus—Report of the ILAE Task Force on Classification of Status Epilepticus.” <i>Epilepsia</i> , 56(10):1515-1523 (2015) (“Trinka”)
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 6 th 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: 3 α -Hydroxy-3 β -methyl-5 α -pregnan-20-one), a Selective, High-Affinity, Steroid Modulator of the γ -Aminobutyric Acid _A Receptor,” <i>The Journal of Pharmacology and Experimental Therapeutics</i> , 280(3):1284-95 (1997)

1029	Saporito et al., Intravenous Administration of Ganaxolone Attenuates Electroencephalographic Seizures in a Diazepam Resistant Model of Status Epilepticus, <i>Neurobiology</i> , 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, <i>Neurology</i> 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,” <i>Annals of Neurol.</i> 80 (suppl 20), S326 published October 26, 2016.
1032	Declaration of Deanna Reichel in Support of Motion for pro hac vice Admission
1033	Supplemental Declaration of Michael Saporito
1034	Table of Contents, <i>Neurology</i> Issue 86 (16 Supplement), dated April 5, 2016; available at https://n.neurology.org/content/86/16_Supplement
1035	Saporito et al., Ganaxolone Administered Intravenously Prevents Behavioral Seizures and Promotes Survival in the Rat Lithium-Pilocarpine Model of Status Epilepticus (I11.003), <i>Neurology</i> 86 (16 Supplement), Abstract, published April 5, 2016, available at https://n.neurology.org/content/86/16_Supplement/I11.003
1036	Intentionally Left Blank
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1041	Supplemental Declaration of Dr. Michael A. Rogawski (“Second Rogawski Declaration”)
1042	Transcript of Deposition of Dr. Raman Sankar, February 9, 2024 (“Sankar Deposition Transcript”)

1043	Beale and Ostrander, “Sizing up Dogs,” <i>Current Biology</i> 22(9):R315-6 (2012) (“Beale”)
1044	Intentionally Left Blank
1045	Clinicaltrials.gov record for NCT03350035
1046	Marinus PCT/US2020/044843 (WO 2021/026124))
1047	Excerpts from the File History of the ’817 Patent
1048	Ovid’s 2022 Annual Report
1049	Intentionally Left Blank
1050	Patterson, “Status Epilepticus and Cluster Seizures,” <i>Vet Clin Small Anim</i> 44:1103-1112 (2014) (“Patterson”)
1051	Charlambous et al., “ACVIM Consensus Statement on the Management of Status Epilepticus and Cluster Seizures in Dogs and Cats,” <i>J Vet Intern Med</i> 2023:1-22 (2023). DOI: 10.1111/jvbm.16928 (“Charlambous”)
1052	Rosetti and Lowenstein, “Management of Refractory Status Epilepticus in Adults,” <i>Lancet. Neurol.</i> 10(10):922-30 (2011) (“Rosetti”)
1053	Shorvon and Ferlisi, “The Treatment of Super-Refractory Status Epilepticus: a Critical Review of Available Therapies and a Clinical Treatment Protocol,” <i>Brain</i> 134:2802-18 (2011) (“Shorvon”)
1054	Nohria and Giller, “Ganaxolone,” <i>Neurotherapeutics</i> 4:102-105 (2007) (“Nohria”)
1055	Supplemental Information to Vaitkevicius et al., “Intravenous Ganaxolone for the Treatment of Refractory Status Epilepticus: Results from an Open-Label, Dose-Finding Phase 2 Trial,” <i>Epilepsia</i> 63:2381-91 (2022) (“ <i>Epilepsia</i> Supplemental Information” or “ <i>Epielpsia</i> SI”)
1056	Publication of Marinus’s U.S. Patent Application Serial No. 17/729,427 (US20220265680)
1057	Publication of Marinus’s U.S. Patent Application Serial No. 17/186,569 (US20210186987)
1058	Declaration of Sharon Baughman, Ph.D.

I. INTRODUCTION

Marinus has pioneered the development of ganaxolone for the treatment of neurological disorders for the last two decades, sponsoring more than twenty clinical trials and laying the foundation for use of the drug in treating status epilepticus (SE). For Ovid, who is not developing and has never developed ganaxolone for any treatment, to suggest that “Ovid’s ’817 patent is the bedrock of Marinus’s clinical development for treating SE” is specious.¹ Notably, every piece of prior art relied on in this proceeding is *Marinus’s* work, from its initial work on ganaxolone in animals to its approval to proceed into human clinical trials, all before Ovid even filed the priority application for the ’817 patent. And the “unexpected results” that Ovid cites to support its claims are from *Marinus’s* clinical trial, for which results were initially *published* before Ovid even added the Challenged Claims to its application.² It is Ovid who has used Marinus’s work as a “roadmap” to exploit the patent system to obtain patents on work Marinus has already done to try to coerce money from Marinus.³

But Ovid’s strategy should fail because its claims are all invalid in view of

¹ Ex. 1041, ¶¶11-17; Ex. 1045; Ex. 1047; Ex. 1048.

² *Id.*

³ *Id.*

Marinus's published work on the use of ganaxolone to treat SE. Before this proceeding was instituted, Ovid statutorily disclaimed 23 of its 31 claims rather than defending them.⁴ This is unsurprising; they are indefensible over the Marinus prior art. Ovid continues, however, to defend invalid claims reciting improvement (claim 22) or doses (claims 25-31). Ovid does so by relying entirely on a claim construction that ignores the definition of "patient" in its own patent, brushing aside results from "a well-established, clinically translatable" animal model,⁵ and providing *Marinus's* clinical trial results as evidence of "unexpected results" of its alleged "invention" even though those results depend on dosing regimens found nowhere in Ovid's broad claims.

Ovid's remaining claims, just like those it disclaimed, are anticipated and obvious over the cited Marinus prior art.⁶ Alternatively, those claims are enabled only by what Marinus disclosed first.

II. REMAINING GROUNDS

Ovid's statutory disclaimer leaves the following grounds remaining:

⁴ POPR, 4; Ex. 2001.

⁵ Ex. 1013, Overview; Ex. 1006, 1.

⁶ Ex. 1041, ¶¶1-3.

Ground	Claims	Basis for Rejection
1	22, 25-31	Anticipation by Zhang (Ex. 1009)
2	22, 25-31	Obviousness over Zhang
3	22, 25-31	Obviousness over Zhang and Saporito P1 (Ex. 1013) and/or Saporito P2 (Ex. 1014)
4	22, 25-31	Obviousness over Zhang, Marinus's Orphan Drug Press Release (Ex. 1011), and Marinus's Phase I Press Release (Ex. 1022)
7	22, 25-31	Lack of enablement

III. THE PARTIES' EXPERT DECLARATIONS

Ovid asserts the Board should not credit Dr. Rogawski's declaration for bias and/or failure to render an independent opinion—first, because Dr. Rogawski's CV did not list his role on Marinus's scientific advisory board ("SAB"), and second because he is allegedly "nothing but a mouthpiece for Petitioner's attorneys."⁷

These arguments are meritless. Dr. Rogawski's role on Marinus's SAB is publicly available information.⁸ Dr. Rogawski did not list any of his many advisory roles⁹

⁷ POR, 13–17.

⁸ Ex. 2012.

⁹ *See, e.g.*, Ex. 2015, 33:25-34:15.

on his CV¹⁰, so the alleged “omission” of Marinus was plainly not intended to mislead. As to the contents of the declaration, as Dr. Rogawski explains, “[a] very rudimentary rough draft was provided” by Petitioner’s attorneys, which he “extensively rewrote” and “added substantial additional materials.”¹¹ He is not a mouthpiece; quite the opposite.

Dr. Sankar, however, is very apparently a mouthpiece for Ovid’s attorneys. Dr. Sankar did not begin forming his opinions until August 2023,¹² two months *after* Ovid submitted their preliminary response. Yet his declaration tracks that preliminary response nearly word-for-word.¹³

In any case, the Board should discount Dr. Sankar’s declaration entirely because Dr. Sankar admits that his opinions are all premised on Ovid’s faulty claim construction, discussed further below.

¹⁰ Ex. 1003, Exhibit A.

¹¹ Ex. 2015, 15:23-16:4.

¹² Ex. 1042, 13:16-18, 98:5-22.

¹³ Compare, e.g., POPR, ¶¶13-22 to Ex. 2014 at 5-10; ¶¶32-33 to 18-19; ¶59-60 to 28-29.

IV. CLAIM CONSTRUCTION

A. “A method of treating status epilepticus comprising administering to a patient in need thereof” (claims 22 and 25-31)

Ovid continues to take the position that “treating status epilepticus comprising administering to a patient in need thereof” in Claim 21 means “treating a human patient suffering from SE.”¹⁴ This is contrary to the specification, which expressly defines “patient[s]” to include patients other than humans.¹⁵ This definition covers not only rats, but also other veterinary patients, which Ovid and Dr. Sankar ignore.¹⁶ The veterinary market was and continues to be significant for SE, and the inclusion of various animal species in the definition of “patient” is consistent with the understanding of the term in the art.¹⁷ Furthermore, use of the word “treatment” does not limit “patient” to “humans”—the ’817 patent itself uses “treatment” in the context of administering ganaxolone to rats suffering from SE.¹⁸ Finally, none of Ovid’s other purported distinctions support a limitation to human

¹⁴ POR, 17-24; Ex. 1041, ¶20.

¹⁵ Ex. 1001, 32:65-67; Ex. 1041, ¶21.

¹⁶ Ex. 1041, ¶¶22-23; Ex. 1042, 88:23-91:3-92:14; Ex. 1050; Ex. 1051.

¹⁷ *Id.*

¹⁸ Ex. 1041, ¶27; Ex. 1001, Example 3; Figs. 2, 7, 6A-6B.

patients.¹⁹ Nothing in the intrinsic record supports Ovid’s narrow construction, as the Board properly found at Institution.

None of the limitations of claims 22 or 25-31 suggest any limitation on the term “patient” either. Any patient may exhibit “improvement” as recited in claim 22. And even if the recited doses of claims 25-31 would be more appropriate for a human-sized patient than a rat-sized patient, this does not support a limitation to humans—a dog or porcine patient (both included in the ’817’s definition), may weigh as much as a human.²⁰

Ovid’s cited cases do not support its construction because, unlike the ’817 claims, they involve claims that specifically recite “human” treatment.²¹ If Ovid wanted to prosecute claims limited to “treating a human patient,” they could have

¹⁹ Ex. 1041, ¶¶24-31.

²⁰ Ex. 1041, ¶¶29-30; Ex. 1043.

²¹ POR, 18, citing *Jansen v. Rexall Sundown, Inc.*, 342 F.3d 1329, 1330 (Fed. Cir. 2003) (claiming a “method of treating or preventing [disease X] in humans . . .”); and *Grünenthal GmbH v. Antecip Bioventures II LLC*, PGR2019-00028, Institution Decision, Paper 6, 6 (PTAB Aug. 20, 2019) (claiming a “method of treating” comprising administering a therapeutic “to a human being suffering from [a disease].”)

done so (and are doing so in other applications in this family). But here, they didn't.

B. “wherein the pharmaceutical composition provides improvement to the patient after administration for more than 8 hours” (claim 22)

Claim 22 requires “intravenous” administration of “a pharmaceutical composition” of ganaxolone “wherein the pharmaceutical composition provides improvement to the patient after administration for more than 8 hours.” It does not require any specific dosing regimen. Ovid concedes that the claim allows for a multiple dose regimen but argues that “improvement” must be measured after all doses are given.²² The intrinsic evidence does not support this construction.

The '817 patent explains that “improvement” refers to a relative change in symptoms, which may be measured “in a subject prior to treatment, and again one or more times after treatment is *initiated*.”²³ *Initiated*, not completed. This is consistent with how those in clinical practice measure improvement during treatment.²⁴

Assessing “improvement . . . after administration for more than 8 hours”

²² See POR, 24.

²³ Ex. 1041, ¶¶32-33; Ex. 1001, 29:57-60; 9:43-46; 13:35-38.

²⁴ Ex. 1041, ¶¶34-37.

does not require “starting the clock after the first administration of only part of [a] dose,” as Dr. Sankar asserts.²⁵ It simply requires measuring symptoms at a time more than 8 hours after treatment is initiated, as the ’817 describes.²⁶

V. GROUND I: ZHANG ANTICIPATES THE CHALLENGED CLAIMS

Ovid’s anticipation arguments, and Dr. Sankar’s declaration, rely entirely on an incorrect construction limiting the claims to human patients.²⁷ The claims are not so limited,²⁸ and Ovid’s arguments can be rejected for that reason alone.

Ovid also makes much ado about the absence of data in Zhang showing clinical efficacy in humans.²⁹ Even if the claims were limited to human patients, anticipation does not require proof of efficacy. *See Impax Labs., Inc. v. Aventis Pharms., Inc.* 468 F.3d 1366, 1383 (Fed. Cir. 2006) (proof of efficacy not required for anticipation where the claim recited a “method for treating a mammal with [disease X], comprising the step of administering to said mammal in recognized

²⁵ Ex. 2014, ¶¶66.

²⁶ Ex. 1041, ¶¶32-41.

²⁷ POR, 25:8-28:10; Ex. 1042, 42:8-43:1.

²⁸ *See* Section IV.

²⁹ POR, 26:8-28:10.

need of said treatment an effective amount of [compound Y] or a pharmaceutically acceptable salt thereof”); *see also Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1325-26 (Fed. Cir. 2005). Zhang anticipates claim 21 because it “describes the claimed invention sufficiently to enable a person of ordinary skill in the art to carry out the invention.” *See id.*

1. Claim 22

Claim 22 adds that “the pharmaceutical composition provides improvement to the patient after administration for more than 8 hours.” It does not, however, recite any further limitations as to *how* ganaxolone is administered. As described below, Zhang anticipates claim 22, expressly and inherently.

Zhang contains a working example of administering ganaxolone IV to rats that demonstrates the claimed “improvement.”³⁰ The rats showed a reduced percentage of observed seizures in the first five hours after administration—which a POSA would understand provides improvement after eight hours because of the importance of reducing the time in spent in SE.³¹ As Dr. Sankar puts it: “time is brain.”³²

³⁰ Ex. 1003, ¶¶92-95; Ex. 2015, 81:1-12; Ex. 1009, Example 8.

³¹ Ex. 1041, ¶¶38-41, 46-49; Ex. 1003, ¶¶92-94.

³² Ex. 1042, 19:22-20:15.

As Dr. Rogawski explained, administering multiple doses of ganaxolone, would naturally “provide sustained treatment for more than 8 hours” after initiation of treatment, whether in a human or veterinary patient.³³ Ovid has no response on this point other than its incorrect construction that measures improvement 8 hours after the *completion* of treatment.

Zhang also anticipates the 8-hour limitation inherently because of the natural result of the treatment steps it teaches, even though the rats were sacrificed after 5 hours, as shown in Saporito P1 (Ex. 1013)³⁴ and the ’817 patent itself.³⁵ Zhang’s rats were treated with 12 or 15 mg/kg IV ganaxolone administered at 15 and 60 minutes after SE onset.³⁶ The rats in Saporito P1 were treated with ganaxolone in the same manner and with the same dose and showed improvement after 8 hours in the form of increased 24-hour survival rates.³⁷ The ’817 patent also shows that administration of 10 and 20 mg/kg ganaxolone, which bracket the 12 and 15 mg/kg

³³ Ex. 1003, ¶94.

³⁴ Ex. 1041, ¶49; Ex. 1013.

³⁵ Ex. 1001, Fig. 4; Institution Decision at 27.

³⁶ Ex. 1041, ¶49; Ex. 1013.

³⁷ *Id.*

in Zhang, led to improved 24-hour survival.³⁸ Dr. Sankar agrees that increased survival is a “beneficial outcome in treatment,” and thus reflects an “improvement” as required by claim 22.³⁹

Because the claimed improvement naturally results from performance of the same steps disclosed in the prior art, claim 22 is inherently anticipated. *See Bristol-Myers Squibb Co. v. Ben Venue Labs, Inc.*, 246 F.3d 1368, 1376 (Fed. Cir. 2001) (finding claims reciting efficacy of a cancer drug anticipated where “the claimed process [was] the same use, and [consisted] of the same steps as described [in the prior art]”).

2. Claims 25-31

Claims 25-31 add dose ranges to claim 21.⁴⁰ Zhang teaches weight-based

³⁸ Ex. 1001, Fig 4; Institution Decision, 27.

³⁹ Ex. 1042, 37:12-21, 32:19-34:3; Ex. 1041, ¶¶42-50.

⁴⁰ Ovid asserts that “it is not true that ‘any dose of ganaxolone would function to treat [SE] patients *and result in improvement to the patient as required by claims 25-31*,” quoting the Institution Decision at 30. POR at 38 (emphasis added). As the Board notes, however, claims 25-31 “depend from claim 21 and *therefore do not recite the ‘more than 8 hours’ language found in claim 22.*” Institution Decision at 30 (emphasis added).

dosing of ganaxolone in the amounts recited in claims 25-31.⁴¹ Zhang's entire disclosure is related to intravenous ganaxolone for treatment of seizure disorders, specifically including status epilepticus.⁴² The background and examples focus on SE.⁴³ In light of that disclosure, a POSA would understand that the disclosed dose ranges apply to treatment of SE in patients, which include human patients.⁴⁴ There is no "picking and choosing" required to conclude that Zhang describes administering IV ganaxolone to a patient in the claimed amounts sufficiently to enable a POSA to do so. Zhang anticipates claims 25-31.

VI. GROUNDS 2-4: OBVIOUSNESS

A. The Challenged Claims are Obvious

As with anticipation, all Ovid's obviousness arguments are admittedly based on the faulty assumption that the claims are limited to human treatment.⁴⁵ Thus, Ovid again has no arguments under the proper claim construction.

⁴¹ Ex. 1003, ¶¶99-105; Ex. 1009, ¶¶[0069]-[0085].

⁴² Ex. 1009, Title, Abstract, ¶¶[0001]-[0004], [0022], [0069]-[0089], Example 8; Ex. 1052; Ex. 1053.

⁴³ Ex. 1041, ¶44; Ex. 1009, ¶[0001], Example 8; Ex. 1053.

⁴⁴ Ex. 1041, ¶45.

⁴⁵ POR, 52, 58-59, 67-68, 72, 73, 74; Ex. 1042, 76:7-78:22.

Moreover, Ovid applies an overly high standard to reasonable expectation of success. Reasonable expectation of success does not require absolute certainty. *Hoffmann-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1331 (Fed. Cir. 2014) (“Conclusive proof of efficacy is not necessary to show obviousness.”); *see also Par Pharm., Inc. v. TWi Pharms., Inc.*, 773 F.3d 1186, 1198 (Fed. Cir. 2014). Nor does it require human clinical data, as Dr. Sankar wrongly believes.⁴⁶ The “point of animal research,” particularly in a widely-accepted animal model, is “to apply the information to human treatments.” *See Ex parte Sylvie Beljanski and John Hall*, Appeal 2015-001712, Decision at 14 (PTAB Mar. 17, 2017) (citing *In re Brana*, 51 F.3d 1560, 1568 (Fed. Cir. 1995); *see also Pharmastem Therapeutics, Inc. v. Viacell, Inc.*, 491 F.3d 1342, 1364-65 (Fed. Cir. 2007) (finding obviousness where inventors “simply provided experimental proof that the cord blood could be used to effect hematopoietic reconstitution of mice and, by extrapolation, could be expected to work in humans as well”); *Cubist Pharms., Inc. v. Hospira, Inc.*, 805 F.3d 1112, 1124-25 (Fed. Cir. 2015). A POSA would have had a reasonable expectation of success at arriving at the Challenged Claims.⁴⁷ Ovid presents *no* evidence to the contrary.

⁴⁶ Ex. 1042, 78:7-19.

⁴⁷ Ex. 1041, ¶¶51-61.

1. Ground 2: Zhang

Zhang teaches a POSA that ganaxolone was already known to be “useful for treating seizures in adult and pediatric patients.”⁴⁸ It also points to previous studies on the pre-clinical and clinical pharmacology of ganaxolone.⁴⁹ These studies described oral human doses: 50 to 1500 mg to healthy human volunteers; up to 750 mg to humans with migraines; 1500 mg/d and 1875 mg/d in adult human patients with epilepsy; and up to 36 (mg/kg)/day in pediatric patients.⁵⁰

In the section titled “Methods of Treatment,” Zhang describes treating SE by “administering an effective amount of [injectable ganaxolone] to a patient.”⁵¹

Zhang teaches that in some embodiments the method of treatment is administration of a single bolus doses of from about 1-20 mg/kg, (which is 70-1,400 mg for a 70 kg human), as well as multiple bolus doses over 1 to 10 days at intervals of 1 to 24 hours in the same amount as the single bolus.⁵² Zhang’s doses and, therefore, the doses of claims 25-31, are consistent with what a POSA already knew about the

⁴⁸ Ex. 1041, ¶53; Ex. 1009, ¶[0027] (citing Ex. 1054).

⁴⁹ *Id.*

⁵⁰ *Id.*

⁵¹ Ex. 1041, ¶54; Ex. 1009, ¶¶[0022], [0069]-[0089]; Ex. 1003, ¶¶102-104.

⁵² *Id.*

clinical pharmacology of ganaxolone.

Zhang describes studies showing that ganaxolone administered intravenously to rats experiencing SE at 12 and 15 mg/kg results in an improvement.⁵³ With these results in Zhang's "well established and clinically translatable" rat model,⁵⁴ a POSA would have had a reasonable expectation of success at treating other patients experiencing SE.⁵⁵ And the POSA would have found it obvious to dose at the levels Zhang taught to achieve a therapeutic effect.⁵⁶ The Challenged Claims are obvious in view of Zhang.⁵⁷

2. Ground 3: Zhang and Saporito Posters

Despite Ovid's argument,⁵⁸ the Saporito Posters are prior art. These posters were presented at the 2016 AAN Annual Meeting,⁵⁹ a gathering attended by thousands of clinicians and researchers (including POSAs) interested in treatments

⁵³ Ex. 1041, ¶¶56, Ex. 1009, Example 7, ¶[0016], Figure 2.

⁵⁴ Ex. 1006.

⁵⁵ Ex. 1041, ¶¶51-58.

⁵⁶ Ex. 1041, ¶¶67-71; Ex.1003, ¶¶159.

⁵⁷ Ex. 1041, ¶¶51-61.

⁵⁸ POR, 61-65.

⁵⁹ Ex. 1015, ¶¶5-15; Ex. 1033, ¶¶1-11.

for neurological disorders like SE.⁶⁰ Dr. Saporito, who presented the posters, explained that the exhibits are, in fact, the same as the posters he presented, and that the sessions at which he presented them were well attended and did not prohibit those in attendance from taking notes and photographs.⁶¹ These posters were “sufficiently accessible to the public interested in the art.” *In re Klopfenstein*, 380 F.3d 1345, 1348 (Fed. Cir. 2004); *see also Jockmus v. Leviton*, 28 F.2d 812, 813-14 (2d Cir. 1928) (a reference, “however ephemeral its existence,” may be a “printed publication” if it “goes direct to those whose interests make them likely to observe and remember whatever it may contain that is new and useful”).

Beyond that, Ovid’s arguments on this ground largely mirror its incorrect “human” claim construction and its incorrect arguments that POSAs would not have expected efficacy in humans based on rat data.⁶² Those arguments should be rejected for the same reasons discussed above. POSAs would have considered the data in Saporito P1 and P2 to provide further support for Zhang’s teachings on the use of ganaxolone to treat SE (including in humans), and an additional reason to

⁶⁰ *Id.*; Ex. 1003, ¶37.

⁶¹ Ex. 1015, ¶¶8-15; Ex. 1033, ¶¶3-4, 6-7; Ex. 1034; Ex. 1035.

⁶² POR, 66-71.

expect success.⁶³ Relevant to claim 22, the only claim to recite an “improvement,” Saporito P1 teaches that improvement in the form of increased 24-hour survival rates for rats treated with ganaxolone using the doses taught in Zhang, as discussed in Section V.1.

3. Ground 4: Zhang and Marinus Press Releases

Ovid’s arguments on ground 4 again depend on its flawed construction requiring human treatment and overly high requirement for expectation of success⁶⁴ and should be rejected for the same reasons.

Ovid’s suggestion that a POSA would not have had reason to combine Zhang, which specifically discusses ganaxolone to treat SE, with press releases that show FDA moving forward Marinus’s clinical development of ganaxolone to treat SE defies credulity. And its efforts to minimize the importance of FDA allowing a drug to move forward with clinical development for SE as a factor that impacts reasonable expectation of success is simply unsupported. As Dr. Sankar admitted, because FDA was allowing Marinus to move forward with its Phase 1 trial, “it seems logical” that FDA believed this was a “promising approach to that,

⁶³ Ex. 1041, ¶¶56-58.

⁶⁴ POR, 74.

otherwise they wouldn't have gone into phase 1.”⁶⁵ *See Vanda Pharms., Inc. v. Teva Pharms., Inc.*, 2023-1247, 2023 U.S. App. LEXIS 11416, at *9 (Fed. Cir. May 10, 2023) (citing ongoing clinical trials as part of reasonable expectation of success analysis).

B. Ovid Cannot Rely on Marinus's Clinical Trial Results as “Unexpected Results”

Because it did nothing to develop ganaxalone, Ovid tries to offer *Marinus's* clinical trial work as evidence of “unexpected results” of the Challenged Claims, all of which were added to Ovid's application *after* Marinus began to publish its clinical trial work.⁶⁶ But Ovid conveniently ignores and/or misrepresents the details of Marinus's work, which are absent from Ovid's claims.

Ovid offers different theories for “unexpectedness,” all based on Marinus's Phase II clinical trial results (Ex. 2003), which were discussed in the Hulihan Declarations (Ex. 2007; Ex. 2008) Marinus presented during prosecution of its own patents (Ex. 1056; Ex. 1057), as follows:

⁶⁵ Ex. 1042, 86:13-87:4; *see also* Ex. 1041, ¶¶59-61.

⁶⁶ Ex. 1041, ¶¶11-17; Ex. 1046; Ex. 1047.

Claim(s)	Allegedly Unexpected Result from Ex. 2003	POPR, POR & Sankar Declaration
22	Lack of treatment escalation 24 h following completion of infusion (Table 2, row 3) Lack of relapse in 85% of evaluable patients four weeks after completion of infusion (page 2386)	POR, 45; Ex. 1014, ¶113
	Rapid & sustained effect observed for “High” dose cohort in clinical trial (page 2386)	POR, 45-48 and 49
25-31	“Rapid” seizure cessation and reduction in seizure burden (page 2388)	POR, 44; Ex. 1014, ¶¶109-112
	Lack of recurrence of SE after discontinuation of ganaxolone infusion (page 2388)	
30	Rapid & sustained effect observed for “High” dose cohort in clinical trial (page 2386)	POR, 45-48; Ex. 1014, ¶¶113-116

All these results were achieved with Marinus’s specific dosing regimens that represent, at best, a few of the countless embodiments that are covered by Ovid’s broad claims. These results are nowhere near commensurate in scope with the Challenged Claims and, therefore, cannot be used as evidence of non-obviousness.⁶⁷ *See, e.g., In re Inland Steel Co.*, 265 F.3d 1354, 1365 (Fed. Cir. 2001) (finding no unexpected results where the applicant relied on data for a particular alloy composition prepared with specific process steps and conditions, but there was no basis for assuming that similar results could be obtained with other compositions and processes within the scope of the claim); *see also Allergan*,

⁶⁷ Ex. 1041, ¶¶62-70.

Inc. v. Apotex Inc., 754 F.3d 952, 963 (Fed. Cir. 2014).

1. Marinus's Clinical Trial (Ex. 2003)

Marinus conducted an open-label, phase 2 trial to evaluate dosing regimens for ganaxolone in the treatment of refractory status epilepticus (RSE).⁶⁸

Patients were given ganaxolone infusions starting with an IV bolus over 3 minutes, followed by continuous infusion of decreasing infusion rates for 48-96 hours and then an 18-hour taper.⁶⁹ The detailed dosing information, which Dr. Sankar did not consider⁷⁰ and Ovid did not provide to the Board, appears in Supplemental Table 1 to the *Epilepsia* article (referred to in section 2.2 titled "Treatment") (Ex. 1055), reproduced below:⁷¹

⁶⁸ Ex. 2003, 2383.

⁶⁹ *Id.*, Abstract.

⁷⁰ Ex. 1042, 58:7-18

⁷¹ Ex. 1041, ¶65; Ex. 2003, 2383.

Vaitkevicius et al. **Supplemental Material**

Supplemental Table 1. Ganaxolone dosing used in this study

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

^aInitial bolus was delivered over 3 min.

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

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

The three dosing cohorts were referred to as the “Low” “Medium,” and “High” cohorts, all of which included a bolus for the “rapid loading of ganaxolone (plasma concentration ~ 900 ng/ml) designed to abort SE” followed by continuous infusion to administer “maintenance doses aimed at sustaining seizure control.”⁷² After 2 days, if the patient was deriving continuing benefit, investigators were allowed to extend infusions for an additional 2 days (4 days total) before beginning

⁷² *Id.*

the 18-hour taper.⁷³

The study's primary end point was "the number of patients not requiring escalation to IV anesthetic treatment within 24 h of ganaxolone initiation."⁷⁴

The initial bolus doses, included with all three dosing cohorts resulted, as predicted, "in rapid reductions in seizure burden within the first 15 min of infusion."⁷⁵ The continuous infusions allowed for a sustained response.⁷⁶

The study also measured and reported the number of patients who were "[s]tatus-free" and/or required "no escalation to additional IV ASMs or to third-line IV anesthetics for status relapse" "during 24 h following infusion completion."⁷⁷ Marinus found that "no patient required escalation to third-line IV anesthetics during the 24-h period following ganaxolone initiation."⁷⁸

2. The Hulihan Declarations (Exs. 2007 and 2008)

Marinus made some unexpected discoveries in their clinical trial, but none

⁷³ *Id.*

⁷⁴ Ex. 2003, 2384, Table 2.

⁷⁵ *Id.*, 2386.

⁷⁶ *Id.*

⁷⁷ *Id.*, Table 2.

⁷⁸ *Id.*, 2381.

of those results are tied to Ovid's claims.

Marinus scientists “unexpectedly discovered that SE could be rapidly *and persistently* suppressed using less ganaxolone and for a much shorter period of time than was anticipated.”⁷⁹ They discovered that the bolus plus continuous infusions that “achieve[d] and maintain[d] a ganaxolone plasma concentration of about 500 ng/ml to about 1000 ng/ml for about 8 to about 12 hours,” resulted “in rapid and persistent suppression of SE, without recurrence of SE when the rate of ganaxolone infusion was reduced and treatment was terminated.”⁸⁰ They also discovered that a “transient” ganaxolone plasma concentration of about 500-1000 ng/ml was not sufficient to achieve persistent suppression of SE.⁸¹ “In fact, when the plasma concentration dropped below 500 ng/ml prior to completing 8 to 12 hours of treatment, seizures rapidly recurred.”⁸² For persistent suppression, “it is important to *maintain that ganaxolone plasma concentration [500 to 1000 ng/ml] for about 8 to about 12 hours.*”⁸³ The persistent suppression after 8-12 hours,

⁷⁹ Ex. 2007, 31; Ex. 2008, 27 (emphasis added).

⁸⁰ *Id.*

⁸¹ *Id.*

⁸² *Id.*

⁸³ *Id.*

achieved with Marinus's specific bolus plus continuous infusion dosing regimens, was unexpected.

Marinus discussed these results during prosecution of its 17/729,427 and 17/186,569 applications in declarations from Dr. Hulihan.⁸⁴ At that time those declarations were submitted, the claims of both Marinus applications required that "*ganaxolone is administered as a bolus plus continuous infusion*" to maintain plasma concentrations of 500-1000 ng/mL for 8-12 hours.⁸⁵ Ovid's claims contain no such limitations.

Indeed, Ovid presents no evidence that dosing regimens other than those in the Marinus trial, which are only a tiny fraction of the countless dosing regimens covered by the Challenged Claims, would achieve these results.⁸⁶ Even in the Marinus clinical trial, ganaxolone plasma levels ≥ 500 ng/ml were achieved for 8 hours, along with "the most durable reduction in seizure burden," only in the high cohort (not the low or medium cohorts), showing the importance of the particular

⁸⁴ Ex. 2007, 29-32; Ex. 2008, 25-28.

⁸⁵ *Id.*

⁸⁶ Ex. 1041, ¶¶ 65-69.

regimen.⁸⁷ Ovid has claims encompassing all the cohorts, and more.⁸⁸

3. Claim 22

Ovid's attempt to get the benefit of Marinus's clinical results for claim 22 fails. Ovid alleges that the number (and percent) of patients meeting the criteria "[n]o escalation to additional IV ASMs or to third-line IV anesthetics for status relapse during 24 h following infusion completion, *n* (%)" (the third row of Table 2 in the *Epilepsia* paper) are "unexpected results" flowing from claim 22.⁸⁹ Ovid does not even attempt to explain the difference between claim 22 and the prior art (there is none), nor how any purported difference would give rise to the results in Table 2 (it could not).

Claim 22 covers administration of ganaxolone in *any* amount, in *any* intravenous format, and in *any* patient. Dr. Sankar agreed that there is "no dosing regimen described in claim 22 or incorporated in claim 22."⁹⁰ Claim 22 does not require an initial bolus dose followed by a continuous infusion, which all the patients in the Marinus clinical trial received and which was important to achieving

⁸⁷ Ex. 2003, 2388.

⁸⁸ Ex. 1041, ¶¶ 62-70.

⁸⁹ POR, 45.

⁹⁰ Ex. 1042, 46:4-8.

the results.⁹¹ Dr. Sankar admitted that “changing the dosing regimen could change the results” and that, without a bolus, his “suspicion is that [patients] would not have been controlled as rapidly.”⁹² Indeed, without an initial bolus, there is no evidence that SE could be broken at all, let alone sustained. Claim 22, with no limitation on dosing, is not commensurate in scope with Marinus’s results.

In a paragraph unsupported by any evidence, Ovid also suggests that the results achieved for Marinus’s High cohort support non-obviousness of claim 22.⁹³ But again, these results are not commensurate in scope with claim 22, which would encompass all three cohorts plus countless other potential dosing regimens not shown to achieve the same results.

Claim 22 is obvious; Marinus’s clinical trial results, achieved with specific dosing *not* required by claim 22, do not change that.

4. Claims 25-31

The results of the specific dosing regimens used in Marinus’s clinical trial do not support patentability of Claims 25-31. To get the benefit of Marinus’s unexpected results, Ovid must show that substantially all dosing regimens covered

⁹¹ Ex. 1042, 53:24-54:9; 55:1-10; 56:11-15; 65:1-8; Ex. 1058, ¶¶ 14-24.

⁹² Ex. 1042, 67:22-68:12.

⁹³ POR, 49.

by the Challenged Claims would achieve the same unexpected results. Ovid cannot, and doesn't even try to, make that showing.

Claims 25-31 require intravenous administration of ganaxolone in amounts ranging from 500 mg to 1050 mg (per day for claims 25-30). However, the claims do not specify *how* that amount is to be administered and instead cover “all the options as long as they fell within that range,” including single or multiple doses or just a continuous IV drip.⁹⁴ But the particular dosing regimen is central to achieving the results of Marinus's clinical trial and leads to a similar commensurate in scope problem for Ovid as with claim 22.

Ovid first tries to make the case that “[t]he ‘rapid’ seizure cessation and reduction in seizure burden” Marinus observed is an unexpected result.⁹⁵ But that “rapid” cessation and reduction in seizure burden relates to the administration of the bolus dose in the Marinus clinical trial, as Dr. Sankar admitted.⁹⁶ Claims 25-31 do not require that bolus dose and cover many potential dosing regimens that do not use it.

Similarly, Ovid vainly tries to claim the benefit of the lack of recurrence

⁹⁴ Ex. 1042, 46:10-49:2; *see also* Ex. 1041, ¶¶62-70.

⁹⁵ POR, 44.

⁹⁶ *Id.*, 56:9-15, 65:2-8; Ex. 2003, 2383.

results of the specific dosing regimens used in the clinical trial.⁹⁷ Ovid asserts that the “lack of recurrence of SE after discontinuation of the ganaxolone infusion resulting from IV administration of 500 mg/day, 650 mg/day, and 713 mg/day were unexpected over [Marinus’s] expectation that ‘high ganaxolone exposure for a long treatment period of at least 4 days duration, would be required to break SE.’” But again, claims 25-31 do not require any particular dosing regimen, and certainly not the specific regimens that Marinus used to achieve the results in its clinical trial. The amount (daily for claims 25-30 and over any specified time frame for claim 31) could be administered in a single bolus. Or it could be administered in an even dose throughout the day (or unspecified amount of time) with no bolus.⁹⁸ In either case, there is no reason to believe (nor does Ovid attempt to provide one) or any evidence that *all* or even most dosing regimens of 500 mg/day, 650 mg/day, and 713 mg/day would result in lack of recurrence of SE after administration. Indeed, Dr. Sankar acknowledged that the 500 ng/mL plasma concentration that led to the results is “a function of the bolus and then the continuous infusion afterwards.”⁹⁹ Ovid’s claims are not commensurate in scope with Marinus’s

⁹⁷ POR, 44.

⁹⁸ Ex. 1041, ¶67.

⁹⁹ Ex. 1042, 65:9-66:10.

clinical trial results and, Ovid cannot rely on them to support non-obviousness.

See Inland Steel, 265 F.3d at 1365.

Ovid argues separately with respect to claim 30, which recites “700 mg to 725 mg/day ganaxolone.” While this amount facially corresponds to the total amount given in Marinus’s “High” dose cohort, it does not require the specific bolus plus continuous infusion dosing regimen that gives rise to the unexpected results related to maintaining a plasma concentration above 500 ng/ml for at least 8 hours. As described in the Hulihan declarations, it was maintaining the plasma concentration by administering ganaxolone as an IV bolus followed by continuous infusion to achieve a serum concentration above 500 ng/ml “for a short duration of only about 8 to about 12 hours” [as was the case for the High cohort] that gave rise to the unexpected persistent SE suppression.¹⁰⁰ But “when the plasma concentration dropped below 500 ng/ml prior to completing 8 to 12 hours of treatment [as was the case for the Low and Medium cohorts], seizures rapidly recurred.”¹⁰¹ Pharmacokinetics modeling shows that, without the bolus dose, there are dosing regimens covered by Ovid’s claims that fail to even reach plasma

¹⁰⁰ Ex. 2007, 31; Ex. 2008, 27.

¹⁰¹ *Id.*

concentrations of 500 ng/mL within 24 hours.¹⁰²

Claims 25-31 are obvious. Marinus's clinical trial results do not support nonobviousness.

C. Secondary Indicia Do Not Support Nonobviousness

Neither long-felt need nor failure of others supports non-obviousness. On long-felt need, there is no question that SE is a “difficult to treat seizure disorder with limited treatment options.”¹⁰³ However, it is Marinus, not Ovid, who has worked for years to provide that treatment option, as evidenced by the cited art. “[O]nce another supplied the key element, there [is] no long-felt need.” *Newell Cos., Inc. v. Kenney Mfg. Co.*, 864 F.2d 757, 768 (Fed. Cir. 1988); *see also Ohio Willow Wood Co. v. Alps S.*, 735 F.3d 1333, 1344 (Fed. Cir. 2013). That is precisely what Marinus has done in Zhang and Saporito. Ovid's claims add nothing to fill any need.

On failure of others, as the Board already stated, “rather than show failure by others, the evidence of record suggests success by others.”¹⁰⁴ And any supposed failure by non-ganaxolone drugs is irrelevant.

¹⁰² Ex. 1058, ¶¶18-22.

¹⁰³ Ex. 1011, 1.

¹⁰⁴ Institution Decision, 35.

**VII. GROUND 7: THE CHALLENGED CLAIMS ARE NOT
ENABLED**

Ovid's entire argument rests on its incorrect claim construction that the Challenged Claims are limited to the treatment of SE in humans.¹⁰⁵ Yet the '817 patent itself discloses no data on treating SE in humans. Like the Zhang and Saporito prior art relied on in the Grounds, the '817 patent discloses an example of treating SE in rats. While Petitioner believes, as discussed in detail in the Petition and above, that the data in rats renders the claims obvious even if the claims are limited to humans, Ovid disagrees. Indeed, Ovid's own expert, who did *not* opine on enablement,¹⁰⁶ believes that "absent human data the patent cannot claim treating a human patient."¹⁰⁷ If the prior art data in rats is not sufficient to render the claims obvious, then the data in the specification itself is also not sufficient to enable them.

¹⁰⁵ POR, 25:8-28:10; Ex. 1042, 42:8-43:1.

¹⁰⁶ Ex. 1042, 41:19-21.

¹⁰⁷ *Id.*, 78:14-19.

VIII. CONCLUSION

Petitioner has established that the Challenged Claims are unpatentable and respectfully requests that the Board find the same.

Respectfully submitted,

Dated: March 7, 2024

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CERTIFICATION UNDER 37 C.F.R. § 42.24

Under the provisions of 37 CFR § 42.24(d), the undersigned hereby certifies that the word count for the foregoing Petitioner Reply to Patent Owner Response totals 5,556 words, which is less than the 5,600 allowed under 37 CFR § 42.24(c)(1).

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CERTIFICATE OF SERVICE

Pursuant to 37 CFR §§ 42.6(e)(4) and 42.205(b), the undersigned certifies that on March 7, 2024, a complete and entire copy of this Petitioner's Reply to Patent Owner's Response and accompanying exhibits were provided by email to the Patent Owner by serving the correspondence address of record as follows:

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