

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 B2

PATENT OWNER'S SUR-REPLY

TABLE OF CONTENTS

	Page
I. Introduction	1
II. Dr. Rogawski’s Previously Undisclosed Relationships with Marinus and Ovid Undermine His Credibility	2
III. Marinus’s Own Arguments Belie Its Claim-Construction Positions	4
A. “Treating status epilepticus comprising administering to a patient in need thereof” (claims 22 and 25-31)	4
B. “Improvement to the patient after administration for more than 8 hours” (claim 22)	5
IV. Ground 1: Zhang Does Not Anticipate Claims 22 and 25-31	7
A. Zhang does not describe “treating status epilepticus comprising administering to a patient in need thereof” (claims 22 and 25-31)	7
B. Zhang does not describe “improvement to the patient after administration for more than 8 hours” (claim 22).....	8
C. Zhang does not describe the dose ranges in claims 25-31	11
V. Grounds 2-4: Petitioner Has Not Demonstrated that Claims 22 and 25-31 Would Have Been Obvious Over Any of the Asserted References.....	12
A. Objective indicia support nonobviousness	12
1. Unexpected results demonstrate patentability	12
a. The results are commensurate in scope	12
b. Marinus’s “data” is irrelevant	15
2. Failure of others and long-felt unmet need.....	18
B. Ovid Has Applied the Correct Standard for Reasonable Expectation of Success	19
C. Ground 2: Zhang.....	20

D.	Ground 3: Zhang in Combination with Saporito P1 and/or Saporito P2	22
E.	Ground 4: Zhang in Combination with Marinus’s Press Releases	23
VI.	Ground 7: Claims 22 and 25-31 Are Enabled.....	25
VII.	Conclusion.....	25

TABLE OF AUTHORITIES

	Page(s)
Cases	
<i>Ex parte Beljanski</i> , No. 2015-001712, 2017 WL 1032225 (PTAB Mar. 17, 2017)	20
<i>Bettcher Indus., Inc. v. Bunzl USA, Inc.</i> , 661 F.3d 629 (Fed. Cir. 2011)	9
<i>Blasters, Inc. v. Waterblasting, LLC</i> , IPR2018-00504, Paper 26 (PTAB July 16, 2019)	3
<i>Connell v. Sears, Roebuck & Co.</i> , 722 F.2d 1542 (Fed. Cir. 1983)	9
<i>Eli Lilly & Co. v. Teva Pharms. Int’l GmbH</i> , 8 F.4th 1331 (Fed. Cir. 2021)	19, 23
<i>GE Lighting Sols., LLC v. AgiLight, Inc.</i> , 750 F.3d 1304 (Fed. Cir. 2014)	6
<i>Genetics Institute, LLC v. Novartis Vaccines & Diagnostics, Inc.</i> , 655 F.3d 1291 (Fed. Cir. 2011)	13
<i>Henny Penny Corp. v. Frymaster LLC</i> , 938 F.3d 1324 (Fed. Cir. 2019)	8
<i>Hoffman-La Roche Inc. v. Apotex Inc.</i> , 748 F.3d 1326 (Fed. Cir. 2014)	19
<i>Impax Labs., Inc. v. Aventis Pharms. Inc.</i> , 468 F.3d 1366 (Fed. Cir. 2006)	7
<i>In re Inland Steel Co.</i> , 265 F.3d 1354 (Fed. Cir. 2001)	13, 14
<i>Luye Pharma Grp. Ltd. v. Alkermes Pharma Ire. Ltd.</i> , IPR2016-01095, Paper 13 (PTAB Nov. 30, 2016)	11

<i>Medichem, S.A. v. Rolabo, S.L.</i> , 437 F.3d 1157 (Fed. Cir. 2006)	19, 23, 24
<i>OSI Pharms., LLC v. Apotex Inc.</i> , 939 F.3d 1375 (Fed. Cir. 2019)	19, 24
<i>PAR Pharm., Inc. v. TWI Pharms., Inc.</i> , 773 F.3d 1186 (Fed. Cir. 2014)	19
<i>Raytheon Techs. Corp. v. Gen. Elec. Co.</i> , 993 F.3d 1374 (Fed. Cir. 2021)	2
<i>Salazar v. AT&T Mobility LLC</i> , 64 F.4th 1311 (Fed. Cir. 2023)	5
<i>Sandoz Inc. v. Pharmacyclics LLC</i> , IPR2019-00865, Paper No. 8 (PTAB Sept. 26, 2019)	9
<i>Sanofi-Synthelabo v. Apotex, Inc.</i> , 550 F.3d 1075 (Fed. Cir. 2008)	7
<i>SIBIA Neurosciences, Inc. v. Cadus Pharm. Corp.</i> , 225 F.3d 1349 (Fed. Cir. 2000)	21
<i>Vanda Pharmaceuticals Inc. v. Teva Pharmaceuticals USA, Inc.</i> , No. 2023-1247, 2023 WL 3335538 (Fed. Cir. May 10, 2023)	24
<i>ZUP, LLC v. Nash Mfg., Inc.</i> , 896 F.3d 1365 (Fed. Cir. 2018)	14
Rules	
37 C.F.R. § 42.65	16
Rule 132	17

I. Introduction

Marinus has not shown by a preponderance of the evidence that claims 22 and 25-31 of the '817 patent are unpatentable. None of Marinus's cited references describes or suggests the specific methods of treating SE in humans recited in these claims. By Marinus's own admission, the references at most describe "initial work on ganaxolone in animals," not humans, and mere "approval to proceed into human clinical trials." Reply, 1. These references are facially insufficient to prove anticipation or obviousness, and Marinus's Dr. Rogawski has not credibly filled the gaps.

Marinus's attempt to distance the unexpected results shown in the *Epilepsia* Clinical Trial (Ex. 2003) from *Epilepsia*'s use of Ovid's treatment methods and dose amounts recited in claims 22 and 25-31 also fails. As Marinus acknowledges, the claims cover these routes of administration. And the bolus-plus-continuous-infusion dosing protocols described in *Epilepsia* are not inventive, and have been routinely used to treat SE. It is instead the treatment methods and dose amounts recited in claims 22 and 25-31 that underly the unexpected rapid seizure cessation and reduction in seizure burden, and Marinus has not shown otherwise.

Marinus has put forward no additional evidence or arguments in support of its already deficient enablement challenge.

For all the reasons of record and those discussed below, Ovid respectfully requests the Board find Marinus has not proven by a preponderance of the evidence that claims 22 and 25-31—and especially claim 30—are unpatentable.¹

II. Dr. Rogawski’s Previously Undisclosed Relationships with Marinus and Ovid Undermine His Credibility

Marinus justifies Dr. Rogawski’s and its own failure to disclose Dr. Rogawski’s role on Marinus’s Scientific Advisory Board because it is “publicly available information” and because “Dr. Rogawski did not list any of his many advisory roles on his CV.” Reply, 3-4. These reasons do not excuse Marinus’s failure to be candid about its pre-existing relationship with Dr. Rogawski, particularly where Dr. Rogawski’s role with Marinus requires him to substantively comment on Marinus’s SE clinical programs for undisclosed compensation. Ex. 2015, 33:13-34:20.

Dr. Rogawski also failed to disclose his prior consulting relationships with Ovid related to SE treatment, which occurred as recently as November 2023. Ex. 2024, 30:8-31:20. This is relevant because Dr. Rogawski opines that Ovid is not

¹ Marinus’s suggestion that Ovid’s statutory disclaimer of certain claims before institution is an admission those claims are “indefensible over the Marinus prior art” (Reply, 2) is contrary to the law. *See Raytheon Techs. Corp. v. Gen. Elec. Co.*, 993 F.3d 1374, 1379 n.4 (Fed. Cir. 2021).

“engaged in the clinical development of a treatment for status epilepticus” and has a business model that “is primarily to not develop drugs itself.” Ex. 1041, ¶¶16-17 (citing Ex. 1048, 6). Dr. Rogawski reaffirmed these statements in his deposition, stating that “it’s highly unlikely that [Ovid] would have been conducting research in status epilepticus.” Ex. 2024, 27:18-28:23. Dr. Rogawski, however, was aware of contrary information and attempted to clarify his statements, stating that he was only referring to Ovid not having a clinical development program related to ganaxolone. *Id.*, 29:15-30:7. But his change in position came only *after* he was shown portions of Ovid’s website showing otherwise and was questioned about his relationship with Ovid regarding SE treatment. *Id.*, 29:11-34:17. Dr. Rogawski’s statements also belie Examples 3 and 4 in Ovid’s ’817 patent, which expressly evaluated ganaxolone’s ability to block SE. Ex. 1001, 35:31-38:40.

The Board should afford Dr. Rogawski’s testimony little weight because of his undisclosed relationships with Marinus and Ovid and his statements that were inconsistent with his personal knowledge. *See Blasters, Inc. v. Waterblasting, LLC*, IPR2018-00504, Paper 26 at 23 (PTAB July 16, 2019).

Marinus’s criticisms of Dr. Sankar’s declaration also lack merit. Reply, 4. Dr. Sankar testified that he provided scientific input for his declaration and worked collaboratively with Ovid’s counsel. Ex. 1042, 98:5-22. Regardless, Marinus points

to three discrete portions of Dr. Sankar's declaration, none of which are word-for-word replications of Ovid's responses. Reply, 4 n.13.

III. Marinus's Own Arguments Belie Its Claim-Construction Positions

A. "Treating status epilepticus comprising administering to a patient in need thereof" (claims 22 and 25-31)

While asserting that "treating status epilepticus comprising administering to a patient in need thereof" in all claims is not limited to "treating a human patient suffering from SE," Marinus concedes that those claims do not cover rodents. *See* Reply, 6; Ex. 1041, ¶¶29-30; *see also* Ex. 1042, 91:15-92:3, 42:23-43:1, 88:20-89:2; Ex. 2014, ¶¶58-64. Thus, at the very least, "patient" in claims 22 and 25-31 does not encompass treating rats.

Marinus also cannot distinguish Ovid's cited cases. Reply, 6-7. The methods recited in all claims require "*treating* status epilepticus." Ovid's cited cases give limiting effect to a claim's "method of treating" preamble when that preamble provides antecedent basis for the phrase "a patient in need thereof," which appears in the challenged claims. *See* POR, 17-18. Thus, the challenged claims require *treating* SE in a human patient *suffering from* SE. Ex. 2014, ¶58. A POSA would have understood that administering ganaxolone to non-humans for preclinical or research purposes does not result in "treating status epilepticus." *Id.*, ¶¶58-60; Ex. 1042, 88:20-89:2. Nor does administering a lethal dose of ganaxolone to a rodent. Ex. 2014, ¶¶61-64; Ex. 1042, 91:15-92:3.

**B. “Improvement to the patient after administration for more than 8 hours”
(claim 22)**

A POSA would have understood that the “improvement” phrase in claim 22 means improvement to the human patient 8 hours after the full dose of ganaxolone is given, regardless of whether the dose of ganaxolone is given in single or multiple administrations. Relying on Dr. Rogawski and cherry-picked portions of the ’817 patent’s specification, Marinus contends that this claim phrase “requires measuring symptoms at a time more than 8 hours after treatment is initiated.” Reply, 7-8. Marinus is incorrect.

First, Dr. Rogawski construes the wrong claim phrase. *See* Ex. 1041, ¶¶32-41. He construes “improvement to the patient after 8 hours,” which does not appear in any challenged claim and omits the phrases “after administration” and “for more than 8 hours.” Dr. Rogawski thus failed to even consider the language of the claim itself. *See Salazar v. AT&T Mobility LLC*, 64 F.4th 1311, 1315 (Fed. Cir. 2023) (“We begin, as we must, with the claim language itself.”).

Second, Marinus’s contention that claim 22 requires “measuring symptoms at a time more than 8 hours after treatment is initiated”—which relies on the specification’s isolated mention of measuring symptoms “in a subject prior to treatment, and again one or more times after treatment is initiated”—improperly imports language from the specification into the claim. Reply, 7-8 (citing Ex. 1001,

29:57-60, 9:43-46, 13:35-38); *see also* *GE Lighting Sols., LLC v. AgiLight, Inc.*, 750 F.3d 1304, 1308-09 (Fed. Cir. 2014). The phrase “after treatment is initiated” does not appear in claim 22 and Dr. Rogawski admitted that these passages do not tie “after administration” or “improvement” to “after treatment is initiated.” Ex. 2024, 38:15-43:11.

Only Ovid’s construction, which requires measuring improvement after administering the total amount of ganaxolone, accounts for how a POSA would have understood the entire claim phrase in light of the claim language and the specification. Claim 22 expressly requires measuring improvement “after administration” of the pharmaceutical composition with ganaxolone, not after treatment is initiated. The specification, when referring to “improvement,” also specifically states that “improvement” is measured “*after administration of the pharmaceutical composition* to the patient,” meaning the total administered amount of the pharmaceutical composition. *See, e.g.*, Ex. 1001, 14:21-41 (emphasis added), 15:17-19, 15:40-42. This construction is also consistent with how a POSA, in practice, would have measured sustained improvement to a patient after administration of the *total dose*. Ex. 2014, ¶66.

IV. Ground 1: Zhang Does Not Anticipate Claims 22 and 25-31

A. Zhang does not describe “treating status epilepticus comprising administering to a patient in need thereof” (claims 22 and 25-31)

Citing *Impax Laboratories*, Marinus asserts that “anticipation does not require proof of efficacy.” Reply, 8. But *Impax Laboratories* is inapposite, saying only that “proof of efficacy is not required for a prior[-]art reference to be enabling under section 102.” *Impax Labs., Inc. v. Aventis Pharms. Inc.*, 468 F.3d 1366, 1382 (Fed. Cir. 2006). Ovid has not challenged whether Zhang’s disclosure is enabling, only that it does not describe “every element and limitation of the claim[s].” *Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1082 (Fed. Cir. 2008).

Zhang provides no data about treating SE in humans with ganaxolone, which Marinus has not challenged. Animal models, such as the rat lithium-pilocarpine model in Zhang’s Example 8, do not translate directly to human treatment. Ex. 2014, ¶ 71; *see also* Ex. 1042, 80:8-81:11, 82:6-25. Nor would a POSA have directly compared doses administered to rats in animal models to doses administered to humans on a mg/kg basis. Ex. 2014, ¶ 71. As Dr. Rogawski’s experience confirmed, compounds (e.g., neuroactive steroids other than ganaxolone) demonstrating some degree of efficacy in the rat lithium-pilocarpine model often neither advance to clinical trials in humans nor receive FDA approval. Ex. 2015, 23:6-25:7.

Marinus points to Zhang’s paragraphs [0005] and [0031] and Examples, none of which describe treating a human patient suffering from SE and at most describe

formulations of ganaxolone being administered to rats. Ex. 2014, ¶ 70. Marinus tries to cure these deficiencies by pointing to Zhang’s background discussion regarding the difficulties of treating SE but this discussion does not describe administering ganaxolone to treat SE in human patients, as the claims require.

Marinus itself acknowledges that the doses in claims 25-31 “would be more appropriate for a human-sized patient,” (Reply, 6) therefore precluding rodents from their scope. Ex. 2014, ¶¶61-64; Ex. 1042, 91:15-92:3. Accordingly, Marinus cannot establish anticipation of these claims based on Zhang’s rat-model data.

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

After earlier conceding that “Zhang does not expressly disclose that its ganaxolone formulations provide ‘improvement to the patient after administration for more than 8 hours’” (Pet., 45; *see also* Ex. 1003, ¶ 93; POR, 28), Marinus now contends that Zhang anticipates claim 22 both “expressly and inherently” (Reply, 9). Given Marinus’s concession in its petition, Marinus has waived arguing that Zhang expressly anticipates claim 22. *See* PTAB Consolidated Trial Practice Guide, 73-74 (Nov. 2019); *Henny Penny Corp. v. Frymaster LLC*, 938 F.3d 1324, 1330-31 (Fed. Cir. 2019) (affirming Board’s rejection of reply argument presenting “entirely new rationale” for why claim was unpatentable).

Regardless, Marinus’s new express anticipation argument admittedly relies only on data in Zhang’s Example 8 that “rats showed a reduced percentage of observed seizures in the first five hours after administration,” which Marinus alleges “*a POSA would understand* provides improvement after eight hours.” Reply, 9 (emphasis added). This data does not expressly disclose “improvement to the patient after administration for more than 8 hours,” as Marinus improperly relies on the skilled artisan’s knowledge, which has no place in an anticipation analysis. *See, e.g., Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1548 (Fed. Cir. 1983); *Sandoz Inc. v. Pharmacyclics LLC*, IPR2019-00865, Paper No. 8 at 20-21 (PTAB Sept. 26, 2019).

Zhang also does not inherently describe the claimed “improvement.” Dr. Rogawski previously admitted that after the 5-hour mark in Zhang’s Example 8 that “it’s possible that there could be improvement, there might not be improvement. When one is treating a medical condition, there’s always a degree of variability and one doesn’t expect a certain outcome.” Ex. 2015, 155:7-16; *see also* Ex. 2014, ¶¶ 76-78. Because the rats were sacrificed at the 5-hour mark and it is only “possible that there *could be* improvement” beyond this time, Zhang’s Example 8 cannot anticipate claim 22 as a matter of law. *See Bettcher Indus., Inc. v. Bunzl USA, Inc.*, 661 F.3d 629, 639 (Fed. Cir. 2011) (Inherency “may not be established by probabilities or possibilities.”).

Despite Dr. Rogawski's admissions, Marinus improperly points to additional data outside of Zhang—Saporito P1 and the '817 patent—to supply claims 22's limitation and demonstrate inherency. Reply, 10-11. Marinus's reliance on this new evidence now is improper given that Marinus could have relied on this evidence in its petition but chose not to. *See* Patent Trial and Appeal Board Consolidated Trial Practice Guide, 73 (Nov. 2019) ("Petitioner may not submit new evidence or argument in reply that it could have presented earlier, e.g., to make out a prima facie case of unpatentability.").

On the merits, however, this evidence similarly fails the inherent-anticipation standard. Saporito P1's Figure 3 shows that not all rats experienced increased survival when administered 12 mg/kg ganaxolone 15 minutes after SE onset. Ex. 1013. Similarly, the '817 patent specification's description of administering 10 and 20 mg/kg ganaxolone is not the same as those doses administered to rats in Zhang and shows that less than all the rats administered ganaxolone survived after 24 hours. Ex. 1001, Fig. 4, 36:44-62 (Table 2). It cannot be said that "improvement to the patient after administration for more than 8 hours" inevitably would occur or would be the natural result of administering ganaxolone to rats as described in Zhang's Example 8 and the additional references relied upon by Marinus add nothing to further support its inherency arguments.

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

Marinus asserts that Zhang’s “entire disclosure is related to intravenous ganaxolone for treatment of seizure disorders” (Reply, 11-12), however, Zhang’s disclosure is not so narrow. Zhang’s Summary and Detailed Description surmise that ganaxolone formulations could be used to treat at least 31 different diseases or disorders, including “seizures, traumatic brain injury, or stroke.” Ex. 1009, ¶¶[0074], [0006].

Marinus also asserts that “[t]he background and examples focus on SE” (Reply 12), but this is not true. In addition to SE, Zhang’s four-paragraph background extensively discusses PCDH19 female pediatric epilepsy, which Zhang characterizes as “[a]nother serious seizure disorder.” Ex. 1009, ¶¶[0003]-[0004]. And seven of Zhang’s eight examples discuss preparing and testing various formulations of ganaxolone without mentioning SE. Ex. 1009, ¶¶[0104]-[0116]. Only Example 8 discusses evaluating administering discrete ganaxolone doses (at most 5.265 mg) in a model where rats have chemically-induced SE. Ex. 1009, ¶¶[0117]-[0136]. Marinus’s picking and choosing among Zhang’s disclosure of 31 different diseases or disorders and various dosing regimens to arrive at the specific dose ranges for treating SE in the claims remains improper. *See Luye Pharma Grp. Ltd. v. Alkermes Pharma Ire. Ltd.*, IPR2016-01095, Paper 13 at 11 (PTAB Nov. 30, 2016).

V. Grounds 2-4: Petitioner Has Not Demonstrated that Claims 22 and 25-31 Would Have Been Obvious Over Any of the Asserted References

A. Objective indicia support nonobviousness

1. Unexpected results demonstrate patentability

Marinus admits that the recited dose in claim 30 “facially corresponds to the total amount given in Marinus’s ‘High’ dose cohort.” Reply, 29. Marinus admits that the result from its high-dose cohort was unexpected. Ex. 2007, 31, ¶¶7-8 n.1. Real-world evidence shows an unexpected benefit for the daily doses recited in at least claims 25-30. Marinus has not provided any evidence to undermine its own admissions. This ends the inquiry at least for claim 30 and for the other claims, as discussed below.

a. The results are commensurate in scope

Marinus’s only argument regarding unexpected results is that they are allegedly not commensurate in scope with claims 22 and 25-31. Reply, 18-30. Marinus is wrong.

First, Marinus admits that the doses tested in *Epilepsia* are encompassed by the claims. Reply, 25. And Marinus itself focused only on that dosing in public statements regarding the testing described in *Epilepsia*. In fact, Marinus’s June 2023 corporate presentation ties “achiev[ing] [a] target range ≥ 500 ng/mL for ~ 8 hours” and “seizure burden reduction occur[ing] rapidly” to the 500 mg/day, 650 mg/day, and/or 713 mg/day dose amounts tested, without reference to the specific dosing

regimen used. Ex. 2002, 25-27. Marinus cannot back away from these public statements now.

Second, to demonstrate that unexpected results are commensurate in scope with the claims, “absolute identity of scope” is not required. *Genetics Institute, LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1308 (Fed. Cir. 2011). Therefore, Ovid is not required to show that every unrecited possibility provides the same unexpected results. Ovid must instead show only that the treatment or daily dose amounts recited in the claims provide unexpected results. This is particularly true where claims 22 and 25-31 do not recite *how* the claimed treatment or daily dose amounts of ganaxolone are administered. This is exactly what Ovid has done. *See* POR, 39-49.

Third, *In re Inland Steel Co.*, 265 F.3d 1354 (Fed. Cir. 2001) is distinguishable in several ways. The claims in *Inland Steel* are not analogous to the claims here. There, the claims recited a method for producing steel strips, where one of the process steps required using steel having various weight percent ranges of eight elements, including 0.02-0.10 wt% antimony. *Id.* at 1357. The patentee attempted to demonstrate unexpected results based on the particular claimed antimony amounts using data showing that 0.02-0.05 wt% antimony increased the magnetic properties of the produced steel. *Id.* at 1365. The Board rejected those unexpected results because a declaration showed that the prior art produced steel with similar magnetic

properties at a lower concentration of antimony and other data undercutting the patentee's unexpected results. *Id.* at 1365-66.

Here, the claims do not recite how the claimed treatment or daily dose amounts of intravenous ganaxolone are to be administered and Ovid has put forward unexpected results related to multiple amounts of ganaxolone falling within the range of the claims. *See* POR, 39-49. Marinus, on the other hand, has put forward *no* evidence suggesting that something other than the daily dose amounts are responsible for the unexpected results. These data are commensurate with the scope of the claims.

Fourth, Marinus fails to show that something other than the treatment and daily dose amounts cause the unexpected results. While Ovid “bears the burden of production with respect to evidence of secondary considerations of nonobviousness,” the “burden of persuasion remains with the challenger.” *ZUP, LLC v. Nash Mfg., Inc.*, 896 F.3d 1365, 1373 (Fed. Cir. 2018). Ovid satisfied its burden of production for unexpected results with the Hulihan declarations (Exs. 2007, 29-32 and 2008, 25-28) and *Epilepsia*.

Marinus could have submitted its own evidence demonstrating that the treatment and dose amounts recited in the claims do not lead to unexpected results but did not. Marinus instead resorts to making unsupported, vague statements that the claimed treatment methods “could” be administered in several different ways

and that “there is no reason to believe . . . 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.” Reply, 28.

Marinus further argues that the specific dosing regimen used in *Epilepsia* (i.e., a bolus with continuous intravenous infusion), not the claimed treatment methods, are allegedly “central to achieving the results of Marinus’s clinical trial.” Reply, 27. But this is exactly how a POSA would have administered ganaxolone. Both sides’ experts agree that bolus doses are commonly used in SE treatment because SE is an emergency condition where one treatment goal is to rapidly control seizures through “rapidly administering medications” as a bolus dose. Ex. 2024, 15:1-19:8, 21:4-26:9; Ex. 1053, 2812 (Table 2); Ex. 1042, 53:24-54:9. And continuous infusion is commonly used after a bolus dose to “maintain the drip rate.” Ex. 1042, 54:4-9; *see also* Ex. 2024, 16:1-17:22, 25:3-26:9. Accordingly, Marinus’s hypothetical and unsupported “what ifs” do not align with its own expert’s understanding of how SE patients are treated.

b. Marinus’s “data” is irrelevant

For claim 30, which recites treating SE with “700 mg to 725 mg/day ganaxolone,” Marinus submits pharmacokinetic modeling provided by Dr. Baughman to allegedly show that, “without the bolus dose, there are dosing regimens covered by Ovid’s claims that fail to even reach plasma concentrations of 500 ng/mL

within 24 hours.” Reply, 29-30 (citing Ex. 1060, ¶¶18-22). Putting aside that this pharmacokinetic modeling and Dr. Baughman’s declaration should be entitled to no weight, it is a red herring.²

Dr. Baughman’s output is *plasma* concentration, not any measure of treatment efficacy, which the claims recite. *E.g.*, Ex. 1060, ¶¶18-22. Consequently, this unsupported simulation is irrelevant to Ovid’s evidence of unexpected results based on actual treatment outcomes. To the extent Marinus attempts to link plasma concentration to clinical outcome (Reply, 29),³ its own evidence indicates a lack of direct correlation. Marinus reported that “[g]anaxolone plasma levels ≥ 500 ng/ml

² Patent Owner timely objected to the declaration of Dr. Baughman. Paper 26, 9-10. Dr. Baughman admitted that the “pharmacokinetic information related to ganaxolone that Marinus submitted to FDA,” and that she used as the basis for her model, were provided to her by Marinus’s counsel and she was not aware whether it was publicly available. Ex. 2025, 16:24-18:21. Moreover, Marinus has not provided the Board with any source documents underlying these pharmacokinetic parameters. This contravenes at least 37 C.F.R. § 42.65.

³ Marinus fails to point out that its evidence of seizure recurrence at plasma concentrations allegedly below 500 ng/mL is based on “predicted” plasma concentrations. Ex. 2006, 25-26, Figs. 3, 5, 7, 9.

were achieved only briefly during the initial bolus for patients in the medium-dose cohort, whereas those in low- and high-dose cohorts maintained such levels for 4 and 8 h, respectively.” Ex. 2003, 2386. Notwithstanding these dips for the low- and medium-dose cohorts, *all* patients in these cohorts met the primary and secondary endpoints. Ex. 2003, 2386. That Marinus tailored its Rule 132 declaration to the plasma limitations in the claims of its application (*see, e.g.*, Ex. 2007, 20)⁴ does not detract from this real-world evidence of unexpected clinical benefit over the daily doses ranging from ~500-725 mg/day.

Dr. Baughman also only modeled two dosing scenarios administered by continuous intravenous infusion only. Ex. 1060, ¶17. Notably, Dr. Baughman did not model similar dosing scenarios using a bolus dose followed by continuous infusion because counsel did not ask her to do so. *Id.*; Ex. 2025, 24:15-25:13. Therefore, Dr. Baughman did not compare her continuous infusion-only model with a dosing model having a bolus dose with continuous infusion.

Marinus should be held to its own description of its unexpected results. The Hulihan declarations clearly state that it was unexpected that “SE could be rapidly

⁴ Indeed, Marinus tied a “total daily dose of ganaxolone []of about 500 mg” and “about 600 mg” to a ≥ 500 ng/ml plasma limitation. Ex. 2007, 21 (claims 73 & 74).

and persistently suppressed using *less ganaxolone* and for a much shorter period of time than was anticipated.” Ex. 2007, 31, ¶8 (emphasis added). This was contrary to Marinus’s expectation that “a high ganaxolone exposure for a long treatment period of at least 4 days duration, would be required to break SE.” Ex. 2007, 30, ¶7. The use of “less ganaxolone” to suppress SE solely relates to the amount of ganaxolone administered, not any specific dosing regimen. Marinus cannot change course now.

Based on Marinus’s above admissions, and despite Marinus’s attempts to argue otherwise, the improvement recited in claim 22 and the dose ranges recited in claims 25-31 provided unexpected results which support the nonobviousness of the claims.

2. Failure of others and long-felt unmet need

Marinus acknowledges there was a long-felt need for SE treatment options in humans but states that Marinus’s work in Zhang and Saporito filled that need. Reply, 30. This is incorrect. Neither Zhang nor Saporito provides any information about using ganaxolone to treat SE in humans and therefore could not supply “the key element” to meet this long-felt need. Both Zhang and Saporito provide information only about ganaxolone’s use through the rat lithium-pilocarpine model. These animal model data, at best, identified ganaxolone as a promising compound.

Marinus contends that the art shows success in treating SE and that the failure of other, non-ganaxolone drugs is irrelevant. Reply, 30. This too is incorrect. The

relevant references only show ganaxolone's use in the rat lithium-pilocarpine model, identifying ganaxolone as a promising compound for further development. Given that no other neuroactive steroid, like ganaxolone, that has shown promising results in the rat lithium-pilocarpine model has advanced through clinical trials and received FDA approval for treating SE in humans, Marinus's cited art does not demonstrate success.

B. Ovid Has Applied the Correct Standard for Reasonable Expectation of Success

Marinus contends that "Ovid applies an overly high standard to reasonable expectation of success." Reply, 13. Not so. While "[c]onclusive proof of efficacy is not necessary to show obviousness," *Hoffman-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1331 (Fed. Cir. 2014), Marinus must still "show that the skilled artisan would have reasonably expected to achieve success in the treatment" recited in the claims, *Eli Lilly & Co. v. Teva Pharms. Int'l GmbH*, 8 F.4th 1331, 1344 (Fed. Cir. 2021); *see also Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006). Zhang's lack of *any* efficacy data in humans is significant because of the noted difficulties in treating SE. *See* Ex. 1011, 1; *OSI Pharms., LLC v. Apotex Inc.*, 939 F.3d 1375, 1384 (Fed. Cir. 2019); *cf. PAR Pharm., Inc. v. TWI Pharms., Inc.*, 773 F.3d 1186, 1198 (Fed. Cir. 2014) (affirming reasonable-expectation-of-success

finding because prior art “made clear that the use of nanoparticle technology in formulation chemistry had become fairly reliable and showed consistent results”).

Marinus’s reliance on *Ex parte Beljanski*, No. 2015-001712, 2017 WL 1032225 (PTAB Mar. 17, 2017), is inapposite. *See* Reply, 13. In *Beljanski*, the Board found claims related to human treatment obvious because the prior art described a rabbit study and a different prior-art reference “took the next step, applying the treatment found effective in rabbits to a human patient with successful results.” 2017 WL 1032225, at *8. Here, Marinus relies on no reference that takes that next step, i.e., demonstrating intravenous ganaxolone’s successful treatment of SE in humans.

C. Ground 2: Zhang

Marinus continues to fail to explain how a POSA would have been motivated to tie Zhang’s separate general disclosures of a β -cyclodextrin ganaxolone injection that “may be given at intervals of 1 to 24 hours” (Ex. 1009, ¶[0074]) or of a broad range of “about 1 mg/kg to about 20 mg/kg ganaxolone” (Ex. 1009, ¶[0085]) to treating SE or Zhang’s Example 8. This is especially true where neither paragraph 74 nor 85 of Zhang mentions treating SE. The mere allegation that these general and broad disclosures are “consistent with what a POSA already knew about the clinical pharmacology of ganaxolone” is irrelevant where Marinus has not provided a showing of a “suggestion or motivation to modify the teachings of” Zhang. *See, e.g.,*

SIBIA Neurosciences, Inc. v. Cadus Pharm. Corp., 225 F.3d 1349, 1356 (Fed. Cir. 2000).

Moreover, while Zhang cites to Ex. 1054, Ex. 1054 says nothing of ganaxolone's use or efficacy in treating SE, and instead discusses only administering ganaxolone to healthy human volunteers and treating migraines and epilepsy. Ex. 1054, 2-3 (stating that Marinus "plans to conduct further controlled studies" in several diseases, none of which are SE).

Marinus also does not demonstrate a reasonable expectation of success in arriving at the claimed inventions based on Zhang. Dr. Rogawski and Dr. Sankar agree that the rat pilocarpine model at most can predict that a compound potentially could be useful in the treatment of SE in humans. *See, e.g.*, Ex. 1003, ¶¶25, 27, 33; Ex. 2014, ¶71. And even if the model demonstrates some degree of success, this success often does not translate to efficacy in humans, as Dr. Rogawski's personal experience has shown. Ex. 2015, 23:6-25:7; *see also* Ex. 1042, 79:6-18, 81:3-11, 82:6-25, 84:19-24. Therefore, a POSA would have recognized that the effectiveness of certain doses in the rat pilocarpine model do not translate to treating SE in humans. Ex. 2014, ¶71.

With respect to claim 22, Zhang provides no indication of improvement to the patient for more than 8 hours after administration of the full dose of ganaxolone. Zhang's Example 8 provides no data after 5 hours and shows that ganaxolone's

efficacy in reducing seizures in rats diminishes after that time. Ex. 1009, ¶¶[0135]-[0136]; Ex. 2014, ¶¶76-77.

D. Ground 3: Zhang in Combination with Saporito P1 and/or Saporito P2

Marinus does not respond to any of Ovid's facts demonstrating Marinus's failure to establish that Saporito P1 and Saporito P2 were publicly accessible before the '817 patent's priority date. Reply, 15-17. Marinus instead simply repeats the same vague comments made in Dr. Saporito's declaration. *Id.*

To the extent Saporito P1 or Saporito P2 are prior art, they do not cure Zhang's deficiencies. Saporito P1 and Saporito P2 do not describe intravenously administering ganaxolone to a human patient suffering from SE. Petition, 50-52; Ex. 1013, 1; Ex. 1014, 1.

For claim 22, Zhang Example 8 and Saporito P2's Figures 3 and 4 show that ganaxolone's effect on reducing EEG power is largely diminished by 6 hours. Ex. 1009, ¶¶[0135]-[0136]; Ex. 1014, 1; Ex. 2014, ¶134; Ex. 2015, 110:21-112:8. Because there is no data beyond 6 hours, and the evidence shows that any effect ganaxolone has on rats diminishes after 5 hours, a POSA would not have had a reasonable expectation of success in providing improvement to the patient 8 hours after the full dose of ganaxolone is administered, as required by claim 22. Ex. 2014, ¶¶65-66, 96; Ex. 1042, 79:6-18.

For claims 25-31, Marinus adds nothing to cure the deficiencies in its petition. Reply, 15-17. Marinus's assertion that POSAs "would have considered 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)" (Reply, 16) fails because none of the references discloses any information about administering the doses in claims 25-31 to humans or provides any indication that POSAs would have reasonably expected such doses to treat human patients suffering from SE. Ex. 2014, ¶¶105-106.

Because Marinus has failed to "show that [POSAs] would have reasonably expected to achieve success in the treatment" methods required by claims 25-31, claims 25-31 would not have been obvious. *Eli Lilly*, 8 F.4th at 1344.

E. Ground 4: Zhang in Combination with Marinus's Press Releases

Marinus's Press Releases do not cure Zhang's deficiencies. While Dr. Sankar may have testified that the use of ganaxolone may be a "promising approach" to treating humans (Ex. 1042, 86:22-87:4), this is legally insufficient to prove obviousness. To provide the "requisite reasonable expectation of success," the prior art must do more than "teach[] merely to pursue a 'general approach that seemed to be a promising field of experimentation.'" *Medichem*, 437 F.3d at 1165. Marinus's Phase I Press Release's (Ex. 1022) mere disclosure of administering an unknown amount of intravenous ganaxolone in a phase I clinical trial to determine the safety, tolerability, and pharmacokinetics in healthy human volunteers fails to provide more

than a “general approach that seemed to be a promising field of experimentation,” as required to show a reasonable expectation of success of using ganaxolone to treat SE in humans. *Id.*

Moreover, Marinus’s reliance on *Vanda Pharmaceuticals Inc. v. Teva Pharmaceuticals USA, Inc.*, No. 2023-1247, 2023 WL 3335538 (Fed. Cir. May 10, 2023) is misunderstood. Reply at 17-18. In *Vanda*, the Federal Circuit affirmed a district court’s determination that claims reciting a method of entraining a patient were obvious based on a publication discussing a “then-ongoing *phase III*” trial that assessed tasimelteon’s efficacy with other references, including phase II trial results that evaluated tasimelteon’s effect on phase shifting. 2023 WL 3335538, at *3-4 (emphasis added).

Here, Marinus relies on pre-clinical data in rats and press releases that only announce the first dosing of undisclosed amounts of ganaxolone in a phase I trial, not its efficacy in humans with SE. Ex. 1011, 1; Ex. 1022, 1; Ex. 2014, ¶¶149, 158; Ex. 2015, 127:9-128:13. There is no question that the mere discussion in either of Marinus’s Press Releases of ongoing phase I trials in combination with pre-clinical data in rats would not have provided a skilled artisan with a reasonable expectation of success in treating ganaxolone as recited in claims 22 and 25-31. *See OSI Pharms.*, 939 F.3d at 1385-86; Ex. 2014, ¶¶147-152.

VI. Ground 7: Claims 22 and 25-31 Are Enabled

Marinus continues to provide no evidence that the treatment of SE in patients with ganaxolone was unpredictable, that a large quantity of experimentation was necessary to show ganaxolone efficacy, that the scope of the claim was unduly broad, that the guidance of the '817 specification was insufficient guidance for the claim scope, or that the prior art established concerns regarding the claimed treatment. Institution Decision, 47.

The only new “evidence” Marinus offers is its contention that Dr. Sankar “believes that ‘absent human data the patent cannot claim treating a human patient.’” Reply, 31. But Dr. Sankar offered no opinions on enablement in his declaration and when asked during his deposition by Marinus’s counsel whether he was “familiar with the concept of enablement in patent law,” Dr. Sankar responded, “[n]o.” Ex. 1042, 41:19-24. Without any understanding of enablement law, there is no basis to state that Dr. Sankar believed that the challenged claims are not enabled.

Based on the above, Marinus has not demonstrated that the challenged claims are not enabled.

VII. Conclusion

Because Marinus has not established by a preponderance of the evidence that claims 22 and 25-31 of the '817 patent are unpatentable, the Board should determine that claims 22 and 25-31 of the '817 patent are not unpatentable.

Respectfully submitted,

Dated: April 8, 2024

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

Counsel for Patent Owner
Ovid Therapeutics Inc.

CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(d), I, Anthony C. Tridico, certify that **Patent Owner's Sur-Reply** contains 5,586 words, excluding those portions identified in 37 C.F.R. § 42.24(c), as measured by the word-processing system used to prepare this paper.

Dated: April 8, 2024

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

CERTIFICATE OF SERVICE

The undersigned certifies that a copy of the foregoing **Patent Owner's Sur-Reply** was served electronically via email on April 8, 2024, in its entirety on the following:

Martina Tyreus Hufnal
Michael J. Kane
Deanna Reichel
Anita L. Meiklejohn
Katie E. Hyma
Fish & Richardson P.C.
60 South Sixth Street, Suite 3200
Minneapolis, MN 55402
PGR50689-0016PS1@fr.com (referencing Attorney Docket No. 50689-0016PS1)

Petitioner has consented to electronic service by email.

Date: April 8, 2024

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