

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

SUPPLEMENTAL DECLARATION OF DR. MICHAEL A. ROGAWSKI

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REFERENCES CITED

Exhibit / Paper	Description
Paper 6	Patent Owner Preliminary Response (“POPR”)
Paper 21	Patent Owner Response (“POR”)
1001	U.S. Patent No. 11,395,817 to Ovid Therapeutics, Inc. “the ’817” or “the ’817 patent”
1003	Declaration and Curriculum Vitae of Dr. Michael A. Rogawski (“the Rogawski Declaration” or “First Rogawski Declaration”)
1009	WIPO Publication No. WO 2016/127170 (“Zhang”)
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”)
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”)

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”)
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”)
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”)
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
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/jvlim.16928 (“Charlambous”)
1052	Rosetti and Lowenstein, “Management of Refractory Status Epilepticus in Adults,” <i>Lancet. Neurol.</i> 10(10):922-30 (2011) (“Rosetti”)

Supplemental Declaration of Dr. Michael A. Rogawski
in support of Petition for Post-Grant Review
of U.S. Patent No. 11,395,817

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 SI</i> ”)
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)
2003	H. Vaitkevicius et al., Intravenous ganaxolone for the treatment of refractory status epilepticus: Results from an open-label, dose-finding, phase 2 trial, 63 <i>Epilepsia</i> 2381-2391 (2022)
2007	Excerpts from the File History of U.S. Patent No. 11,679,117
2008	Excerpts from the File History of U.S. Patent No. 11,110,100
2014	Declaration of Raman Sankar, M.D., Ph.D
2015	Transcript of Deposition of Dr. Michael A. Rogawski (November 15, 2023)

I, Michael A. Rogawski, declare as follows:

I. INTRODUCTION

1. I am being offered as an expert on behalf of Petitioner Marinus Pharmaceuticals, Inc. (“Marinus”) to provide opinions and testimony in support of Marinus’s Petition for Post-Grant Review of U.S. Patent No. 11,395,817 (Ex. 1001).

2. I previously submitted a declaration, dated March 10, 2023, in this proceeding. (First Declaration, Ex. 1003). My qualifications and professional experience are set forth in my previous declaration at paragraphs 2–15. I submit this supplemental declaration to provide additional opinions and testimony in reply to certain points made in Ovid’s Patent Owner’s Response and the Declaration of Dr. Raman Sankar.

3. Nothing in Ovid's Patent Owner Response or the Declaration of Dr. Sankar alters any of my opinions that claims 22 and 25–31 of the '817 patent are anticipated and obvious.

II. CURRENT SCOPE OF THE POST-GRANT REVIEW

4. In my first declaration, I offered opinions on the invalidity of claims 1–31 of the '817 patent. I understand from Marinus’s counsel that Ovid has disclaimed all claims of the '817 patent except claims 22 and 25–31. As a result,

the scope of this post grant review proceeding is now limited to claims 22 and 25–31.

1. Remaining Grounds

5. I understand that the remaining grounds for invalidity are as follows:

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

6. My opinions in this supplemental declaration, therefore, are directed to those grounds and are responsive to statements made by Ovid and by Dr. Sankar.

2. Remaining Claims (22 and 25–31)

7. Each of the remaining claims (22 and 25–31) depends from claim 21.

8. Claim 21 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 wherein the pharmaceutical composition is administered intravenously.”

9. Claim 22 recites: “The method of claim 21 wherein the pharmaceutical composition provides improvement to the patient after administration for more than 8 hours.”

10. Claims 25–31 each recite “The method of claim 21 wherein the patient is administered [X] ganaxolone,” where [X] is a dose range, as follows:

Claim	[X]
25	about 500 mg to 1000 mg/day
26	about 625 mg to 650 mg/day
27	about 650 mg to 675 mg/day
28	about 675 mg to 700 mg/day
29	about 625 mg to 700 mg/day
30	about 700 mg to 725 mg/day
31	about 1025 mg to 1050 mg

III. OVID’S COMMENTS REGARDING GANAXOLONE DEVELOPMENT

11. In my previous declaration I described the extensive work that Marinus has done to develop ganaxolone as a therapeutic, including for the

treatment for Status Epilepticus (“SE”). (First Declaration, Ex. 1003, paras. 34–41).

12. It is curious to me that Ovid and Dr. Sankar refer to the ’817 patent as “the bedrock of Marinus’s clinical development [of ganaxolone]” (Patent Owner Preliminary Response, Paper 6, page 8, first para.; Patent Owner Response, Paper 21, paragraph spanning pages 6 and 7) and “the basis for Marinus’s clinical development efforts [of ganaxolone products as therapeutics]” (Sankar Declaration, Ex. 2014, para. 18). I described the history of the development of ganaxolone and Marinus’s research and development activities previously (First Declaration, Ex. 1003, paras. 34–41). I am not aware of any evidence supporting Dr. Sankar’s assertions.

13. Marinus’s work in developing ganaxolone was being publicized by at least 2006. By the time that the contents of the ’817 patent specification first published, Marinus had already begun its clinical trials of an intravenous formulation of ganaxolone with the intention of developing it for the treatment of SE. This research was publicly disclosed in Tsai, (Ex. 1020). The results of its Phase II trial (“Intravenous Ganaxolone as Adjunctive Therapy to Treat Subjects With Status Epilepticus”, ClinicalTrials.gov record for NCT03350035, Ex. 1045) were ultimately published in the 2022 *Epilepsia* paper that Ovid now points to in

support of its own claims. (Ex. 2003, with the Clinical Trial Registration number noted on the cover page).

14. Dr. Sankar believed the work described in the '817 patent “probably inspired Marinus to take it and start doing some clinical experimentation,” and was not aware of any earlier publications describing it (Sankar Deposition Transcript, Ex. 1042, page 24, lines 12–18 and page 25, lines 21–22). This cannot be the case, however, as, again, this work was first published *after* Marinus had begun its clinical trials.

15. Furthermore, certain of those Phase II clinical trial results were also published in Marinus’s own patent applications, which were published by February 11, 2021 (Marinus PCT/US2020/044843 (WO 2021/026124), Ex. 1046; *see, for example*, Examples 2 and 3 at paras. [0213]–[0248] and associated Figures). I understand that Ovid added claims 21–31 to the application that would become its '817 patent on May 11, 2022, (Ex. 1047), which was over a year *after* this Marinus patent application published.

16. I am not aware of Ovid having done any of its own clinical study work on ganaxolone or that Ovid is engaged in the clinical development of a treatment for status epilepticus. In its public announcements, including on its official website, on ClinicalTrials.gov, and in its financial filings, Ovid does not

disclose any program of research to develop a product for the treatment of status epilepticus. Given these factors, I conclude that it is unlikely that Ovid is engaged in the clinical development of a treatment for status epilepticus.

17. Furthermore, Ovid has stated publicly that its business model is primarily to not develop drugs itself. According to their 2022 Annual Report, “Ovid conducts limited internal drug discovery” to “maintain lower costs” and, instead, “seek[s] to identify compounds with what [they] believe is untapped value sitting in other organizations’ pipelines and look to in-license or enter into collaborative agreements to secure such assets and advance clinical development.” (Ovid’s 2022 Annual Report (Ex. 1048), page 6).

IV. CLAIM CONSTRUCTION AND SCOPE

18. I understand from counsel that terms in patent claims must be read as they would have been understood by a “person of ordinary skill in the art” at the relevant time period. Here, I understand that the appropriate time period to be the 2016–2017 timeframe.

19. I set forth my understanding of a person of ordinary skill in the art in my prior declaration (at paragraph 56) and incorporate that same definition here.

1. “Treating status epilepticus comprising administering to a patient in need thereof” (Claims 22 and 25–31)

20. I understand that Ovid has taken the position that the plain meaning of “[t]reating status epilepticus comprising administering to a patient in need thereof” in claim 21 (and, therefore, claims 22 and 25–31) means “treating a human patient suffering from SE.” It is my opinion that the patient to which the claims apply may be either a human or animal patient. In the paragraphs below I describe how I have formed this opinion.

21. First, the ’817 patent tells its reader very directly what patient means (Ex. 1001, at column 32, lines 65–67):

“Patient” and “subject” are used interchangeably herein and include, but not limited to, primates such as humans, canines, porcine, ungulates, rodents, poultry, and avian.”

22. This definition indicates that a patient may be a human patient, or may be a non-human animal patient, including, for example, a dog (canine), pig (porcine), or rat (rodent). Perhaps Ovid assumes that there would be no practical use of the claimed inventions of the ’817 patent in species other than humans. This assumption completely ignores the entire veterinary market. (See Sankar Deposition Transcript, Ex. 1042, at page 88, line 20 to page 92, line 14). A veterinarian’s patient is just as much a patient as a medical doctor’s patient, and veterinarians routinely treat their animal patients for SE using medications. (See,

for example, Patterson, “Status Epilepticus and Cluster Seizures,” *Vet. Clin. Small Anim.* 44:1103–1112 (2014) (Ex. 1050); and Charlambous et al., “ACVIM Consensus Statement on the Management of Status Epilepticus and Cluster Seizures in Dogs and Cats,” *J. Vet. Intern. Med.* 2023:1–22 (2023). DOI: 10.1111/jvbm.16928 (Ex. 1051)). Thus, veterinary practice is an important market for medications that treat SE.

23. Dr. Sankar had not considered veterinary practice (which he described as “outside [his] scope”) in forming his opinions. (See Sankar Deposition Transcript, Ex. 1042, page 88, lines 23–24). The ’817 patent (including its claims), though, is clearly not limited to situations where a medical doctor is treating a human patient. A fair reading of the patent would not have led the skilled person to conclude that claims 22 and 25–31 relate *only* to treating humans, at least because of known veterinary indications.

24. Ovid argues that the skilled artisan would understand that the “someone ‘in need’ “would be a human patient suffering from SE” and “not a rat or other animal receiving ganaxolone for research purposes.” (Patent Owner Preliminary Response, Paper 6, page 28, full para.; Patent Owner Response, Paper 21, page 18, top partial para.). Dr. Sankar repeats this argument. (Ex. 2014, para. 60).

25. In support of this argument during his deposition, Dr. Sankar made a distinction between what he does as a medical doctor and as a researcher. (Sankar Deposition Transcript, Ex. 1042, page 88, line 20 to page 89, page 6). As a medical doctor, human patients suffering from SE come to him for treatment. As a researcher, he induces SE in animals to study them. SE may be induced in laboratory animals with chemical convulsant agents. However, inadvertent (such as during a chemical spill) or intentional (such as in a terrorist incident or during warfare) exposure to such chemicals can also cause SE in humans or animals. A medical doctor or veterinarian would be called upon in such a circumstance to provide treatment. Animals in such a circumstance are no less “in need” of treatment than humans.

26. The rats described in the examples of Zhang the '817 patent are experiencing SE, just as a human would. The condition is treated in a similar fashion, whether it occurs as a result of the ordinary causes of SE in humans and animals (e.g., poorly controlled epilepsy, stroke, traumatic brain injury, encephalitis, and so forth) or induced by a chemical agent. For more than 12 years I conducted research supported by grants from the National Institutes of Health, an agency of the U.S. federal government, which had the aim of identifying more effective treatments for SE induced by chemical nerve agents. My research was

part of the Countermeasures Against Chemical Threats (CounterACT) Program that supports research and development of new and improved therapeutics against chemical threat agents to which civilians might be exposed during a chemical accident, terrorist incident, or act of war. The type of chemically induced SE that was the focus of my grant supported research is similar to the chemically induced SE occurring in the rats in Zhang's and the '817 patent's examples.

27. Ovid attempts to distinguish between “treating” and “administering” (POPR, Paper 6, page 29, first full para.; POR, Paper 21, page 19, first full para.), arguing that only humans are “treated,” while experimental rats are “administered.” I disagree. In my experience, the term treatment is commonly used in preclinical research with animals, including in relationship to administering a therapeutic agent. Indeed, at various places in the figures and specification of the '817 patent, the term “treat” is used specifically in relation to administering ganaxolone to a rat suffering from SE for the purpose of treating the SE (e.g., “dose/treatment/group” captions to Fig. 2 and Fig. 7; “Post-Treatment Seizures” title of Fig. 5; “Treatment” axis label of Fig. 6A; “Treatment”, caption to Fig. 6B; column 35, lines 62–3, and 67; column 36, lines 14 and 42; column 37, lines 8, 40, and 65; and column 38, lines 13, 18, and 33).

28. The use of the term “treatment” in claims 22 and 25–31 would not have led the skilled person to conclude that these claims relate *only* to treating humans, but rather that the claims are relevant to a rat patient and indeed to any patient encompassed by the definition of “patient” in the specification, which includes a wide variety of animals (including rats).

29. Finally, with respect to claims 25–31, Ovid distinguishes between the likely effect of the claimed doses on humans v. rats; in particular, that the claimed doses would be too high for a rat. (POPR, Paper 6, page 29, last full para. and para. spanning page 30; POR, Paper 21, page 19, last full para. to para. spanning pages 20 and 21). Dr. Sankar also repeats this argument. (Sankar Declaration, Ex. 2014, paras. 61–64).

30. But once again, Ovid and Dr. Sankar completely ignore veterinary patients. Rats are not the only non-human animal that a person of skill in the art would understand are covered by the term “patient.” Indeed, dogs are susceptible to status epilepticus and when this occurs, they are in need of treatment. Many types of dogs have body weights that would be similar to the weight range of humans. (See Beale and Ostrander, “Sizing up Dogs,” *Current Biology* 22(9):R315–6 (2012) (Ex. 1043), which indicates that “the very smallest breeds, such as the Chihuahua and Pekingese, weigh no more than a couple of pounds,

while the very largest, including the Newfoundland and the St. Bernard, can weigh over 200 lbs.”). That the specific doses set forth in claims 25–31 may be higher than the dose that would likely be given to a rat does not suggest to a person of skill in the art that the term “patient” in the claims is limited to humans. Those doses could apply to any number of species that are also covered by the ’817 patent’s definition of “patient.”

31. In my opinion, the skilled person would understand the patient in claims 22 and 25–31 to be just as the ’817 patent specification says: to “include, but not [be] limited to, primates such as humans, canines, porcine, ungulates, rodents, poultry, and avian.”

2. The meaning of “improvement to the patient after 8 hours” in claim 22

32. I understand that Ovid has taken the position that the plain meaning of “improvement to the patient after 8 hours” means that “there is improvement to the human patient more than 8 hours after the full dose of ganaxolone is given, regardless of whether the full amount of ganaxolone is given in a single administration or multiple administrations.” (Patent Owner Response, Paper 21, page 24). I disagree.

a. “after 8 hours”

33. Ovid’s interpretation is inconsistent with the ’817 patent specification, which explains that an improvement in symptoms refers to a relative change, and explicitly states that such a change may be measured “in a subject prior to treatment, and again one or more times after treatment is *initiated*.” (Ex. 1001, column 29, lines 57–60; column 9, lines 43–46; column 13, lines 35–38.). The ’817 patent thus does not speak in terms of measuring improvement only after treatment is completed.

34. Indeed, measuring an improvement at intervals after *initiation* of treatment is consistent with how improvement is measured in clinical practice when SE is treated. Patients exhibiting SE are critically ill and they are monitored closely and continuously for changes in their condition after the start of treatment, not only after a treatment ends.

35. It is also consistent with how therapeutics are administered to SE patients. In the treatment of refractory status epilepticus, it is standard practice when using certain agents to administer the full dose as a continuous infusion or broken into multiple, repeated administrations, possibly over a long period of time including for more than 8 hours

36. In fact, this is how ganaxolone was dosed and how improvement was measured in Marinus’s clinical trials, as show, for example, in the *Epilepsia* publication (Ex. 2003). In the study described in this publication, improvement was measured both after initiation (at 24 hours, while continuous infusions were ongoing—rows 1 and 2) and after completing an entire dosing regimen (relapse during 24 h following infusion completion, row 3) (Table 2).

37. In the treatment of SE, a POSA would understand that it is reasonable and ordinary practice to spread a dose of the treatment agent over a period of time to suppress the status epilepticus and prevent its recurrence. Therefore, a POSA would understand that to achieve patient improvement for more than 8 hours, the dose of ganaxolone could be spread out over time by, for example, multiple bolus dose injections as specified in the Zhang Publication (*e.g.*, Ex. 1009, at ¶ [0085]), and that improvement would be measured over the course of those doses, not just after the last dose was given.

b. “improvement”

38. Ovid does not explicitly address *what* the improvement in claim 22 requires.

39. The ’817 patent describes improvement broadly as “treatment of symptoms or conditions associated with epileptic disorders, measured relative to at

least one symptom or condition of the metabolic disease.” (Ex. 1001, column 29, lines 57–60. “Metabolic disease” appears to be a typographical error. I assume the intent was to refer to “at least one symptom or condition of the *epileptic disorder*.” The specification of the ’817 patent uses the following language in relation to ways of assessing treatment success: “frequency or severity of seizures,” “reducing behavioral abnormalities (or otherwise improving behavior),” “provid[ing] a desired pharmacological and/or physiological effect, for example, reducing, inhibiting, or reversing one or more of the underlying pathophysiological mechanisms underlying the neurological dysfunction, increasing dopamine levels or signaling, or a combination thereof.” (Ex. 1001, column 9, lines 19–33).

40. I have noted previously in this declaration that SE is a severe life-threatening medical emergency, which is associated with a high risk of permanent neurological damage and death. As a physician attempting to treat SE during its dynamic and evolving course over minutes and hours, I would consider any degree of improvement at any time point to be clinically worthwhile even if the extent of improvement is of a lesser degree than had been obtained at a different point in treatment.

41. Furthermore, improvement for a limited period of time (e.g., for five hours) reduces overall risk of a worse outcome at later times (e.g., at eight hours or

more). For example, initial or transient improvement provides an opportunity for natural healing (such as clearing of a brain infection by the immune system), time for a curative treatment (such as an antibiotic) to be administered, or time for patients to be transferred to a facility that can provide a greater level of care. Any of these would provide improvement in the overall risks of adverse consequences of SE (such as brain damage, permanent disability, and death) at eight hours and beyond.

V. RESPONSE TO OVID'S POSITIONS ON ZHANG

A. Zhang's Anticipatory Teachings

42. I previously set forth my understanding of the legal standard for anticipation and offered my opinion that Zhang anticipate claims 22 and 25–31 (First Declaration, Ex. 1003, paras. 49 and 60–105). Furthermore, I understand, as explained to me by Marinus's attorneys, that Zhang does not need to show an experimental example where ganaxolone was administered to an SE patient (human or otherwise) or data demonstrating clinical efficacy of the same in order to anticipate claim 21. Rather, it need only teach administering a composition comprising ganaxolone or a pharmaceutically acceptable salt thereof intravenously to a patient with status epilepticus (human or otherwise).

43. Ovid argues that Zhang does not disclose treating a patient (which, according to Ovid's interpretation, is only a human patient) with intravenous ganaxolone as set forth in claims 22 and 25–31 of the '817 patent. As I have discussed above, it is evident that the claims encompass treating SE not only in humans, but also in non-human animals including, for example, rats.

44. Zhang does provide an example with an animal (rat) patient. However, it is evident to me that a person of skill in the art would read Zhang as teaching a treatment method that is also relevant to a human patient. The background section of Zhang discusses the standard of care for SE and cites articles that relate to the treatment of SE in humans. (Ex. 1009, para [0001], citing Rosetti and Lowenstein, "Management of Refractory Status Epilepticus in Adults," *Lancet. Neurol.* 10(10):922–30 (2011) (Ex. 1052), and Shorvon and Ferlisi, "The Treatment of Super-Refractory Status Epilepticus: a Critical Review of Available Therapies and a Clinical Treatment Protocol," *Brain* 134:2802–18 (2011) (Ex. 1053).

45. Moreover, Zhang explicitly defines the intended treatment population to include human patients (Ex. 1009, at paragraph 22, indicating that its patients include "human or non-human animal[s] in need of medical treatment."). There would be no reason to read Zhang's disclosure as *excluding* humans. To do so

would defy common sense and be contrary to the arguments that Ovid has made regarding the construction of its own claims.

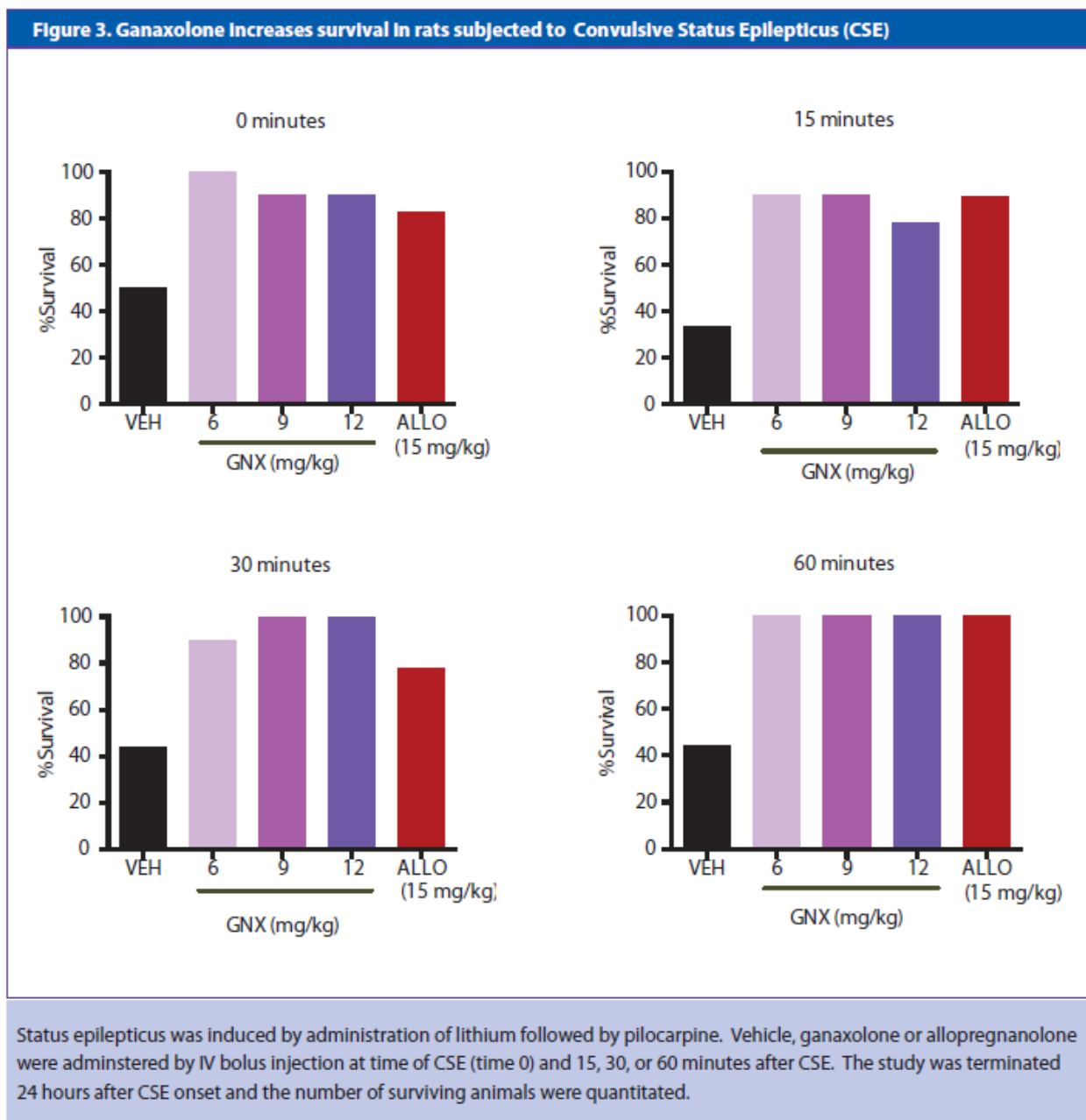
46. Zhang anticipates claim 22 even if it were limited to human patients, as Ovid asserts. Claim 22 does not specify anything further (beyond what claim 21 requires) regarding how or how much ganaxolone is administered; it only specifies that the treatment (somehow) “provides improvement to the patient after administration for more than 8 hours.”

47. As I noted previously (First Declaration, Ex. 1003, paras. 92–95) and explained to Ovid’s counsel during my deposition (Ex. 2015, page 81, lines 1–12), Example 8 of Zhang provides *data* from the rat lithium pilocarpine model up to the point where they were sacrificed at 5 hours. The data presented in Zhang’s Example 8, in conjunction with the rest of Zhang’s teachings, provides information relevant to longer time periods as well. When taken in context with the rest of Zhang’s teachings, it is clear that to the extent that improvement to the patient were to occur after the 5-hour mark (when Zhang’s animals were sacrificed), it would be the natural result of administering the ganaxolone formulations in the manner taught by Zhang (to a rat patient or a human patient).

48. And what is more, as I described above, even transient improvement (e.g., during the first five hours, as demonstrated in Zhang’s Example 8) provides

an improvement in the overall risks of adverse consequences of SE (such as brain damage, permanent disability, and death) at eight hours and beyond.

49. Improvement beyond 8 hours is shown explicitly, for example, in the experimental results presented in Saporito Poster 1 (Ex, 1013), presented publicly at the 2016 Annual Meeting of the American Academy of Neurology. Rats in Example 8 of Zhang rats were treated with 12 or 15 mg/kg IV ganaxolone administered at 15 and 60 minutes after SE onset. (Ex. 1009, paras. [0126]–[0127]. In the experiments presented in Saporito Poster 1, rats were treated intravenously with ganaxolone in the same manner as Zhang (including intravenously at a dose of 12 mg/kg) but were *not* sacrificed at five hours. As shown in Figure 3 of the Saporito Poster (excerpted below), rats receiving a single bolus IV administration of ganaxolone at all doses (including the 12 mg/kg dose) administered at all time points after SE onset (including 15 and 60 minutes after SE onset) exhibited markedly increased rates of survival at 24-hours compared to vehicle, such that nearly all animals survived. (Ex. 1013, Methods, Figure 3, Conclusions). Thus, there was dramatic improvement after eight hours whether this is assessed after initiation or completion of treatment administration.



3. Claims 25–31

50. Claims 25–31 specify dose ranges of ganaxolone to be administered. As I had previously described (First Declaration, Ex. 1003, paragraphs 99–105), Zhang anticipates claims 25–31.

B. Obviousness

51. I previously set forth my understanding of the legal standard for obviousness and offered my opinion that claims 22 and 25–31 are obvious over Zhang (alone or in combination with the Saporito Posters (Ex. 1013 and Ex. 1014) and the Marinus Press Releases (Ex. 1011 and Ex. 1022) (First Declaration, Ex. 1003, paras. 50–54 and 106–151).

52. Ovid now argues that Zhang does not disclose treating a human patient. Even if it was, I would still conclude that the claims would have been obvious over Zhang (alone or in combination with the Saporito Posters (Ex. 1013 and Ex. 1014) and the Marinus Press Releases (Ex. 1011 and Ex. 1022)).

53. Zhang discloses how ganaxolone was known to be “useful for treating seizures in adult and pediatric patients.” (Ex. 1009, ¶ [0027]), and directs the POSA to a description of existing studies on the pre-clinical and clinical pharmacology of ganaxolone. (*Id.*, citing Nohria and Giller, “Ganaxolone,” *Neurotherapeutics* 4:102–105 (2007) (Ex. 1054)). 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 (or the maximum tolerated dose) in pediatric patients. (Nohria, Ex. 1054, pages 103–104).

54. In its methods of treatment section (paras [0069]–[0089]; which includes human patients, according to para. [0022]), Zhang describes that in some embodiments the method of treating SE includes administration of a single bolus doses of from about 1 mg/kg to about 20 mg/kg (which, for a 70 kg human, is 70 to 1,400 mg), 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 (e.g., a daily bolus of 70 to 1,400 mg for a 70kg human). (Ex. 1009, para [0085]; First Declaration, Ex. 1003, paras. 102–104).

55. Ovid and Dr. Sankar argue that the data in Zhang provides no reasonable expectation of success in achieving the inventions in claims 22 and 25–31. I disagree.

56. As I have previously discussed extensively, Zhang presents a working example of treating SE in rats. The experiments described in Saporito Poster 1 and Saporito Poster 2 (displayed April 2016) provide additional data showing treatment of SE in rats. The experimental approach used is, in my opinion, generally considered to be predictive of clinical efficacy. I previously explained that the rat pilocarpine model is a well accepted model in the field. While it is certainly true that the animal studies do not invariably predict the outcome of human clinical trials, in my opinion, there is a reasonable expectation that a treatment which

demonstrates improvement in animals experiencing SE as in the examples of Zhang, as well as Saporito P1 and P2, will also demonstrate some improvement in SE when administered to humans suffering from the same.

57. I note that the '817 patent (Ex. 1001, column 29, lines 29–51) contemplates “treating” broadly:

As used herein, the term “treating” or “treatment” refers to alleviating, attenuating or delaying the appearance of clinical symptoms of a disease or condition in a subject that may be afflicted with or predisposed to the disease or condition, but does not yet experience or display clinical or subclinical symptoms of the disease or condition. In certain embodiments, [“]treating” or “treatment” may refer to preventing the appearance of clinical symptoms of a disease or condition in a subject that may be afflicted with or predisposed to the disease or condition, but does not yet experience or display clinical or subclinical symptoms of the disease or condition. “Treating” or “treatment” may also refer to inhibiting the disease or condition, e.g., arresting or reducing its epileptic or at least one clinical or subclinical symptom thereof. “Treating” or “treatment” further refers to relieving the disease or condition, e.g., causing regression of the disease or condition or at least one of its clinical or subclinical symptoms. The benefit to a subject to be treated may be

statistically significant, mathematically significant, or at least perceptible to the subject and/or the physician. Nonetheless, prophylactic (preventative) and therapeutic treatment are two separate embodiments of the disclosure herein.

58. As I have noted, Zhang Example 8 and the results presented in the Saporito posters provide strong and convincing evidence of a treatment effect. Considering how expansively the '817 patent defines “treating” provides further support that a POSA would have a reasonable expectation that administering ganaxolone will provide a treatment effect in a human.

59. The Marinus press releases (Ex. 1011 announcing that “Marinus received FDA Orphan Drug Designation for Ganaxolone IV to Treat Status Epilepticus”; and Ex. 1022 announcing that “Marinus Pharmaceuticals Doses First Subject in Phase 1 Clinical Trials for Ganaxolone IV”) show *additional* evidence demonstrating the reasonableness of expecting that administering ganaxolone IV to humans, as taught by Zhang, would treat status epilepticus in humans, specifically.

60. As I previously noted, a POSA would have known that to obtain Orphan Drug Designation, the FDA Office must have concluded that there was sufficient “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 treating of that disease or condition.”

(First Declaration, Ex. 1003, para. 125).

61. Also as previously noted, a POSA would have understood that for the FDA to allow a Phase I trial to commence, that it has determined that IV ganaxolone was reasonably likely to be successful in the treatment of SE in humans. (First Declaration, Ex. 1003, para. 126).

VI. UNEXPECTED RESULTS

62. I note that Ovid is relying on Marinus’s clinical trial results as unexpected results to support the patentability of the ’817 claims.

63. I understand that unexpected results can support that a claim is nonobvious. But I further understand that, to support nonobviousness, those unexpected results must be commensurate in scope with the claims they are offered to support. In other words, the showing of unexpected results should occur over the entire claimed range, not just for a limited number of potential embodiments.

64. The results that Ovid relies on as being “unexpected” results of their claimed methods are from Marinus’s Phase II clinical trial results, which were published in *Epilepsia* in 2022 (Ex. 2003). These results are not, as I show below, commensurate in scope with claims 22 and 25-31.

65. As an initial matter, it is important to recognize that the Marinus Phase II clinical trial used specific, complex dosing regimens, which are shown in Supplemental Table S1, as noted in Section 2.2 “Treatment”. (Ex. 2003, page 2383), which is available on the publisher’s website. Supplemental Table S1 is provided in Exhibit 1055, and also reproduced below.

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.

66. These specific dosing regimens resulted in certain clinical results described in the publication. However, ganaxolone could be administered according to many other regimens that would result in the same or different total

daily doses. Ovid provides no information as to whether those other dosing regimens would result in the same clinical results described in the publication. All dosing regimens used in the Marinus study involved a bolus followed by continuous infusion. Importantly, Ovid provides no information as to whether the results described in the *Epilepsia* paper would be obtained if the bolus is eliminated.

67. The claims of the '817 patent specify no mg dose at all (claim 22), a mg dose per day (claims 25–30) or a total mg dose (claim 31). None of the claims specifies the specific dosing regimens described in the *Epilepsia* publication. Claim 22 doesn't even specify the amount of ganaxolone to be administered. The daily amounts recited in claims 25–30 could be administered as a single bolus dose at any time point; as a continuous infusion at a constant or variable rate with no bolus; by multiple bolus doses with different infusion rates between boluses; or by some other scheme.

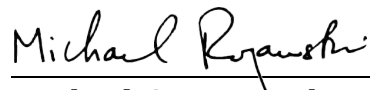
68. To the extent that claims 22 and 25-31 of the '817 patent encompass the treatment that the patients received in Marinus's clinical trials, the dosing regimens actually used (and which resulted in the clinical results described in the *Epilepsia* paper) are specific cases within the broad universe of dosing regimens encompassed by the claims.

69. Ovid makes separate arguments as to the dose range recited in claim 30 (700 mg to 725 mg/day), relying on the results that were described in Dr. Houlihan's declarations during the prosecution of Marinus's patents (Ex. 2007, submitted during prosecution of Marinus's 17/729,427 application (published as US20220265680, Ex. 1056); Ex. 2008, submitted during prosecution of Marinus's 17/186,569 application (published as US20210186987 Ex. 1057)). Those results show, as Ovid notes, that only the High cohort dosing regimen in which a 713 mg/day dose was administered as a bolus + continuous infusion (as shown in Table S1) is expected to sustain ganaxolone plasma concentrations of at least 500 ng/ml for at least 8 hours, which results in the "greatest decrease in seizure burden." However, this sustained plasma concentration (and any associated benefits) is the result of Marinus's specific dosing regimen. Ovid's broad claims include many dosing regimens that do not produce the required sustained ganaxolone plasma concentrations of at least 500 ng/ml for at least 8 hours. For example, the claims include dosing regimens where the total daily dose is administered in the form of several boluses, which do not produce the required sustained ganaxolone plasma concentrations.

70. To the extent that any of these results would have been unexpected at all, they are tied to Marinus's specific dosing regimens, which Ovid does not claim. Ovid's claims are much broader and encompass countless possible dosing regimens. In short, Ovid's claims are not commensurate in scope with Marinus's clinical trial results.

I declare under the penalty of perjury that the foregoing is true and correct.

Executed on March 7, 2024.



Michael A. Rogawski