Marinus Pharmaceuticals, Inc. v. Ovid Therapeutics Inc.

Patent Owner's Demonstratives | May 22, 2024

Case PGR2023-00020
U.S. Pat. No. 11,395,817

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

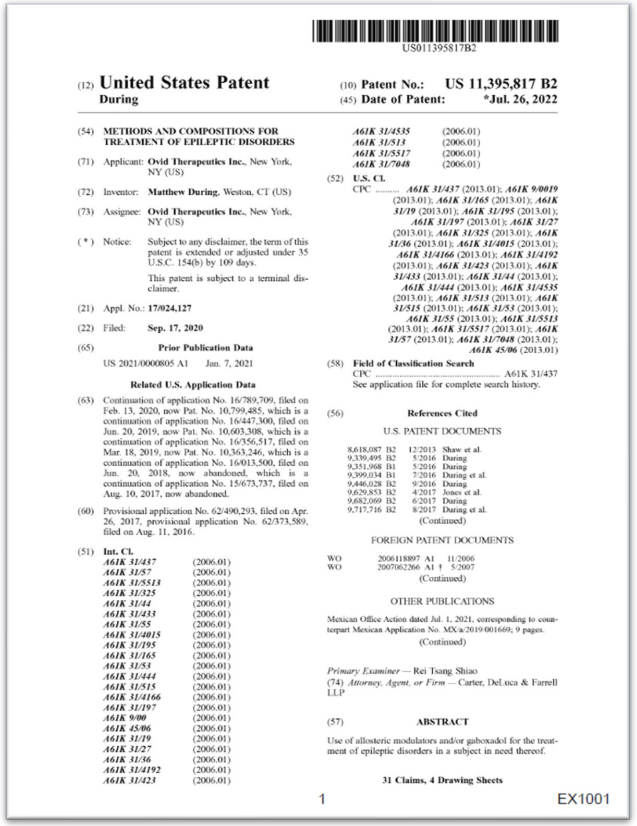
Outline

- Claims 22 and 25-31 Require Treating a Human Patient
- Claim 22 Requires Measuring Improvement After the Total Dose of Ganaxolone Is Administered
- Zhang Does Not Anticipate Claims 22 and 25-31
- Zhang and Other References Do Not Render Claims 22 and 25-31 Obvious
- Claims 22 and 25-31 Are Enabled

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Ovid Therapeutics

The Claimed Invention



US011395817B2

(12) **United States Patent**
During

(10) **Patent No.: US 11,395,817 B2**
(45) **Date of Patent: *Jul. 26, 2022**

(54) **METHODS AND COMPOSITIONS FOR TREATMENT OF EPILEPTIC DISORDERS**

(71) Applicant: **Ovid Therapeutics Inc.**, New York, NY (US)

(72) Inventor: **Matthew During**, Weston, CT (US)

(73) Assignee: **Ovid Therapeutics Inc.**, New York, NY (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 109 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **17/024,127**

(22) Filed: **Sep. 17, 2020**

(65) **Prior Publication Data**

US 2021/0000805 A1 Jan. 7, 2021

Related U.S. Application Data

(63) Continuation of application No. 16/789,709, filed on Feb. 13, 2020, now Pat. No. 10,799,485, which is a continuation of application No. 16/447,300, filed on Jun. 20, 2019, now Pat. No. 10,603,308, which is a continuation of application No. 16/356,517, filed on Mar. 18, 2019, now Pat. No. 10,363,246, which is a continuation of application No. 16/013,500, filed on Jun. 20, 2018, now abandoned, which is a continuation of application No. 15/673,737, filed on Aug. 10, 2017, now abandoned.

(60) Provisional application No. 62/490,293, filed on Apr. 26, 2017, provisional application No. 62/373,589, filed on Aug. 11, 2016.

(51) **Int. Cl.**

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A61K 31/36	(2006.01)
A61K 31/4192	(2006.01)
A61K 31/423	(2006.01)
A61K 31/4535	(2006.01)
A61K 31/513	(2006.01)
A61K 31/5517	(2006.01)
A61K 31/7048	(2006.01)

(52) **U.S. Cl.**
CPC ***A61K 31/437*** (2013.01); ***A61K 9/0019*** (2013.01); ***A61K 31/165*** (2013.01); ***A61K 31/19*** (2013.01); ***A61K 31/195*** (2013.01); ***A61K 31/197*** (2013.01); ***A61K 31/27*** (2013.01); ***A61K 31/325*** (2013.01); ***A61K 31/36*** (2013.01); ***A61K 31/4015*** (2013.01); ***A61K 31/4166*** (2013.01); ***A61K 31/4192*** (2013.01); ***A61K 31/423*** (2013.01); ***A61K 31/433*** (2013.01); ***A61K 31/44*** (2013.01); ***A61K 31/444*** (2013.01); ***A61K 31/4535*** (2013.01); ***A61K 31/513*** (2013.01); ***A61K 31/515*** (2013.01); ***A61K 31/53*** (2013.01); ***A61K 31/55*** (2013.01); ***A61K 31/5513*** (2013.01); ***A61K 31/5517*** (2013.01); ***A61K 31/57*** (2013.01); ***A61K 31/7048*** (2013.01); ***A61K 45/06*** (2013.01)

(58) **Field of Classification Search**
CPC A61K 31/437
See application file for complete search history.

(56) **References Cited**

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(Continued)

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(Continued)

Primary Examiner — Rei Tsang Shiao
(74) *Attorney, Agent, or Firm* — Carter, DeLuca & Farrell LLP

(57) **ABSTRACT**

Use of allosteric modulators and/or gaboxadol for the treatment of epileptic disorders in a subject in need thereof.

31 Claims, 4 Drawing Sheets

1 EX1001

21. 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.

22. The method of claim **21** wherein the pharmaceutical composition provides improvement to the patient after administration for more than 8 hours.

25. The method of claim **21** wherein the patient is administered about 500 mg to 1000 mg/day ganaxolone.

26. The method of claim **21** wherein the patient is administered about 625 mg to 650 mg/day ganaxolone.

27. The method of claim **21** wherein the patient is administered about 650 mg to 675 mg/day ganaxolone.

28. The method of claim **21** wherein the patient is administered about 675 mg to 700 mg/day ganaxolone.

29. The method of claim **21** wherein the patient is administered about 625 mg to 700 mg/day ganaxolone.

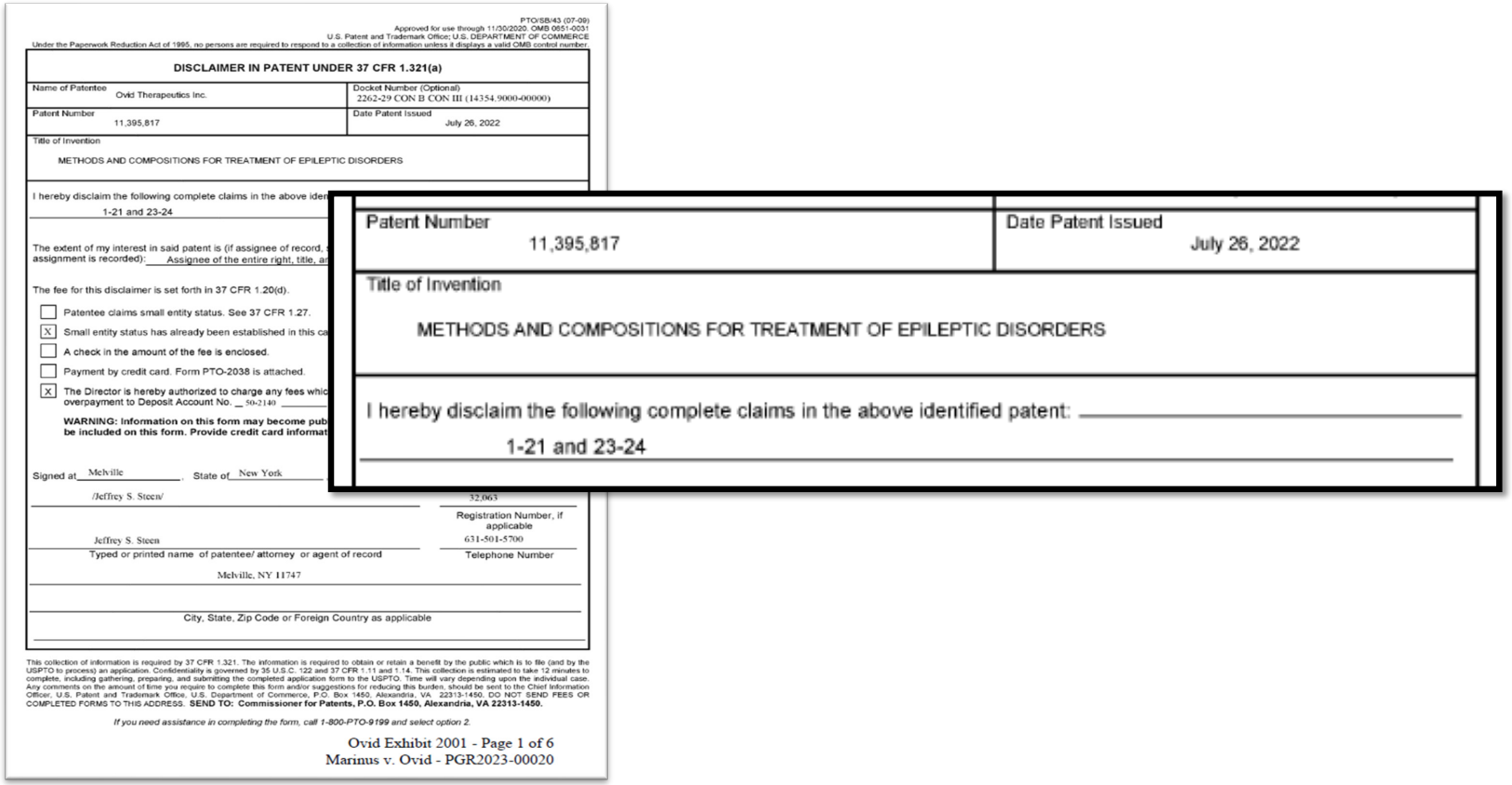
30. The method of claim **21** wherein the patient is administered about 700 mg to 725 mg/day ganaxolone.

31. The method of claim **21** wherein the patient is administered about 1025 mg to 1050 mg ganaxolone.

Challenged Claims

Ex. 1001 at 40:8-33; Patent Owner's Response at 12.

Statutory Disclaimer



PTO/SB/43 (07-09)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

DISCLAIMER IN PATENT UNDER 37 CFR 1.321(a)

Name of Patentee	Docket Number (Optional)
Ovid Therapeutics Inc.	2262-29 CON B CON III (14354.9000-00000)
Patent Number	**Date Patent Issued**
11,395,817	July 26, 2022

Title of Invention
METHODS AND COMPOSITIONS FOR TREATMENT OF EPILEPTIC DISORDERS

I hereby disclaim the following complete claims in the above iden
1-21 and 23-24

The extent of my interest in said patent is (if assignee of record, assignment is recorded): Assignee of the entire right, title, ar

The fee for this disclaimer is set forth in 37 CFR 1.20(d).

- ☐ Patentee claims small entity status. See 37 CFR 1.27.
- ☒ Small entity status has already been established in this ca
- ☐ A check in the amount of the fee is enclosed.
- ☐ Payment by credit card. Form PTO-2038 is attached.
- ☒ The Director is hereby authorized to charge any fees whic overpayment to Deposit Account No. 50-2140

WARNING: Information on this form may become pub be included on this form. Provide credit card informat

Signed at Melville, State of New York

/Jeffrey S. Steen/ — 32,063 (Registration Number, if applicable)

Jeffrey S. Steen — 631-501-5700 (Telephone Number)
Typed or printed name of patentee/ attorney or agent of record

Melville, NY 11747
City, State, Zip Code or Foreign Country as applicable

This collection of information is required by 37 CFR 1.321. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Ovid Exhibit 2001 - Page 1 of 6
Marinus v. Ovid - PGR2023-00020

Patent Number	Date Patent Issued
11,395,817	July 26, 2022

Title of Invention
METHODS AND COMPOSITIONS FOR TREATMENT OF EPILEPTIC DISORDERS

I hereby disclaim the following complete claims in the above identified patent:
1-21 and 23-24

Ex. 2001 at 1; Patent Owner's Response at 12-13.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Statutory Disclaimer Is Not an Admission



"Disclaimed claims are treated as if they never existed, and disclaimer does not legally constitute 'an admission that the subject of the disclaimer appears in the prior art.'"

Raytheon Techs. Corp. v. Gen. Elec. Co., 993 F.3d 1374, 1379 n.4 (Fed. Cir. 2021) (citations omitted).

Patent Owner's Response at 12-13; Patent Owner's Sur-Reply at 2 n.1.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Ovid Therapeutics

Instituted Grounds

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

*Grounds 5 and 6 related to claims that have been statutorily disclaimed.

Institution Decision, Paper 9 at 5, 48.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Claims 22 and 25-31 Require Treating a Human Patient

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Ovid Therapeutics

"Treating Status Epilepticus Comprising Administering to a Patient in Need Thereof"



Paper No. 21
Filed: November 30, 2023

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MARINUS PHARMACEUTICALS, INC.,
Petitioner,

v.

OVID THERAPEUTI
Patent Owner.

Case PGR2023-00
Patent 11,395,817

PATENT OWNER'S RESPONSE

21. 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.

"Treating status epilepticus comprising administering to a patient in need thereof" in claims 22 and 25-31 means "treating a human patient suffering from SE."

Patent Owner's Response at 17-23; Ex. 1001 at 40:9-13;
see also Patent Owner's Sur-Reply at 4.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Ovid Therapeutics

"Patient" Must Be Someone "In Need Thereof"

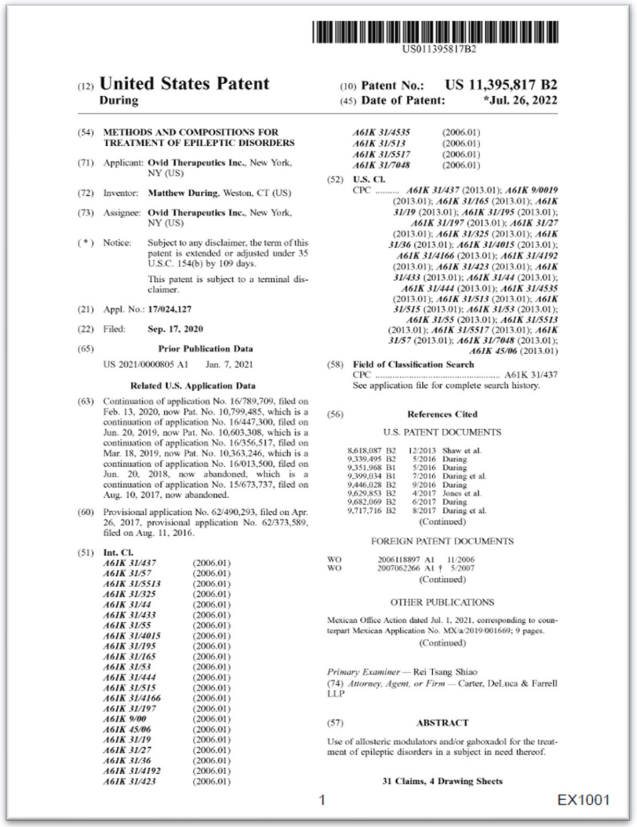
21. A method of treating status epilepticus comprising administering to a patient in need thereof a pharmaceutical composition comprising ganaxolone or a pharmaceutically acceptable salt thereof wherein the pharmaceutical composition is administered intravenously.

"[T]he claim preamble sets forth the objective of the method, and the body of the claim directs that the method be performed on someone 'in need.' In both cases, the claims' recitation of a patient or a human 'in need' gives life and meaning to the preambles' statement of purpose."

Jansen v. Rexall Sundown, Inc., 342 F.3d 1329, 1333 (Fed. Cir. 2003).

Patent Owner's Response at 17-18; Ex. 1001 at 40:9-13.

"Treatment" Refers to Addressing Clinical Symptoms, Not Research in Rats



US011395817B2

(12) **United States Patent**
During

(10) **Patent No.: US 11,395,817 B2**
(45) **Date of Patent: *Jul. 26, 2022**

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(72) Inventor: **Matthew During**, Weston, CT (US)

(73) Assignee: **Ovid Therapeutics Inc.**, New York, NY (US)

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(21) Appl. No.: **17/024,127**

(22) Filed: **Sep. 17, 2020**

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US 2021/0000805 A1 Jan. 7, 2021

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(58) **Field of Classification Search**
CPC A61K 31/437
See application file for complete search history.

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Primary Examiner — Rei-Tsang Shiao
(74) *Attorney, Agent, or Firm* — Carter, DeLuca & Farrell LLP

(57) **ABSTRACT**

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31 Claims, 4 Drawing Sheets

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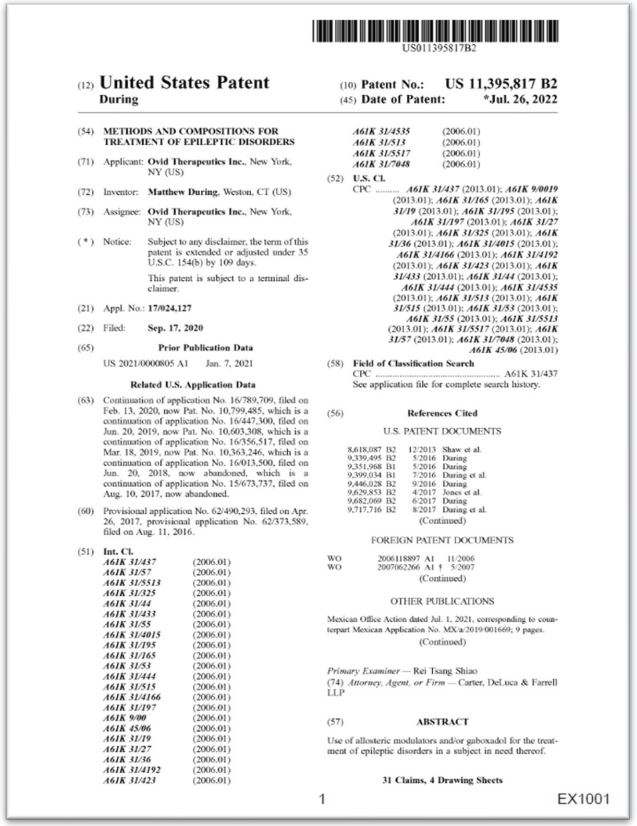
As used herein, the term "treating" or "treatment" refers to alleviating, attenuating or delaying the appearance of clinical symptoms of a disease or condition in a subject that may be afflicted with or predisposed to the disease or condition, but does not yet experience or display clinical or subclinical 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 (preventive) and therapeutic treatment are two separate embodiments of the disclosure herein.

"Effective amount" or "therapeutically effective amount" means a dosage sufficient to alleviate one or more symptom of a disorder, disease, or condition being treated, or to otherwise provide a desired pharmacological and/or physiologic effect.

Ex. 1001 at 29:29-56; Patent Owner's Response at 18-19; Patent Owner's Sur-Reply at 4; *see also* Ex. 2014 at ¶ 59.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

The ’817 Patent Uses “Treatment” for Humans, “Administration” for Rats



US011395817B2

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During

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(57) **ABSTRACT**

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31 Claims, 4 Drawing Sheets

1

EX1001

Example 1

Gaboxadol Plasma Concentration Profiles

This study was composed of separate groups of 10 healthy adult subjects (at least 4 of each gender) who participated in a 6-period, double-blind, randomized, crossover study designed to access the dose proportionality and absolute bioavailabilty of 5 single oral doses of gaboxadol across the dose range of 2.5 to 20 mg. The order in which the subjects received the 5 single oral doses of gaboxadol (2.5; 5; 10; 15; and 20 mg) was randomized within Treatment Periods 1 through 5. Each subject was expected to complete all 6 treatment periods and there was a washout of at least 4 days between each treatment period.

Each oral dosing within Treatment Periods consisted of 2 capsules of test drug taken simultaneously at each scheduled dosing. The treatment designations for the orally administered study drugs were as follows: Treatment A—one 2.5 mg gaboxadol capsule and 1 matching placebo capsule; Treatment B—one 5 mg gaboxadol capsule and 1 matching placebo capsule; Treatment C—one 10 mg gaboxadol capsule and 1 matching placebo capsule; Treatment D—one 15 mg gaboxadol capsule and 1 matching placebo capsule; and Treatment E—20 mg gaboxadol (two 10 mg gaboxadol capsules). Subjects received their study drug after an overnight fast with 240 mL of water in the morning about 8:00 AM. Water was permitted ad libitum except within 1 hour prior to and after study drug administration. No food was allowed for 4 hours post dose.

Example 4

Prospective Study for the Characterization of the Ability of Allopregnanolone, Ganaxolone, and Gaboxadol to Block Benzodiazepine-Resistant Status Epilepticus

Initial dose-response studies with intraperitoneal (i.p.) administration of allopregnanolone (ALLO), ganaxolone (GNX), and gaboxadol (GBD) suggests the potential for efficacy against benzodiazepine-resistant status epilepticus (Example 3). This study will assess the potential for synergistic activity of gaboxadol with either allopregnanolone, ganaxolone, or the benzodiazepine, lorazepam (LZP), against benzodiazepine-resistant status epilepticus in the Li-Pilo model in rats. Specifically, gaboxadol at low-doses (e.g. 0.5 mg/kg) will be administered in combination with a fixed dose of either allopregnanolone, ganaxolone, or lorazepam. The doses of allopregnanolone and ganaxolone will be those that were previously found to confer anticonvulsant effect in Example 3 (Table 2). The dose of lorazepam will be 2 mg/kg (Walton and Treiman. 1990. *Neurology* 40: 990-994 1990). The activity of each compound will also be evaluated alone. A vehicle-treatment group will be included. At 30 min post-status epilepticus onset, a single i.p. dose of each dose or dose combination (Table 3) will be administered to rats (n=13/group). Rats will be observed for presence or absence of further convulsive activity.

Ex. 1001 at 33:25-34:17, 37:17-44; Patent Owner’s Response at 18-19;
see also Ex. 2014 at ¶ 59.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Ovid Therapeutics

Same Claim Term Can Have Different Meanings Depending on Context

"As used in claims 1 and 7, the term 'condition code' must mean either a storage unit or a value derived from the output of the storage unit depending on the context in which its used, yet both claims are facially nonsensical if either of these definitions is used exclusively."

Microprocessor Enhancement Corp. v. Texas Instruments, 520 F.3d 1367, 1375 (Fed. Cir. 2008).

"We have previously held that the same claim term can have different constructions depending upon the context of how the term is used within the claims and specification."

Aventis Pharms. Inc. v. Amino Chems. Ltd., 715 F.3d 1363, 1374 (Fed. Cir. 2013) (citing *Microprocessor Enhancement*, 520 F.3d at 1375).

Patent Owner's Response at 22-23; Patent Owner's Sur-Reply at 4.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Doses Recited in Claims 25-31 Hundreds of Times Larger Than Doses for Rats

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MARINUS PHARMACEUTICALS, INC.,
Petitioner,

v.

OVID THERAPEUTICS, INC.,
Patent Owner.

PGR2023-00020
Patent No. 11,395,817 B2

DECLARATION OF RAMAN SANKAR, M.D., PH.D.



Raman Sankar, M.D., Ph.D.

61. Further, in the context of claims 25-31, a POSA would have understood that the doses of ganaxolone recited in these claims would not be administered in a rat to treat SE. The doses in these claims (ranging from 500 mg to 1050 mg) are 130 to 200 times larger than the doses of ganaxolone administered to rats in Examples 3 (2.5 mg (20 mg/kg x 0.125 kg weight of rat)) and 4 (3.75 mg (30 mg/kg x 0.125 kg weight of rat)) of '817 patent. Ex. 1001, 35:44-48 ("male Sprague Dawley rats (n = 10 time or treatment/group, 100-125 g; Charles Rivers Laboratories)"); *id.*, 36:22-24 ("The doses administered for allopregnanolone, ganaxolone, or gaboxadol are 0.5 mg/kg, 2 mg/kg, 5 mg/kg, 10 mg/kg, or 20 mg/kg."); *id.*, 37:62-66 ("male Sprague Dawley rats (n = 13 time or treatment/group; 100-125 g at arrival from Charles Rivers Laboratories)"); *id.*, 37:45-60 (Table 3 providing highest dose of ganaxolone (GNX) as 30 mg/kg).

Ex. 2014 at ¶ 61; Patent Owner's Response at 21.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Doses Recited in Claims 25-31 Thousands of Times Larger Than ED_{50} for Rats



The Journal of PHARMACOLOGY And Experimental Therapeutics

Characterization of the Anticonvulsant Properties of Ganaxolone (CCD 1042; 3α-Hydro 20-one), a Selective, High-Affinity, γ-Aminobutyric Acid$_A$ Receptor

RICHARD B. CARTER, PAUL L. WOOD, SCOTT WIELAND, JON JEREMY J. LAMBERT, H. STEVE WHITE, HAROLD H. WOLF, SE MICHAEL B. BOLGER, NANCY C. LAN and KELVIN W. GEE

Departments of Pharmacology (R.B.C., P.L.W., S.W., J.E.H.) and Medicinal C Department of Pharmacology, University of Dundee, Scotland (D.B., J.J.L.); A University of Utah, Salt Lake City, Utah (H.S.W., H.H.W.); School of Pharmac (M.B.B.); and Department of Pharmacology, College of Medicine, University o

Accepted for publication November 14, 1996

ABSTRACT

Ganaxolone (CCD 1042) is a 3β-methyl-substituted analog of the endogenous neuroactive steroid 3α-hydroxy-5α-pregnan-20-one. Ganaxolone inhibited binding of the γ-aminobutyric acid (GABA)$_A$ receptor-chloride channel ligand *t*-[^{35}S]butylbicyclophosphorothionate (IC_{50} of 80 nM) and enhanced binding of the benzodiazepine site ligand [^{3}H]flunitrazepam (EC_{50} of 125 nM) and the GABA site ligand [^{3}H]muscimol (EC_{50} of 86 nM), consistent with activity as a positive allosteric modulator of the $GABA_A$ receptor. Electrophysiological recordings showed that, whereas nanomolar concentrations of ganaxolone potentiated GABA-evoked chloride currents in *Xenopus* oocytes expressing the human $GABA_A$ receptor subunits $\alpha1\beta1\gamma2_L$, $\alpha2\beta1\gamma2_L$ or $\alpha3\beta1\gamma2_L$, direct activation of chloride flux occurred to a limited extent only at micromolar concentrations. Ganaxolone was effective in nontoxic doses against clonic convulsions induced by s.c. pentylenetetrazol administration in mice and rats (ED_{50} values of 4.3 and 7.8 mg/kg i.p., respectively). Ganaxolone also exhibited potent anticonvulsant activity against seizures induced by s.c. bicuculline (ED_{50} of 4.6 mg/kg i.p.), i.p. TBPS (ED_{50} of 11.7 mg/kg i.p.) and i.p. aminophylline (ED_{50} of 11.5

GABA-containing neurons are the predominant inhibitory neural elements within the brain. Correspondingly, GABA-mediated inhibition plays a critical role in the epileptic process by contributing to the termination of the ictal discharge and limiting the spread of hyperexcitability. Potentiation of GABAergic inhibitory function has therefore served as the rational basis for a number of programs targeted toward the

Received for publication April 22, 1996.

ABBREVIATIONS: CD_{97}, 97% convulsive dose; DMSO, dimethylsulfoxide; E_{max}, maximal extent of potentiation; EC_{10}, 10% effective concentration; GABA, γ-aminobutyric acid; MES, maximal electroshock; 3α,5α-P, 3α-hydroxy-5α-pregnan-20-one; 3α,5β-P, 3α-hydroxy-5β-pregnan-20-one; PI, protective index; PTZ, pentylenetetrazol; TBPS, *t*-butylbicyclophosphorothionate.

1284

1

EX1028

ABSTRACT

Ganaxolone (CCD 1042) is a 3β-methyl-substituted analog of the endogenous neuroactive steroid 3α-hydroxy-5α-pregnan-20-one. Ganaxolone inhibited binding of the γ-aminobutyric acid (GABA)$_A$ receptor-chloride channel ligand *t*-[^{35}S]butylbicyclophosphorothionate (IC_{50} of 80 nM) and enhanced binding of the benzodiazepine site ligand [^{3}H]flunitrazepam (EC_{50} of 125 nM) and the GABA site ligand [^{3}H]muscimol (EC_{50} of 86 nM), consistent with activity as a positive allosteric modulator of the $GABA_A$ receptor. Electrophysiological recordings showed that, whereas nanomolar concentrations of ganaxolone potentiated GABA-evoked chloride currents in *Xenopus* oocytes expressing the human $GABA_A$ receptor subunits $\alpha1\beta1\gamma2_L$, $\alpha2\beta1\gamma2_L$ or $\alpha3\beta1\gamma2_L$, direct activation of chloride flux occurred to a limited extent only at micromolar concentrations. Ganaxolone was effective in nontoxic doses against clonic convulsions induced by s.c. pentylenetetrazol administration in mice and rats (ED_{50} values of 4.3 and 7.8 mg/kg i.p., respectively). Ganaxolone also exhibited potent anticonvulsant activity against seizures induced by s.c. bicuculline (ED_{50} of 4.6 mg/kg i.p.), i.p. TBPS (ED_{50} of 11.7 mg/kg i.p.) and i.p. aminophylline (ED_{50} of 11.5 mg/kg i.p.) in mice. Although ganaxolone effectively blocked tonic seizures induced by maximal electroshock in mice (ED_{50} of 29.7 mg/kg i.p.), it did so only at doses that produced ataxia on the Rotorod (TD_{50} of 33.4 mg/kg i.p.). Conversely, ganaxolone was a potent anticonvulsant against fully kindled stage 5 seizures induced by corneal kindling in rats (ED_{50} of 4.5 mg/kg i.p.), producing these effects at doses well below those that resulted in ataxia (TD_{50} of 14.2 mg/kg i.p.). The seizure threshold, as determined by an increase in the dose of i.v. infused pentylenetetrazol required to induce clonus, was also significantly elevated by nontoxic doses of ganaxolone in mice. In summary, these data indicate that ganaxolone is a high-affinity, stereoselective, positive allosteric modulator of the $GABA_A$ receptor complex that exhibits potent anticonvulsant activity across a range of animal procedures. The profile of anticonvulsant activity obtained for ganaxolone supports clinical evaluation of this drug as an antiepileptic therapy with potential utility in the treatment of generalized absence seizures as well as simple and complex partial seizures.

Ex. 1028 at 1284; Patent Owner's Response at 21-22; Ex. 2014 at ¶ 64.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Ovid Therapeutics

Doses Recited in Claims 25-31 Would Be Toxic to a Rat



Raman Sankar, M.D., Ph.D.

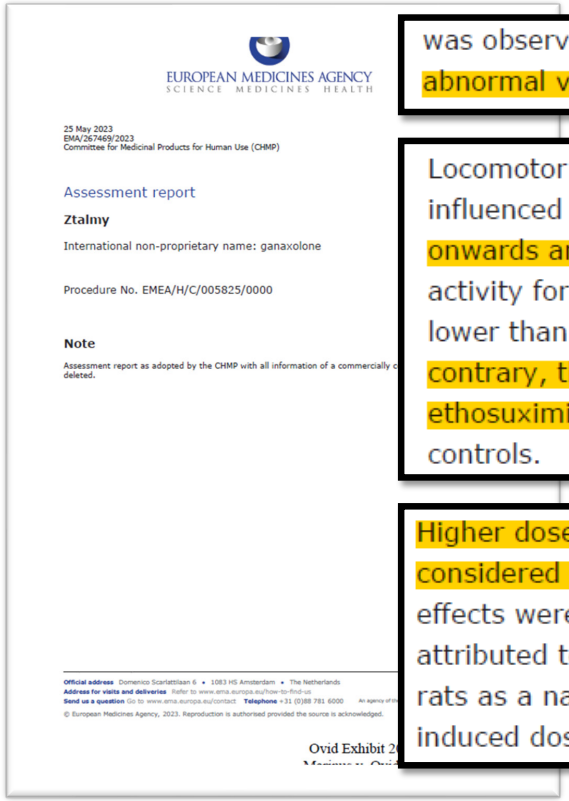
Q. But your opinions are all based on the idea that the claims in the patent are limited to human?
MS. PEHRSON: Objection to the extent it mischaracterizes his testimony. Vague.
THE WITNESS: The claims at the end of this?
BY MR. KANE:
Q. Yes.
A. I think they pertain to proposed human use.
Q. So they're limited to human use?
A. But the dosages are not consistent with some other species.

Q. Why do you say that?
A. Doses in the range you would not be able to administer to a rodent.

Ex. 1042 at 91:15-92:3; Patent Owner's Sur-Reply at 4.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Doses Recited in Claims 25-31 Would Be Toxic to a Rat



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 May 2023
EMA/267469/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Ztalmy

International non-proprietary name: ganaxolone

Procedure No. EMEA/H/C/005825/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially c
deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact Telephone +31 (0)88 781 6000 An agency of the
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Ovid Exhibit 2
Marinus v. Ovid

was observed in all dose groups. At 20 mg/kg onwards, the only GNX-related CNS effects were abnormal visual responses and ataxia. Ataxia was considered to be dose-dependent. Mild to moderate

Locomotor activity (both mice and rats) and cognitive function (mice) studies were dose-dependently influenced by GNX. In mice, dose-dependent effects of GNX on motor function started from 20 mg/kg onwards and in rats at 5 mg/kg. The lowest dose, which produced a significant decrease in locomotor activity for GNX was 16-fold lower than valproate (GNX 50 mg/kg vs valproate 800 mg/kg) and 18-fold lower than ethosuximide (GNX 50 mg/kg vs ethosuximide 900 mg/kg) in mice. In rats, on the contrary, the minimum sedative dose for GNX (15 mg/kg) was 53-fold lower than valproate and ethosuximide (800 mg/kg), suggesting that GNX has more potent sedative effects compared to controls.

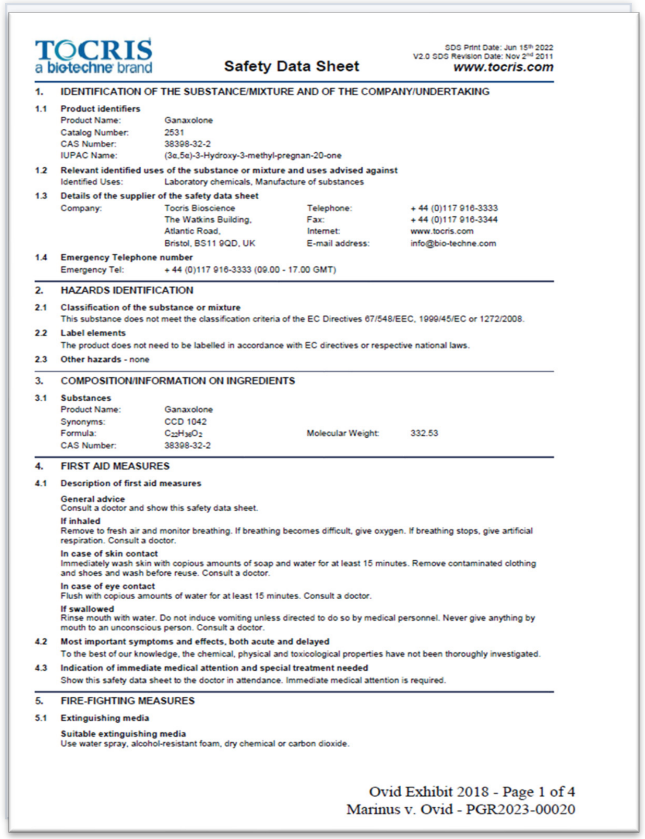
Higher doses (40 mg/kg in mice and 20 mg/kg in rats) also caused a loss of righting reflex, which was considered adverse. Cognitive function was significantly impaired at a dose of 30 mg/kg. These GNX effects were presented as deficits in motor function or in the latency to learn a response and were attributed to the sedative effect of GNX. GNX had strong sedative properties when administered IV to rats as a nanosuspension formulation or a Captisol formulation. In both formulations, GNX transiently induced dose-dependent, deep sedation but not full anaesthesia, starting from the low dose.

Ex. 2017, 25; Patent Owner's Response at 22;
Ex. 2014 at ¶ 64; Patent Owner's Sur-Reply at 4.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Ovid Therapeutics

Doses Recited in Claims 25-31 Would Be Toxic to a Rat



TOCRIS
a biotechne brand

Safety Data Sheet

SDS Print Date: Jun 15th 2022
V2.0 SDS Revision Date: Nov 2nd 2011
www.tocris.com

1. IDENTIFICATION OF THE SUBSTANCE/MIXTURE AND OF THE COMPANY/UNDERTAKING

1.1 Product identifiers
Product Name: Ganaxolone
Catalog Number: 2531
CAS Number: 38398-32-2
IUPAC Name: (3α,5α)-3-Hydroxy-3-methyl-pregnan-20-one

1.2 Relevant identified uses of the substance or mixture and uses advised against
Identified Uses: Laboratory chemicals, Manufacture of substances

1.3 Details of the supplier of the safety data sheet
Company: Tocris Bioscience, The Watkins Building, Atlantic Road, Bristol, BS11 9QD, UK
Telephone: + 44 (0)117 916-3333
Fax: + 44 (0)117 916-3344
Internet: www.tocris.com
E-mail address: info@bio-techne.com

1.4 Emergency Telephone number
Emergency Tel: + 44 (0)117 916-3333 (09.00 - 17.00 GMT)

2. HAZARDS IDENTIFICATION

2.1 Classification of the substance or mixture
This substance does not meet the classification criteria of the EC Directives 67/548/EEC, 1999/45/EC or 1272/2008.

2.2 Label elements
The product does not need to be labelled in accordance with EC directives or respective national laws.

2.3 Other hazards - none

3. COMPOSITION/INFORMATION ON INGREDIENTS

3.1 Substances
Product Name: Ganaxolone
Synonyms: CCD 1042
Formula: $C_{22}H_{36}O_2$
Molecular Weight: 332.53
CAS Number: 38398-32-2

4. FIRST AID MEASURES

4.1 Description of first aid measures

General advice
Consult a doctor and show this safety data sheet.

If inhaled
Remove to fresh air and monitor breathing. If breathing becomes difficult, give oxygen. If breathing stops, give artificial respiration. Consult a doctor.

In case of skin contact
Immediately wash skin with copious amounts of soap and water for at least 15 minutes. Remove contaminated clothing and shoes and wash before reuse. Consult a doctor.

In case of eye contact
Flush with copious amounts of water for at least 15 minutes. Consult a doctor.

If swallowed
Rinse mouth with water. Do not induce vomiting unless directed to do so by medical personnel. Never give anything by mouth to an unconscious person. Consult a doctor.

4.2 Most important symptoms and effects, both acute and delayed
To the best of our knowledge, the chemical, physical and toxicological properties have not been thoroughly investigated.

4.3 Indication of immediate medical attention and special treatment needed
Show this safety data sheet to the doctor in attendance. Immediate medical attention is required.

5. FIRE-FIGHTING MEASURES

5.1 Extinguishing media

Suitable extinguishing media
Use water spray, alcohol-resistant foam, dry chemical or carbon dioxide.

Ovid Exhibit 2018 - Page 1 of 4
Marinus v. Ovid - PGR2023-00020

11. TOXICOLOGICAL INFORMATION

11.1 Information on toxicological effects

Acute Toxicity
SCU-RAT TDLo: 3.46mg/kg; IPR-MUS TDLo: 17mg/kg

Ex. 2018 at 3; Patent Owner's Response at 22;
Ex. 2014 at ¶ 64; Patent Owner's Sur-Reply at 4.

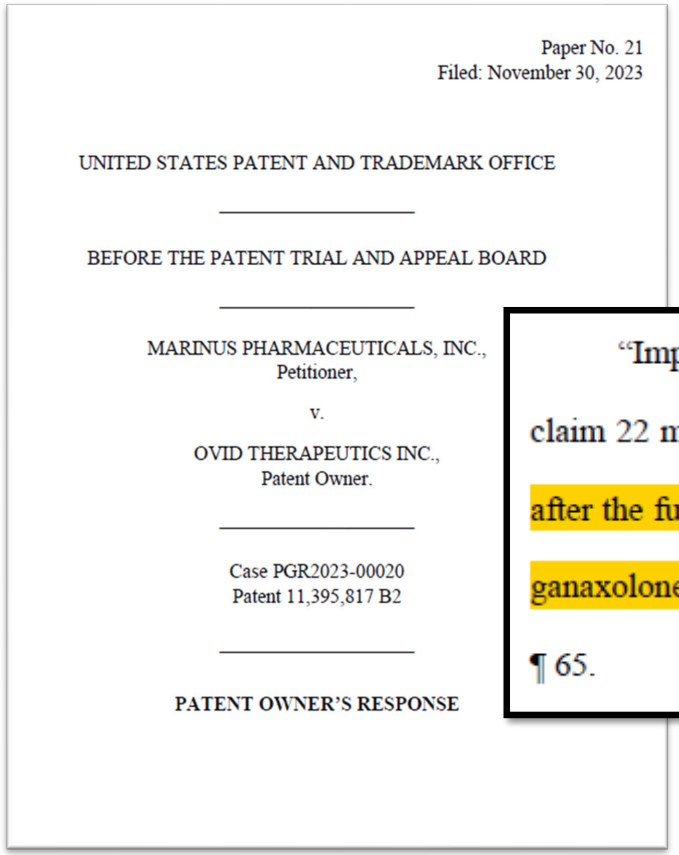
DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Ovid Therapeutics

Claim 22 Requires Measuring Improvement After the Total Dose of Ganaxolone is Administered

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

"Improvement to the Patient After Administration for More than 8 Hours"



Paper No. 21
Filed: November 30, 2023

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 RESPONSE

22. The method of claim **21** wherein the pharmaceutical composition provides improvement to the patient after administration for more than 8 hours.

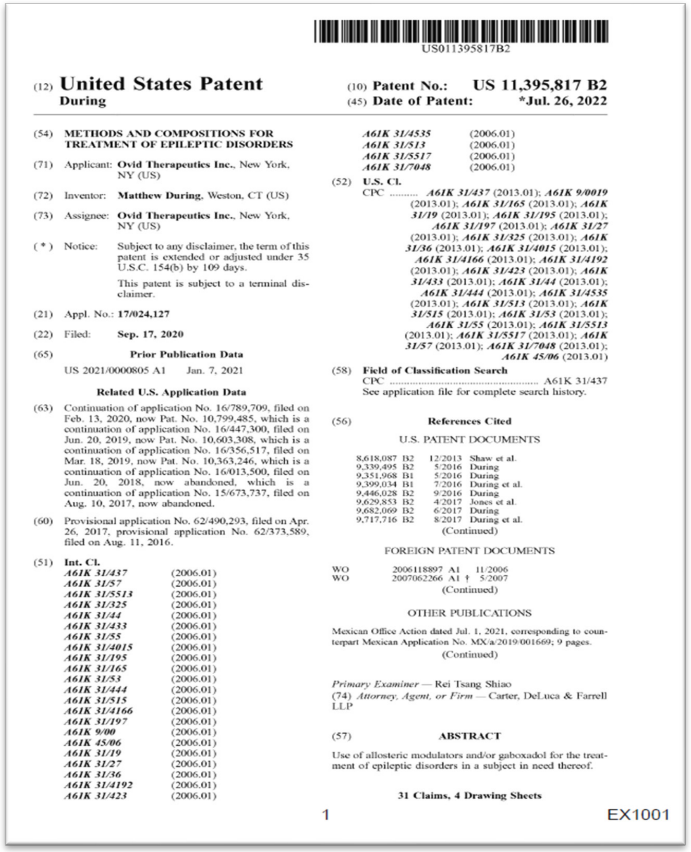
"Improvement to the patient after administration for more than 8 hours" in claim 22 means that there is improvement to the human patient more than 8 hours after the full dose of ganaxolone is given, regardless of whether the full amount of ganaxolone is given in a single administration or multiple administrations. Ex. 2014, ¶ 65.

Patent Owner's Response at 24-25; Ex. 1001 at 40:14-16;
see also Ex. 2014 at ¶¶ 65-67; Patent Owner's Sur-Reply at 5-6.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Ovid Therapeutics

Improvement Measured After Administering the Full Dose of Ganaxolone



US011395817B2

(12) **United States Patent**
During

(10) **Patent No.: US 11,395,817 B2**
(45) **Date of Patent: *Jul. 26, 2022**

(54) **METHODS AND COMPOSITIONS FOR TREATMENT OF EPILEPTIC DISORDERS**

(71) Applicant: **Ovid Therapeutics Inc.**, New York, NY (US)

(72) Inventor: **Matthew During**, Weston, CT (US)

(73) Assignee: **Ovid Therapeutics Inc.**, New York, NY (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 109 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **17/024,127**

(22) Filed: **Sep. 17, 2020**

(65) **Prior Publication Data**

US 2021/0000805 A1 Jan. 7, 2021

Related U.S. Application Data

(63) Continuation of application No. 16/789,709, filed on Feb. 13, 2020, now Pat. No. 10,799,485, which is a continuation of application No. 16/447,300, filed on Jun. 20, 2019, now Pat. No. 10,603,308, which is a continuation of application No. 16/356,517, filed on Mar. 18, 2019, now Pat. No. 10,363,246, which is a continuation of application No. 16/013,500, filed on Jun. 20, 2018, now abandoned, which is a continuation of application No. 15/673,737, filed on Aug. 10, 2017, now abandoned.

(60) Provisional application No. 62/490,293, filed on Apr. 26, 2017, provisional application No. 62/373,589, filed on Aug. 11, 2016.

(51) **Int. Cl.**

A61K 31/437	(2006.01)
A61K 31/57	(2006.01)
A61K 31/5513	(2006.01)
A61K 31/325	(2006.01)
A61K 31/44	(2006.01)
A61K 31/433	(2006.01)
A61K 31/55	(2006.01)
A61K 31/4015	(2006.01)
A61K 31/795	(2006.01)
A61K 31/165	(2006.01)
A61K 31/53	(2006.01)
A61K 31/444	(2006.01)
A61K 31/515	(2006.01)
A61K 31/4166	(2006.01)
A61K 31/197	(2006.01)
A61K 9/00	(2006.01)
A61K 45/06	(2006.01)
A61K 31/19	(2006.01)
A61K 31/27	(2006.01)
A61K 31/36	(2006.01)
A61K 31/4192	(2006.01)
A61K 31/423	(2006.01)
A61K 31/4535	(2006.01)
A61K 31/513	(2006.01)
A61K 31/5517	(2006.01)
A61K 31/7048	(2006.01)

(52) **U.S. Cl.**
CPC ***A61K 31/437*** (2013.01); ***A61K 9/0019*** (2013.01); ***A61K 31/165*** (2013.01); ***A61K 31/19*** (2013.01); ***A61K 31/195*** (2013.01); ***A61K 31/197*** (2013.01); ***A61K 31/27*** (2013.01); ***A61K 31/325*** (2013.01); ***A61K 31/36*** (2013.01); ***A61K 31/4015*** (2013.01); ***A61K 31/4166*** (2013.01); ***A61K 31/4192*** (2013.01); ***A61K 31/423*** (2013.01); ***A61K 31/433*** (2013.01); ***A61K 31/44*** (2013.01); ***A61K 31/444*** (2013.01); ***A61K 31/4535*** (2013.01); ***A61K 31/513*** (2013.01); ***A61K 31/515*** (2013.01); ***A61K 31/53*** (2013.01); ***A61K 31/55*** (2013.01); ***A61K 31/5513*** (2013.01); ***A61K 31/5517*** (2013.01); ***A61K 31/57*** (2013.01); ***A61K 31/7048*** (2013.01); ***A61K 45/06*** (2013.01)

(58) **Field of Classification Search**
CPC A61K 31/437
See application file for complete search history.

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(Continued)

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(Continued)

Primary Examiner — Rei Tsang Shiao
(74) *Attorney, Agent, or Firm* — Carter, DeLuca & Farrell LLP

(57) **ABSTRACT**

Use of allosteric modulators and/or gaboxadol for the treatment of epileptic disorders in a subject in need thereof.

31 Claims, 4 Drawing Sheets

1 EX1001

In embodiments, provided herein are methods of treating an epileptic disorder wherein the patient is provided improvement of at least one symptom for more than 4 hours after administration of the pharmaceutical composition to the patient. In embodiments, the improvement of at least one symptom for more than 6 hours after administration of the pharmaceutical composition to the patient is provided in accordance with the present disclosure. In embodiments, improvement of at least one symptom for more than, e.g., 8 hours, 10 hours, 12 hours, 15 hours, 18 hours, 20 hours, or 24 hours after administration of the pharmaceutical composition to the patient is provided in accordance with the present disclosure. In embodiments, improvement in at least one symptom for at least e.g., 8 hours, 10 hours, 12 hours, 15 hours, 18 hours, 20 hours, or 24 hours after administration of the pharmaceutical composition to the patient is provided in accordance with the present disclosure. In embodiments, improvement in at least one symptom for 12 hours after administration of the pharmaceutical composition to the patient is provided in accordance with the present disclosure.

Ex. 1001 at 14:21-41, 15:17-19, 15:40-42; Patent Owner's Sur-Reply at 6.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Patent Owner's Construction Is Consistent with POSA's Understanding

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MARINUS PHARMACEUTICALS, INC.,
Petitioner,

v.

OVID THERAPEUTICS, INC.,
Patent Owner.

PGR2023-00020
Patent No. 11,395,817 B2

DECLARATION OF RAMAN SANKAR, M.D., PH.D.



Raman Sankar, M.D., Ph.D.

66. A POSA would have understood this to be the plain and ordinary meaning of the claim phrase because whether a patient with SE has sustained any improvement after administration of a drug is typically assessed at a point in time after a full dose is administered, rather than starting the clock after the first administration of only part of the dose. This is because the full dose of the drug is generally required to provide the expected effect.

Ex. 2014 at ¶ 66; Patent Owner's Response at 24-25; Patent Owner's Sur-Reply at 6.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Ovid Therapeutics

Dr. Rogawski Construes the Wrong Claim Phrase

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MARINUS PHARMACEUTICALS, INC.,
Petitioner

v.

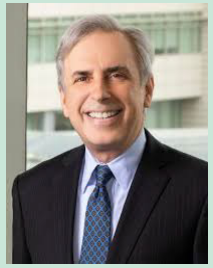
OVID THERAPEUTICS, INC.,
Patent Owner

Case PGR2023-00020
Patent 11,395,817

SUPPLEMENTAL DECLARATION OF DR. MICHAEL A. ROGAWSKI

MARINUS 1041
Marinus v. Ovid
PGR2023-00020

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Michael A. Rogawski, Ph.D., M.D.

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.

22. The method of claim **21** wherein the pharmaceutical composition provides improvement to the patient after administration for more than 8 hours.

Ex. 1041 at ¶¶ 32-41; Patent Owner's Sur-Reply at 5; Ex. 1001 at 40:14-16; *see also* Petitioner's Reply at 9-11.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Ovid Therapeutics

Petitioner Improperly Imports Language into Claim 22

> Assessing "improvement . . . after administration for more than 8 hours" 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]

Petitioner's Reply at 7.

> treatment. In embodiments, the symptom, pharmacologic, and/or physiologic indicator is measured in a subject prior to treatment, and again one or more times after treatment is initiated. In embodiments, the control is a reference level, or average determined based on measuring the symptom, pharmacologic, or physiologic indicator in one or more subjects that do not have the disease or condition to be treated (e.g., healthy subjects). In embodiments, the effect of the treatment is compared to a conventional treatment that is known the art.

'817 patent at 9:43-46.

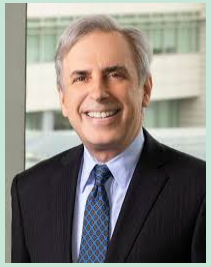


"As we have repeatedly held, it is improper 'to import limitations from the specification into the claims.'"

Pulse Elecs., Inc. v. U.D. Elec. Corp., 860 F. App'x 735, 737 (Fed. Cir. 2021) (quoting *Hill-Rom Servs., Inc. v. Stryker Corp.*, 755 F.3d 1367, 1371-72 (Fed. Cir. 2014).

Patent Owner's Sur-Reply at 5-6; Ex. 1001 at 9:43-46; Petitioner's Reply at 7.

Petitioner Improperly Imports Language into Claim 22



Michael A. Rogawski, Ph.D., M.D.

The word "improvement" is not stated in Column 9, lines 43 through 46, correct?

A. That is correct.

Q. The phrase "after eight hours" does not appear in Column 9, lines 43 through 46; is that correct?

A. I don't see the words "eight hours" there, no.

Q. And the word "improvement" does not appear in the paragraph that lines 43 through 46 is in; is that correct?

A. Well, I would have to scan down there, but I'll take your word for it if you --

Q. You're welcome to scan, if you would like.

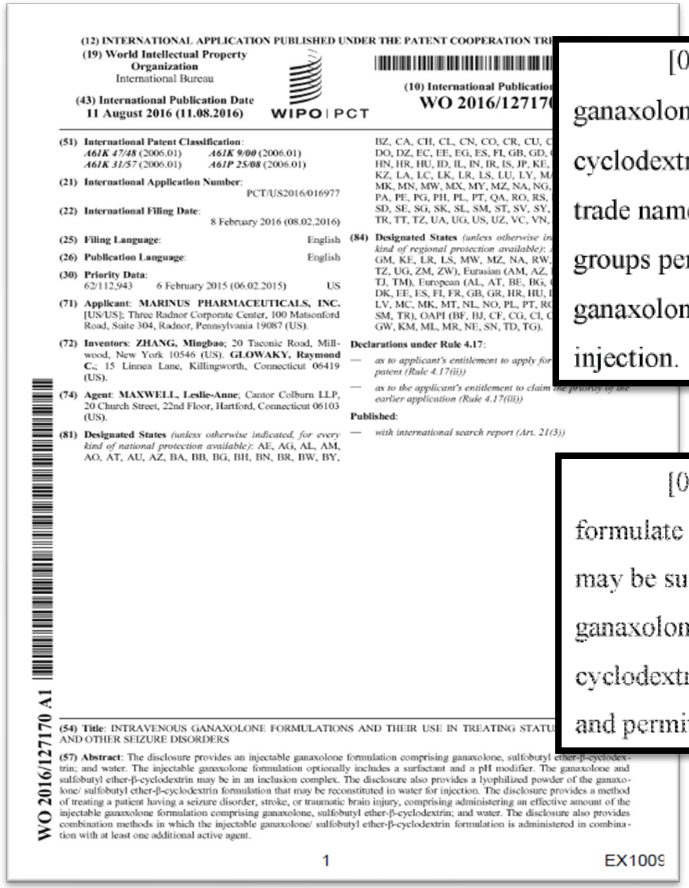
A. I may have missed it, but I don't -- I'm not -- on a quick read, I didn't see the word "improvement," no.

Ex. 2024 at 40:24:41:13; Patent Owner's Sur-Reply at 5-6.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Zhang Does Not Anticipate Claims 22 and 25-31

Zhang Does Not Describe Treating SE in Humans



(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TR

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
11 August 2016 (11.08.2016)

WIPO | PCT

(10) International Publicatio
WO 2016/12717

(51) International Patent Classification:
A61K 47/48 (2006.01) *A61K 9/00* (2006.01)
A61K 31/57 (2006.01) *A61P 25/08* (2006.01)

(21) International Application Number:
PCT/US2016/016977

(22) International Filing Date:
8 February 2016 (08.02.2016)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/112,943 6 February 2015 (06.02.2015) US

(71) Applicant: **MARINUS PHARMACEUTICALS, INC.** [US/US]; Three Radnor Corporate Center, 100 Matsonford Road, Suite 304, Radnor, Pennsylvania 19087 (US).

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BZ, CA, CH, CL, CN, CO, CR, CU, C
DO, DZ, EC, EE, EG, ES, FI, GB, GD,
HN, HR, HU, ID, IL, IN, IR, IS, JP, KE,
KZ, LA, LC, LK, LR, LS, LU, LY, M
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SD, SE, SG, SK, SL, SM, ST, SV, SY,
TR, TT, TZ, UA, UG, US, UZ, VC, VN,

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SM, TR), OAPI (BF, BJ, CF, CG, CI,
GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for patent (Rule 4.17(ii))*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:
— *with international search report (Art. 21(3))*

(54) Title: INTRAVENOUS GANAXOLONE FORMULATIONS AND THEIR USE IN TREATING STATU AND OTHER SEIZURE DISORDERS

(57) Abstract: The disclosure provides an injectable ganaxolone formulation comprising ganaxolone, sulfobutyl ether-β-cyclodextrin; and water. The injectable ganaxolone formulation optionally includes a surfactant and a pH modifier. The ganaxolone and sulfobutyl ether-β-cyclodextrin may be in an inclusion complex. The disclosure also provides a lyophilized powder of the ganaxolone/ sulfobutyl ether-β-cyclodextrin formulation that may be reconstituted in water for injection. The disclosure provides a method of treating a patient having a seizure disorder, stroke, or traumatic brain injury, comprising administering an effective amount of the injectable ganaxolone formulation comprising ganaxolone, sulfobutyl ether-β-cyclodextrin; and water. The disclosure also provides combination methods in which the injectable ganaxolone/ sulfobutyl ether-β-cyclodextrin formulation is administered in combination with at least one additional active agent.

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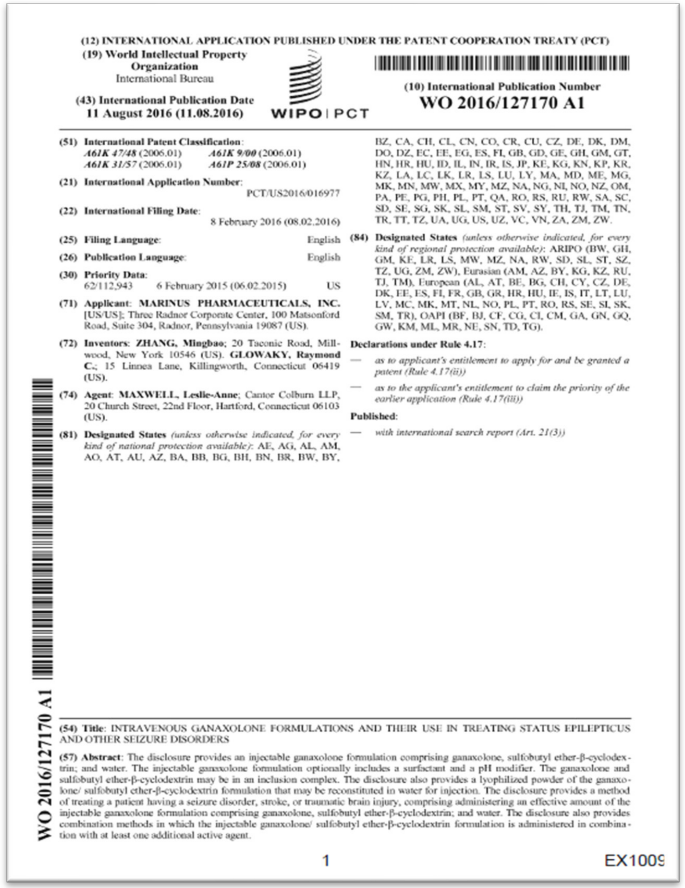
EX1009

[0005] The disclosure provides an injectable ganaxolone formulation comprising ganaxolone, sulfobutyl ether-β-cyclodextrin; and water. The ganaxolone and sulfobutyl ether-β-cyclodextrin may be in an inclusion complex. Sulfobutyl ether β-cyclodextrin is marketed under the trade name, CAPTISOL® (Ligand Pharmaceuticals), which contains an average 6-7 sulfobutyl ether groups per cyclodextrin molecule. The disclosure also provides a lyophilized powder of the ganaxolone/ sulfobutyl ether-β-cyclodextrin formulation that may be reconstituted in water for injection.

[0031] Ganaxolone is very poorly soluble in water (< 0.001 mg/ mL) and thus is difficult to formulate as an aqueous injectable. The inventors have found that the water-solubility of ganaxolone may be sufficiently increased to allow it to be formulated as an aqueous injectable by complexing ganaxolone with a substituted β-cyclodextrin, such as CAPTISOL. In effect, the substituted β-cyclodextrin inhibits precipitation of the ganaxolone at the injection site, providing reduced irritation and permitting injection without unacceptable injection-site irritation.

Ex. 1009 at ¶¶ [0005], [0031]; Patent Owner's Response at 28; Patent Owner's Sur-Reply at 7-8; Ex. 2014 at ¶ 70.

Zhang Does Not Describe Treating SE in Humans



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(43) International Publication Date
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WIPO | PCT

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EX1009

EXAMPLES

EXAMPLE 1. PREPARATION OF INJECTABLE GANAXOLONE FORMULATION

EXAMPLE 2. PREPARATION OF INJECTABLE GANAXOLONE-CAPTISOL SOLUTION (5 MG/ML)

EXAMPLE 3. PREPARATION OF A LYOPHILIZED GANAXOLONE-CAPTISOL POWDER

EXAMPLE 4. BUFFERED GANAXOLONE-CAPTISOL SOLUTIONS

EXAMPLE 5. INJECTABLE GANAXOLONE- 30% CAPTISOL SOLUTION CONTAINING POLYSORBATE 80

EXAMPLE 6. PREPARATION OF GANAXOLONE/30% CAPTISOL SOLUTION BY PRIOR DRY MIXING OF GANAXOLONE AND CAPTISOL

EXAMPLE 7. PLASMA LEVELS OF GANAXOLONE IN RATS INJECTED AND INFUSED WITH GANAXOLONE-CAPTISOL SOLUTION

EXAMPLE 8. GANAXOLONE EFFECT ON PILOCARPINE-INDUCED STATUS EPILEPTICUS IN RATS

Ex. 1009 at ¶¶ [0104]-[0136]; Patent Owner's Response at 28-29; Patent Owner's Sur-Reply at 7-8; Ex. 2014 at ¶¶ 70-71.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Petitioner Improperly Relies on Understanding of POSA

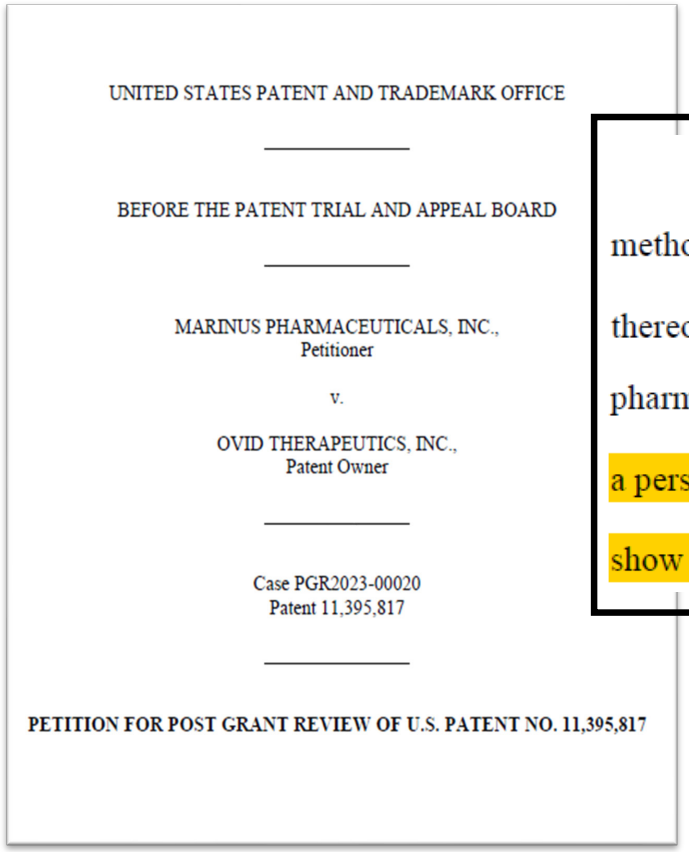
"The opinion says anticipation may be shown by less than 'complete anticipation' if ***one of ordinary skill may in reliance on the prior art 'complete the work required for the invention,'*** and that 'it is sufficient for an anticipation "if the general aspects are the same and the differences in minor matters is only such as would suggest itself to one of ordinary skill in the art."' ***Those statements relate to obviousness, not anticipation***. Anticipation requires the presence in a single prior art disclosure of all elements of a claimed invention arranged as in the claim."

Connell v. Sears, Roebuck & Co., 722 F.2d 1542, 1548 (Fed. Cir. 1983) (emphasis added).

Patent Owner's Response at 26.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Petitioner Improperly Relies on Understanding of POSA



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

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

In sum, Zhang not only discloses an actual reduction to practice of "a method of treating status epilepticus comprising administering to a patient in need thereof a pharmaceutical composition comprising ganaxolone or a pharmaceutically acceptable salt thereof" in a rat with SE, but seeing those results, a person skilled in the art would have reasonably believed that ganaxolone would show efficacy in treatment of SE in human patients as well.[145]

Petition at 37-38; Patent Owner's Response at 26.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Animal Models Do Not Translate Directly to Human Treatment

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MARINUS PHARMACEUTICALS, INC.,
Petitioner,

v.

OVID THERAPEUTICS, INC.,
Patent Owner.

PGR2023-00020
Patent No. 11,395,817 B2

DECLARATION OF RAMAN SANKAR, M.D., PH.D.

Ovid Exhibit 2014 - Page 1 of 68
Marinus v. Ovid - PGR2023-00020



Raman Sankar, M.D., Ph.D.

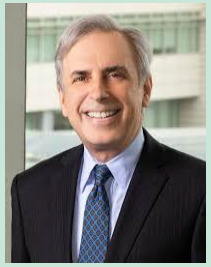
71. Instead, Zhang's discloses animal data. Examples 7 and 8 disclose data from ganaxolone administered to rats with pilocarpine-induced SE. *See* ¶¶ [0116]-[0136]. It is common knowledge to a POSA that animal models do not translate directly to human treatment. For example, in the rat lithium pilocarpine model, SE is chemically induced using pilocarpine, while in humans, SE typically comes about due to a variety of clinical circumstances such as infection, inadvertently missing doses of anti-seizure medicines, trauma, stroke, or carcinomatous meningitis. Because SE is chemically induced in rats using pilocarpine, this has resulted in "variations in SE induction and pilocarpine sensitivity between different batches of the same strain of rats" and "most likely result[s] in the wide-ranging experimental data reported from different laboratories." Ex. 1006, 3. Moreover, one cannot directly compare doses of ganaxolone administered to rats with doses administered to humans because rats metabolize compounds at a much faster rate than humans by the hepatic microsomal system. As a result, higher doses (in mg/kg) of a compound are typically administered to rats than humans. Therefore, data from the rat lithium pilocarpine model only provides information as to what compounds could potentially be used to treat SE in humans and does not provide specific information regarding effective doses of any such compound in humans. Nothing in Zhang describes the administration of ganaxolone for treating a human suffering from SE.

Ex. 2014 at ¶ 71; Patent Owner's Response at 26-27; Patent Owner's Sur-Reply at 7.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Ovid Therapeutics

Animal Models Do Not Translate Directly to Human Treatment



Michael A. Rogawski, Ph.D., M.D.

Q. Have you done research in any other neurosteroids besides ganaxolone and allopregnanolone for treating SE?

A. **I have.**

Q. Which ones are those?

A. **There were a variety of neuroactive steroids that we studied in the beginning of our research effort in this area many years ago -- this would be in the 1980s. And I can't recall precisely what compounds we studied. Those are listed in our publication. But they all had some degree of activity in -- in status epilepticus.**

Q. And when you say there's "some degree of activity," was that in an animal model?

A. **That was in an animal model, yes -- or several animal models, I should say.**

Q. Okay. And did any of those other compounds advance to clinical trials in humans?

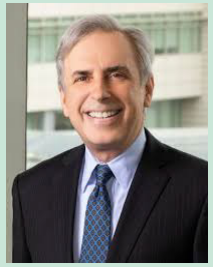
A. **Not that I'm aware of, no.**

Ex. 2015 at 24:14-25:7; Patent Owner's Response at 28-29; Patent Owner's Sur-Reply at 7.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Ovid Therapeutics

Animal Models Do Not Translate Directly to Human Treatment



Michael A. Rogawski, Ph.D., M.D.

Q. And what was the general kind of nature of that research?

A. We have developed a treatment based on animal research in the laboratory, and we had an opportunity to collaborate with a group of clinicians who were studying status epilepticus -- or treating status epilepticus in humans. And we provided our treatment to them, and that resulted in jointly authored publications. I believe there were three -- about three jointly authored publications that resulted from that clinical research.

Q. And what drug compound was that research done with?

A. That was with allopregnanolone.

Q. Did allopregnanolone advance to clinical trials in humans for treating SE?

A. It did.

Q. Did it receive approval for treating SE from the FDA?

A. Not that I'm aware of, no.

Q. Do you know why that was?

A. There was a clinical trial in super-refractory status epilepticus where allopregnanolone was not found to meet the predefined endpoints, and therefore the program did not progress.

Ex. 2015 at 21:10-24:13; Patent Owner's Response at 27-28; Patent Owner's Sur-Reply at 7.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Claim 22: Inherency Requires Limitation to Necessarily Be Present

"A single prior art reference may anticipate without disclosing a feature of the claimed invention if such feature is necessarily present, or inherent, in that reference."

Allergan, Inc. v. Apotex Inc., 754 F.3d 952, 958 (Fed. Cir. 2014).

"Inherency can be established when prior art necessarily functions in accordance with, or includes, the claimed limitations. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result is not sufficient."

Bettcher Indus., Inc. v. Bunzl USA, Inc., 661 F.3d 629, 639 (Fed. Cir. 2011) (internal citations and quotations omitted).

Patent Owner's Response at 29-30; Patent Owner's Sur-Reply at 9.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Claim 22: Zhang Only Provides Data up to 5 Hours In Rats, Not Humans

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MARINUS PHARMACEUTICALS, INC.,
Petitioner

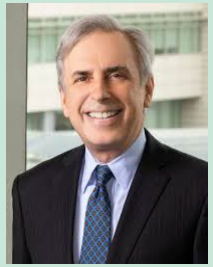
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Case PGR2023-00020
Patent 11,395,817

DECLARATION OF DR. MICHAEL A. ROGAWSKI

1 EX1003



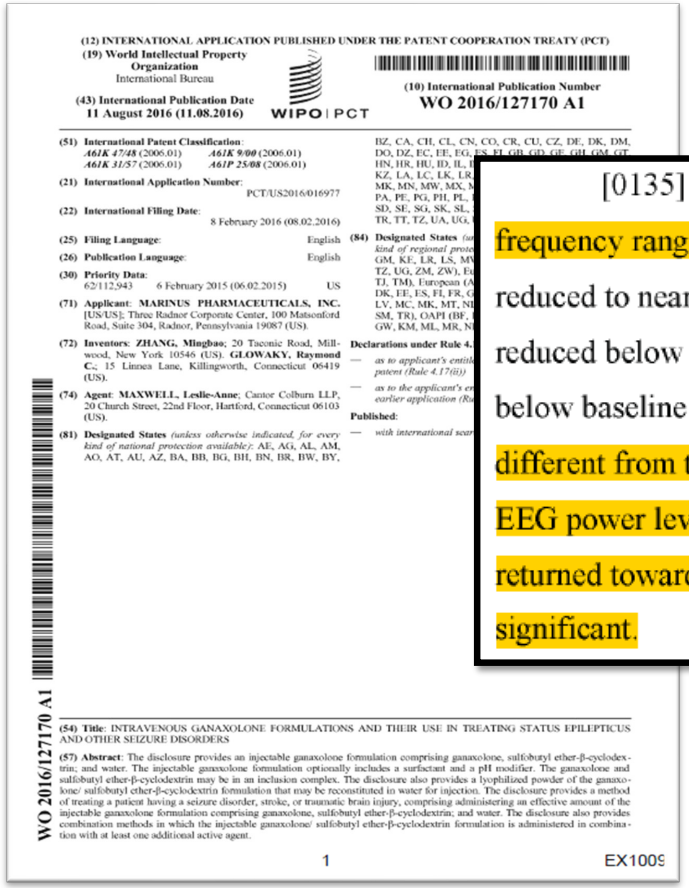
Michael A. Rogawski, Ph.D., M.D.

93. Zhang does not expressly state the composition provides improvement for more than 8 hours after administration. In Zhang's Example 8, the rats experiencing SE were sacrificed after 5 hours and, so, even though some effects of ganaxolone were sustained for the entire 5 hours, because the experiment was stopped at 5 hours, there is no data demonstrating a response "for more than 8 hours."[1] To the extent that improvement to the patient were to occur after that time period, however, it would be the natural result of administering the ganaxolone formulations in the manner taught in Zhang.

Ex. 1003 at ¶ 93; Patent Owner's Response at 28-32; Patent Owner's Sur-Reply at 8-9; Ex. 2014 at ¶¶ 77-78.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Claim 22: Effect of Ganaxolone Diminishes by 5h



(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
11 August 2016 (11.08.2016)

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EX1009

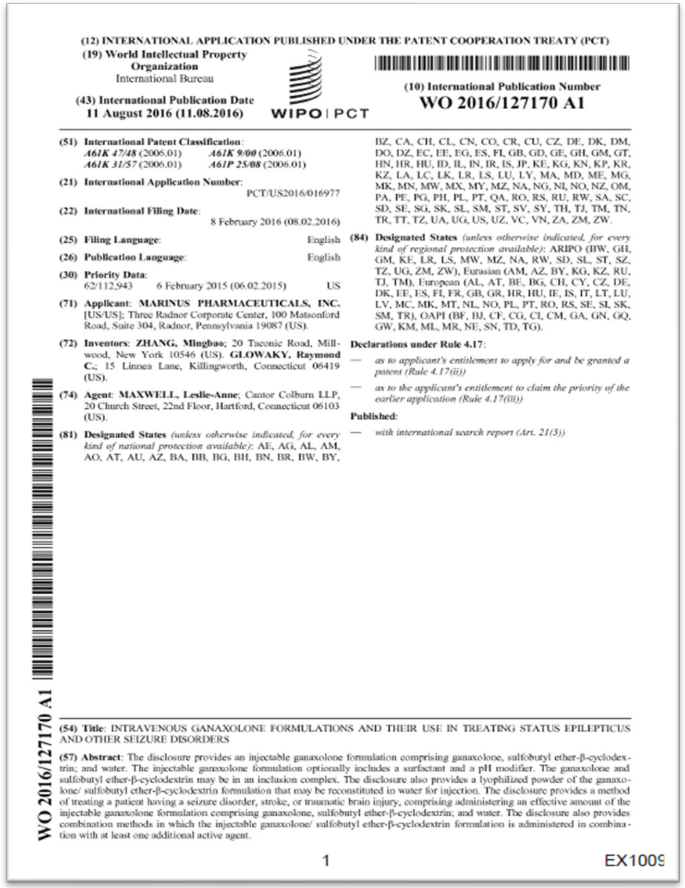
[0135] When dosed 15 minutes after SE-onset, GNX reduced EEG power across all frequency ranges to levels at or below baseline for at up to 5 h. From 5-70 Hz, EEG power was reduced to near the baseline level and remained there for 5 h post dosing. At 0-5 Hz, EEG power was reduced below the baseline level for approximately 90 min, and at 70-96 Hz, EEG power remained below baseline for the entire 5 h. However, between 2 to 5 h, EEG power above 30 Hz was not different from the vehicle group, indicating it was also not significantly different from the baseline EEG power level. Note also that at the higher frequency ranges, EEG power in the vehicle groups returned towards baseline after 2 h, so that differences between the GNX and vehicle groups were not significant.

Ex. 1009 at ¶ [0135]; Patent Owner's Response at 31-32; Patent Owner's Sur-Reply at 9; *see also* Ex. 2014 at ¶ 76.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Ovid Therapeutics

Claim 22: Effect of Ganaxolone Diminishes by 5 Hours



(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
11 August 2016 (11.08.2016)

WIPO | PCT

(10) International Publication Number
WO 2016/127170 A1

(51) International Patent Classification:
A61K 47/48 (2006.01) *A61K 9/00* (2006.01)
A61K 31/57 (2006.01) *A61P 25/08* (2006.01)

(21) International Application Number:
PCT/US2016/016977

(22) International Filing Date:
8 February 2016 (08.02.2016)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/112,943 6 February 2015 (06.02.2015) US

(71) Applicant: **MARINUS PHARMACEUTICALS, INC.** [US/US]; Three Radnor Corporate Center, 100 Matsonford Road, Suite 304, Radnor, Pennsylvania 19087 (US).

(72) Inventors: **ZHANG, Mingbao**; 20 Taconic Road, Millwood, New York 10546 (US). **GLOWAKY, Raymond C.**; 15 Linnea Lane, Killingworth, Connecticut 06419 (US).

(74) Agent: **MAXWELL, Leslie-Anne**; Cantor Colburn LLP, 20 Church Street, 22nd Floor, Hartford, Connecticut 06103 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
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Published:
— *with international search report (Art. 21(3))*

(54) Title: INTRAVENOUS GANAXOLONE FORMULATIONS AND THEIR USE IN TREATING STATUS EPILEPTICUS AND OTHER SEIZURE DISORDERS

(57) Abstract: The disclosure provides an injectable ganaxolone formulation comprising ganaxolone, sulfobutyl ether-β-cyclodextrin; and water. The injectable ganaxolone formulation optionally includes a surfactant and a pH modifier. The ganaxolone and sulfobutyl ether-β-cyclodextrin may be in an inclusion complex. The disclosure also provides a lyophilized powder of the ganaxolone/ sulfobutyl ether-β-cyclodextrin formulation that may be reconstituted in water for injection. The disclosure provides a method of treating a patient having a seizure disorder, stroke, or traumatic brain injury, comprising administering an effective amount of the injectable ganaxolone formulation comprising ganaxolone, sulfobutyl ether-β-cyclodextrin; and water. The disclosure also provides combination methods in which the injectable ganaxolone/ sulfobutyl ether-β-cyclodextrin formulation is administered in combination with at least one additional active agent.

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EX1009

TABLE 6 - Treatment Effects, Rats Treated 15 minutes post SE onset

		Significance, Time post drug administration					
Comparison	Frequency	0-15 min.	15-30	30-60	1-2 hrs	2-3 hrs	3-5 hrs
Vehicle vs. Allo.(15 mg/ml), both administered 15' post SE onset	0-5 Hz	****	****	****	***	*	ns
	5-10 Hz	****	****	****	***	ns	ns
	10-30 Hz	****	****	***	**	ns	ns
	30-50 Hz	****	****	***	ns	ns	ns
	50-70 Hz	***	***	**	ns	ns	ns
	70-96 Hz	***	***	**	ns	ns	ns
Vehicle vs GNX (12 mg/ml) both administered 15 minutes post SE onset	0-5 Hz	****	****	****	****	***	**
	5-10 Hz	****	****	***	**	*	ns
	10-30 Hz	***	****	**	*	ns	ns
	30-50 Hz	***	***	**	*	ns	ns
	50-70 Hz	**	**	*	**	ns	ns
	70-96 Hz	**	**	*	**	ns	ns
Vehicle vs GNX (15 mg/ml) both administered 15 minutes post SE onset	0-5 Hz	****	****	****	****	****	***
	5-10 Hz	****	****	****	****	***	ns
	10-30 Hz	****	****	****	**	*	ns
	30-50 Hz	***	***	***	**	ns	ns
	50-70 Hz	**	**	**	**	ns	ns
	70-96 Hz	**	***	**	**	ns	ns

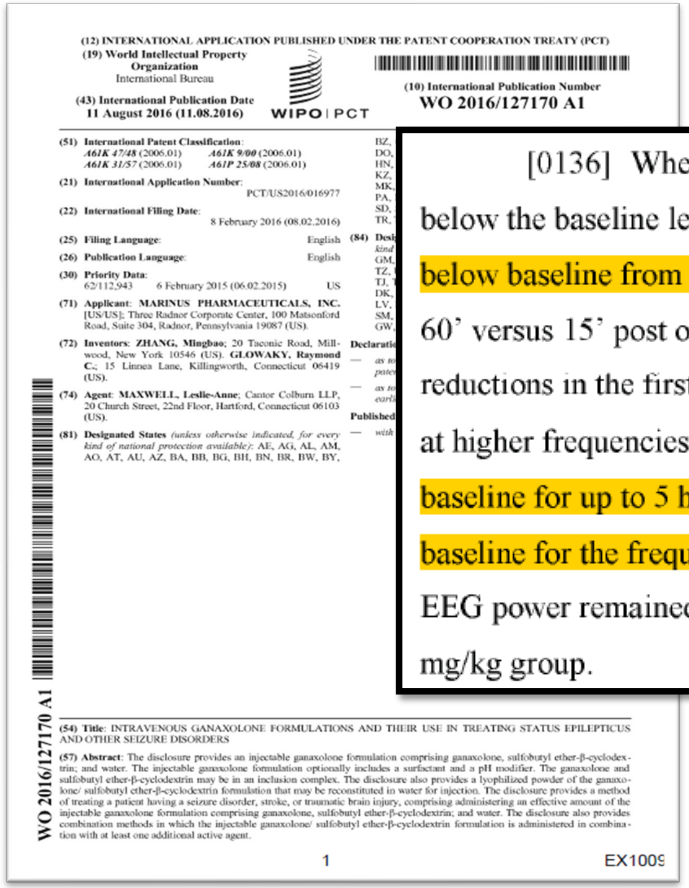
* P < 0.05; ** P < 0.01; *** P < 0.001; **** P < 0.0001, ns = not significant CLAIMS

Ex. 1009 at Table 6; Patent Owner's Response at 31-32; Patent Owner's Sur-Reply at 9; *see also* Ex. 2014 at ¶ 76.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Ovid Therapeutics

Claim 22: Effect of Ganaxolone Diminishes by 5 Hours



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BZ, DO, HN, KZ, MK, PA, SD, TR,

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GM, TZ, TJ, DK, LV, SM, GW,

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— *as to*
— *as to*
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Published
— *with*

WO 2016/127170 A1

(54) Title: INTRAVENOUS GANAXOLONE FORMULATIONS AND THEIR USE IN TREATING STATUS EPILEPTICUS AND OTHER SEIZURE DISORDERS

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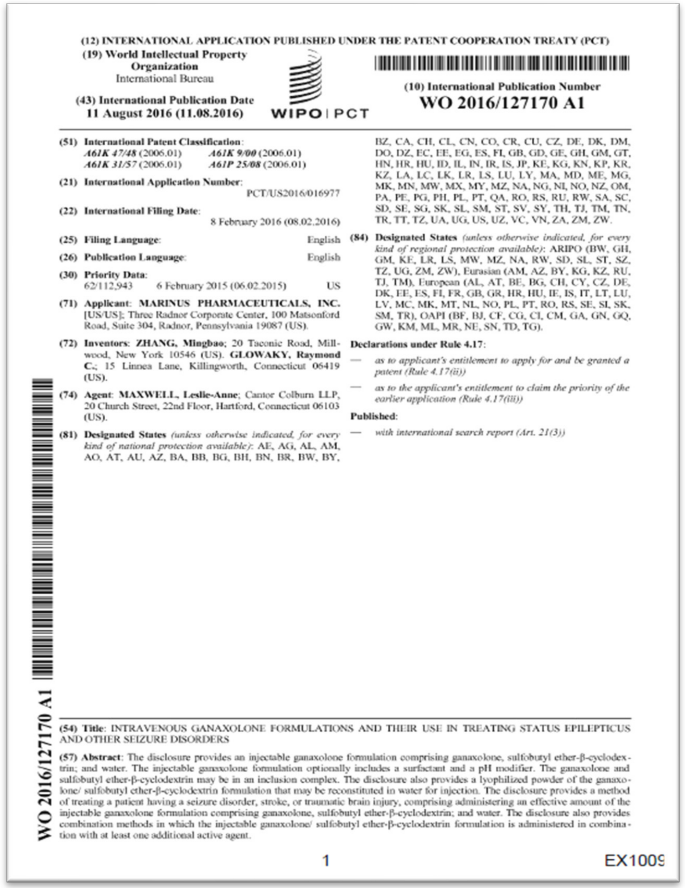
EX1009

> [0136] When dosed at 60' post SE-onset, EEG power was also strongly reduced, but not below the baseline level for frequencies up to 70 Hz. From 70-96 Hz, EEG power appeared to drop below baseline from 1 to 4 h post dosing. The principal difference between effects of GNX dosed at 60' versus 15' post onset were (1) at higher frequencies (> 30 Hz), there were no significant reductions in the first 15' post dosing, and (2) the activity the drug appeared to be stronger especially at higher frequencies at the 2-3 h time point. Again, the EEG power levels were maintained at baseline for up to 5 h post dosing, however, the EEG levels of the vehicle group also returned to baseline for the frequency ranges above 30 Hz so the drug showed no effect. In contrast, at 0-5 Hz, EEG power remained high in the vehicle group, and GNX showed a significant reduction in the 12 mg/kg group.

Ex. 1009 at ¶ [0136]; Patent Owner's Response at 31-32; Patent Owner's Sur-Reply at 9; *see also* Ex. 2014 at ¶ 76.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Claim 22: Effect of Ganaxolone Diminishes by 5 Hours



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EX1009

TABLE 7 - Treatment Effects, Rats Treated 60 minutes post SE onset

		Significance, Time post drug administration					
Comparison	Frequency	0-15 min.	15-30	30-60	1-2 hrs	2-3 hrs	3-5 hrs
Vehicle vs. Allo.(15 mg/ml), both administered 15' post SE onset	0-5 Hz	**	ns	Ns	ns	ns	ns
	5-10 Hz	**	ns	Ns	ns	ns	ns
	10-30 Hz	ns	ns	Ns	ns	ns	ns
	30-50 Hz	ns	ns	Ns	ns	ns	ns
	50-70 Hz	ns	ns	Ns	ns	ns	ns
	70-96 Hz	ns	ns	Ns	ns	ns	ns
Vehicle vs GNX (12 mg/ml) both administered 15 minutes post SE onset	0-5 Hz	***	****	****	****	***	**
	5-10 Hz	****	****	****	***	**	ns
	10-30 Hz	*	**	**	**	*	ns
	30-50 Hz	ns	ns	*	**	*	ns
	50-70 Hz	ns	*	**	**	*	ns
	70-96 Hz	ns	**	***	***	**	ns

TABLE 7 - Treatment Effects, Rats Treated 60 minutes post SE onset

		Significance, Time post drug administration					
Comparison	Frequency	0-15 min.	15-30	30-60	1-2 hrs	2-3 hrs	3-5 hrs
Vehicle vs GNX (15 mg/ml) both administered 15 minutes post SE onset	0-5 Hz	***	***	**	**	**	ns
	5-10 Hz	**	****	****	**	**	ns
	10-30 Hz	ns	ns	*	**	*	ns
	30-50 Hz	ns	ns	*	*	ns	ns
	50-70 Hz	ns	ns	*	**	ns	ns
	70-96 Hz	ns	*	**	**	*	ns

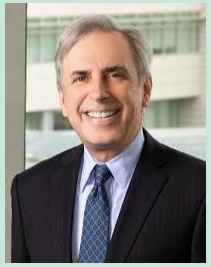
* P < 0.05; ** P < 0.01; *** P < 0.001; **** P < 0.0001, ns = not significant CLAIMS

Ex. 1009 at Table 7; Patent Owner's Response at 31-32; Patent Owner's Sur-Reply at 9; *see also* Ex. 2014 at ¶ 76.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Ovid Therapeutics

Claim 22: Improvement Will Not Necessarily Occur After 5 Hours



Michael A. Rogawski, Ph.D., M.D.

Q. When you say that to the extent that improvement to the patient were to occur after that time period, are you acknowledging that it's possible that the improvement may not be occurring after that time period?

A. I think 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 at 154:16:7-16; Patent Owner's Response at 30; Patent Owner's Sur-Reply at 9.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Claim 22: Petitioner Waived Reliance on Express Anticipation



"Because of the expedited nature of IPR proceedings, [i]t is of the utmost importance that petitioners in the IPR proceedings adhere to the requirement that the initial petition identify with particularity the evidence that supports the grounds for the challenge to each claim."

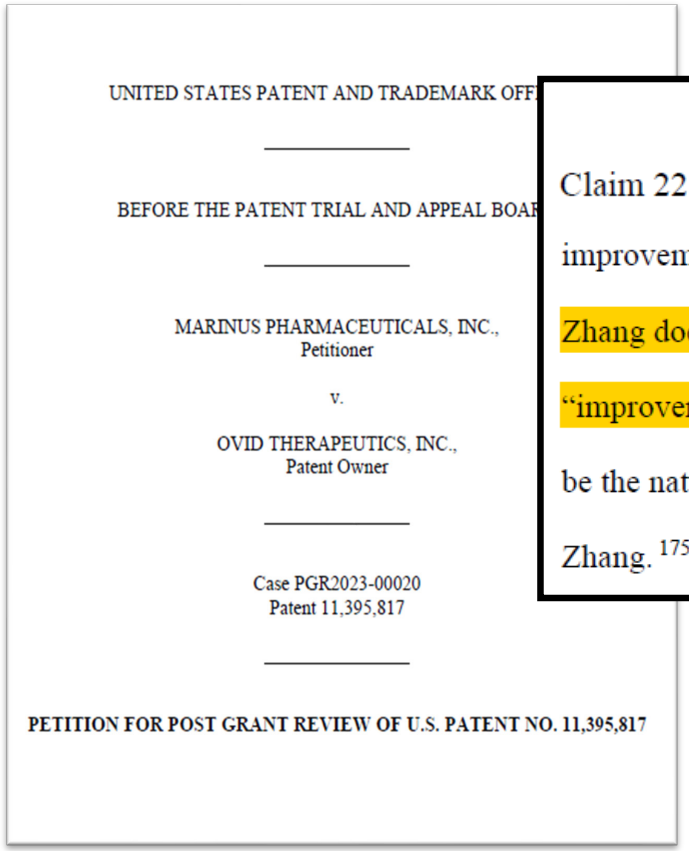
Henny Penny Corp. v. Frymaster LLC, 938 F.3d 1324, 1330-31 (Fed. Cir. 2019).

Patent Owner's Sur-Reply at 8.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Ovid Therapeutics

Claim 22: Petitioner Admitted No Express Anticipation in Petition



UNITED STATES PATENT AND TRADEMARK OFF

BEFORE THE PATENT TRIAL AND APPEAL BOAR

MARINUS PHARMACEUTICALS, INC.,
Petitioner

v.

OVID THERAPEUTICS, INC.,
Patent Owner

Case PGR2023-00020
Patent 11,395,817

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

6. Claim 22

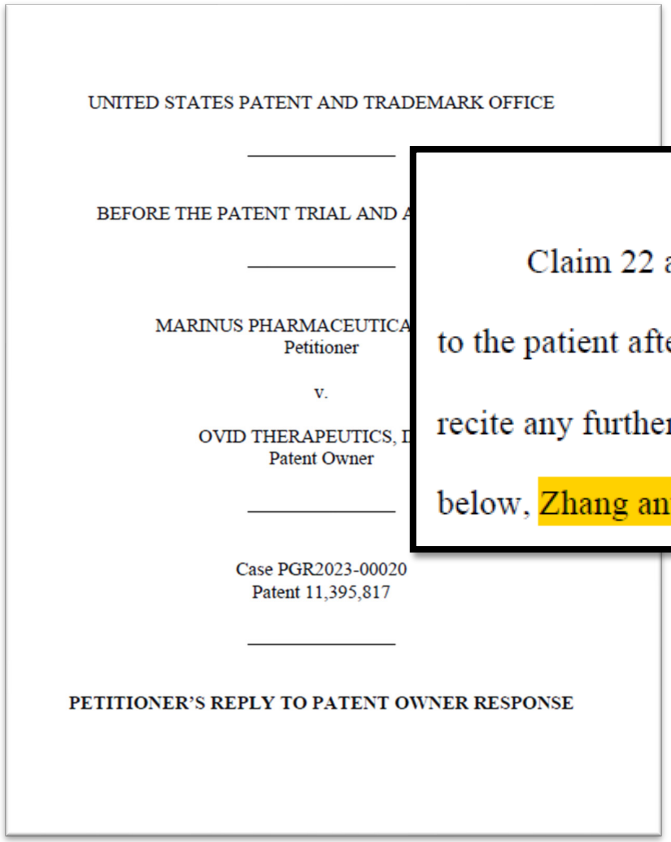
Claim 22 recites "wherein the pharmaceutical composition provides improvement to the patient after administration for more than 8 hours."[174] While Zhang does not expressly disclose that its ganaxolone formulations provide "improvement to the patient after administration for more than 8 hours," this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

Petition at 44-45; Patent Owner's Response at 28-29; Patent Owner's Sur-Reply at 8.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Ovid Therapeutics

Claim 22: Petitioner Cannot Rely on Express Anticipation in Reply



UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND A

MARINUS PHARMACEUTICA
Petitioner

v.

OVID THERAPEUTICS, I
Patent Owner

Case PGR2023-00020
Patent 11,395,817

PETITIONER'S REPLY TO PATENT OWNER RESPONSE

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.

Petitioner's Reply at 9; Patent Owner's Sur-Reply at 8.

Claim 22: Petitioner Improperly Relies on Understanding of POSA



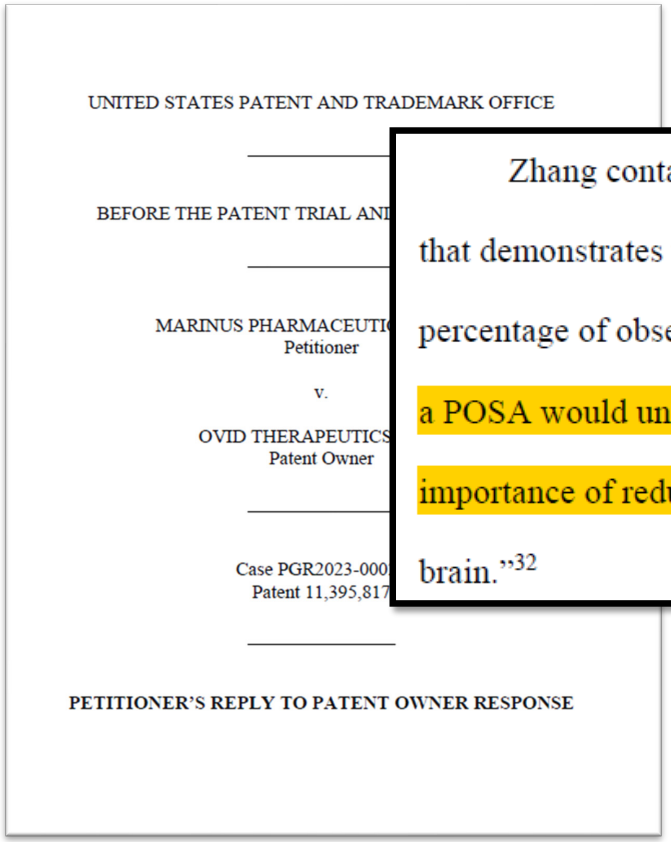
"The opinion says anticipation may be shown by less than 'complete anticipation' if ***one of ordinary skill may in reliance on the prior art 'complete the work required for the invention,'*** and that 'it is sufficient for an anticipation "if the general aspects are the same and the differences in minor matters is only such as would suggest itself to one of ordinary skill in the art."' ***Those statements relate to obviousness, not anticipation***. Anticipation requires the presence in a single prior art disclosure of all elements of a claimed invention arranged as in the claim."

Connell v. Sears, Roebuck & Co., 722 F.2d 1542, 1548 (Fed. Cir. 1983) (emphasis added).

Patent Owner's Sur-Reply at 9.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Claim 22: Petitioner Improperly Relies on Understanding of POSA



UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND

MARINUS PHARMACEUTI
Petitioner

v.

OVID THERAPEUTICS
Patent Owner

Case PGR2023-000
Patent 11,395,817

PETITIONER'S REPLY TO PATENT OWNER RESPONSE

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]

Petitioner's Reply at 9; Patent Owner's Sur-Reply at 9.

Claims 25-31: Petitioner Resorts to Picking and Choosing

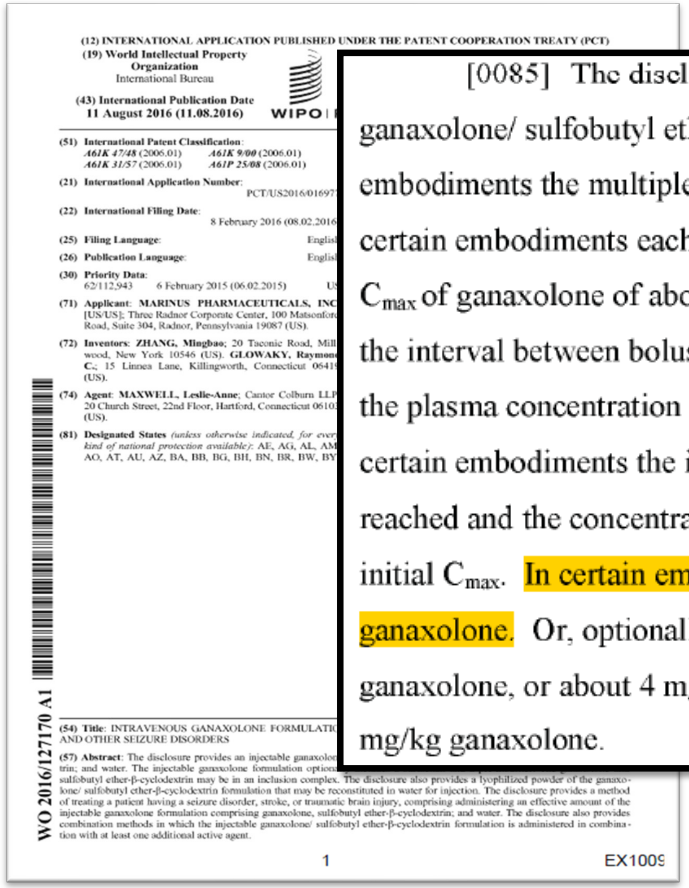
"[T]he [prior art] reference must clearly and unequivocally disclose the claimed [invention] or direct those skilled in the art to the [invention] without *any* need for picking, choosing, and combining various disclosures not directly related to each other by the teachings of the cited reference."

Net MoneyIN, Inc. v. VeriSign, Inc., 545 F.3d 1359, 1371 (Fed. Cir. 2008) (quoting *In re Arkley*, 455 F.2d 586, 587 (CCPA 1972)) (alterations in original).

Patent Owner's Response at 36-39; Patent Owner's Sur-Reply at 11.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Claims 25-31: Petitioner Resorts to Picking and Choosing



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(57) Abstract: The disclosure provides an injectable ganaxolone formulation comprising ganaxolone, sulfobutyl ether-β-cyclodextrin; and water. The injectable ganaxolone formulation optionally sulfobutyl ether-β-cyclodextrin may be in an inclusion complex. The disclosure also provides a lyophilized powder of the ganaxolone/ sulfobutyl ether-β-cyclodextrin formulation that may be reconstituted in water for injection. The disclosure provides a method of treating a patient having a seizure disorder, stroke, or traumatic brain injury, comprising administering an effective amount of the injectable ganaxolone formulation comprising ganaxolone, sulfobutyl ether-β-cyclodextrin; and water. The disclosure also provides combination methods in which the injectable ganaxolone/ sulfobutyl ether-β-cyclodextrin formulation is administered in combination with at least one additional active agent.

1 EX1009

[0085] The disclosure includes embodiments in which multiple bolus doses of the ganaxolone/ sulfobutyl ether-β-cyclodextrin formulation are administered to the patient. In certain embodiments the multiple bolus doses are given over 1 to 10 days at intervals of 1 to 24 hours. In certain embodiments each bolus dose provides a sufficient amount of ganaxolone to produce a plasma C_{max} of ganaxolone of about 100 ng/ mL to about 1000 ng/ mL in the patient. In certain embodiments the interval between bolus doses is from about 10 to about 24 hours and once an initial C_{max} is reached the plasma concentration of ganaxolone is not below 100 ng/ mL at any time between bolus doses. In certain embodiments the interval between bolus doses is 20 to 24 hours and once an initial C_{max} is reached and the concentration of ganaxolone in the patient's plasma does not fall below 25% of the initial C_{max}. In certain embodiment each bolus dose comprises about 1 mg/kg to about 20 mg/kg ganaxolone. Or, optionally the single bolus dose comprises from about 2 mg/kg to about 15 mg/kg ganaxolone, or about 4 mg/kg to about 10 mg/kg ganaxolone, or from about 1 mg/kg to about 30 mg/kg ganaxolone.

Ex. 1009 at ¶ [0085]; Patent Owner's Response at 36-39; Patent Owner's Sur-Reply at 11;
Ex. 2014 at ¶¶ 80, 82; *see also* Petition at 46-47.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Ovid Therapeutics

Claims 25-31: Zhang Discloses Treating 31 Diseases or Disorders

[0069] The disclosure includes methods of treating status epilepticus, refractory status epilepticus, super-refractory status epilepticus, PCDH19 female pediatric epilepsy, and other seizure disorders comprising administering an effective amount of the substituted β-cyclodextrin-ganaxolone injectable formulation to a patient suffering from any of these seizure disorders.

[0070] Seizure disorders that may be treated with the substituted β-cyclodextrin-ganaxolone injectable formulation include status epilepticus, e.g., convulsive status epilepticus, e.g., early status epilepticus, established status epilepticus, refractory status epilepticus, super-refractory status epilepticus, e.g., super-refractory generalized status epilepticus; non-convulsive status epilepticus, e.g., generalized status epilepticus, complex partial status epilepticus; a seizure, e.g., acute repetitive seizures, cluster seizures, infantile spasms, Lennox-Gastaut syndrome, West syndrome, PCDH19 female pediatric epilepsy, and catamenial epilepsy.

[0071] The substituted β-cyclodextrin-ganaxolone injectable formulation may also be used to treat provoked seizures such as seizures resulting from low blood sugar, electrolyte imbalance, high fever, brain infection (such as brain infections due to encephalitis, malaria, meningitis, toxoplasmosis, or amoebic infection), adverse reaction to prescription drugs, or alcohol or drug overdose.

[0072] The disclosure also includes methods of using substituted β-cyclodextrin-ganaxolone injectable formulation to treat traumatic brain injury and stroke comprising administering an effective amount of the formulation to a patient suffering from recent traumatic brain injury or a recent stroke.

[0073] The disclosure further includes methods of treating seizures arising from neurodegenerative disorders. Such neurodegenerative disorders include Parkinson's disease, Alzheimer's Disease, Amyotrophic Lateral Sclerosis, and Huntington's Disease. The disclosure includes methods of treating seizure arising from inflammatory disorders, such as multiple sclerosis. The disclosure includes methods of treating seizure disorders arising from lysosomal storage disorders including Neimann-Pick-C, Tay Sachs, Batten, Sandhoff, and Gaucher disease.

Ex. 1009 at ¶¶ [0069]-[0073]; Patent Owner's Response at 37-38; Patent Owner's Sur-Reply at 11;
Ex. 2014 at ¶¶ 80, 82.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Ovid Therapeutics

Claims 25-31: Zhang Discloses Many Methods of Administering GNX

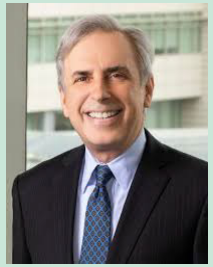
[0074] Methods of treatment include treating a patient suffering from seizures, traumatic brain injury, or stroke by administering a single injection (bolus dose) of a substituted β-cyclodextrin-ganaxolone injectable formulation. The single injection may be administered intramuscularly or intravenously. The dose of the single injection may be from about 1 mg/ kg to about 20 mg/ kg, from about 2 mg/ kg to about 15 mg/ kg, from about 2 mg/ kg to about 10 mg/ kg, or about 2 mg/ kg to about 8 mg/ kg. Methods of treatment also include administering multiple injections of the β-cyclodextrin-ganaxolone injectable formulation over a period of 1 to 10 days. The injections may be given at intervals of 1 to 24 hours. Dosing schedules in which the substituted β-cyclodextrin-ganaxolone injectable formulation is injected every 1 hr, 2 hrs, 4 hrs, 6 hrs, 8 hrs, 12 hrs, or 24 hours are included herein. Dosing schedules in which the substituted β-cyclodextrin-ganaxolone injectable formulation is injected for 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 days are included herein.

Ex. 1009 at ¶ [0074]; Patent Owner's Response at 37-38; Patent Owner's Sur-Reply at 11;
Ex. 2014 at ¶¶ 80, 82.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Ovid Therapeutics

Claims 25-31: Zhang Does Not Tie Dose Amount to Disease/Method



Michael A. Rogawski, Ph.D., M.D.

Q. If we go to paragraph 85. Does paragraph 85 refer to treating any disease or disorder?

A. **Well, if I scan down paragraph 85 specifically, I don't see any disorder mentioned.**

Q. You would agree that there's no method of treating mentioned in paragraph 85?

A. **I would agree that the words "method of treatment" are not contained within that paragraph.**

Q. If you go four lines up from the bottom of paragraph 85, do you see where it says, "In certain embodiment, each bolus dose is comprised of about 1 milligram per kilogram to about 20 milligrams per kilogram ganaxolone"?

A. **I do.**

Q. And this sentence doesn't mention that the bolus dose is being used to treat any disease; is that correct?

A. **Well, you're correct. I don't see the words relating to a specific disease in that sentence.**

Ex. 2015 at 75:6-76:2; Patent Owner's Response at 37-38.

Objective Evidence Supports the Nonobviousness of the Claims

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Ovid Therapeutics

Post-Filing Data Can Demonstrate Unexpected Results

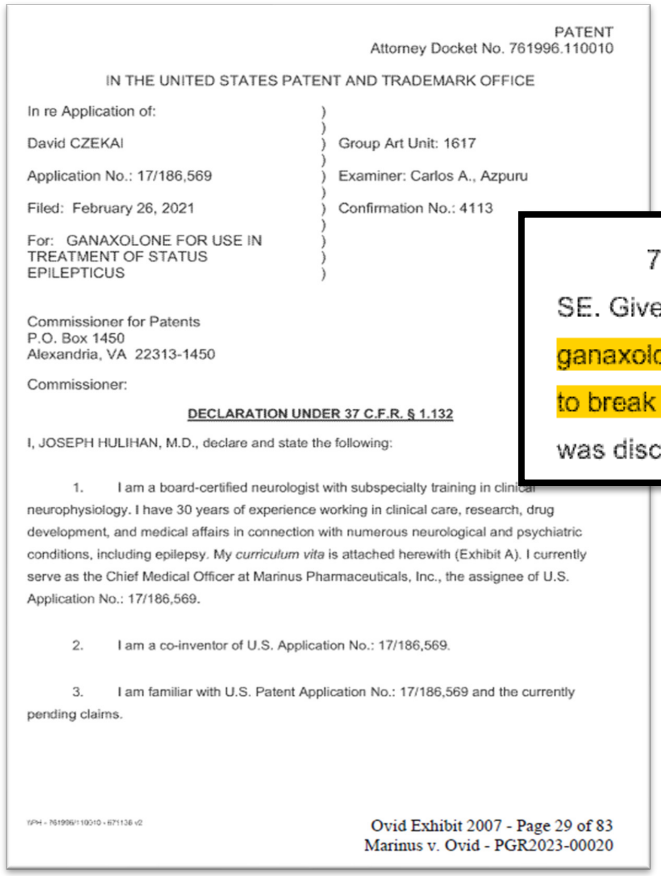


"***Evidence developed after the patent grant is not excluded from consideration***, for understanding of the full range of an invention is not always achieved at the time of filing the patent application. It is not improper to obtain additional support consistent with the patented invention, to respond to litigation attacks on validity. ***There is no requirement that an invention's properties and advantages were fully known before the patent application was filed***, or that the patent application contains all of the work done in studying the invention, in order for that work to be introduced into evidence in response to litigation attack. ***Nor is it improper to conduct additional experiments and provide later-obtained data in support of patent validity***."

Knoll Pharm. Co. v. Teva Pharms. USA, Inc., 367 F.3d 1381, 1385 (Fed. Cir. 2004) (emphasis added).

Patent Owner's Response at 41.

Petitioner's POSA Expected High Exposure and Long Treatment Needed



PATENT
Attorney Docket No. 761996.110010

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
David CZEKAI
Application No.: 17/186,569
Filed: February 26, 2021
For: GANAXOLONE FOR USE IN TREATMENT OF STATUS EPILEPTICUS

Group Art Unit: 1617
Examiner: Carlos A., Azpuru
Confirmation No.: 4113

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

DECLARATION UNDER 37 C.F.R. § 1.132

I, JOSEPH HULIHAN, M.D., declare and state the following:

1. I am a board-certified neurologist with subspecialty training in clinical neurophysiology. I have 30 years of experience working in clinical care, research, drug development, and medical affairs in connection with numerous neurological and psychiatric conditions, including epilepsy. My *curriculum vita* is attached herewith (Exhibit A). I currently serve as the Chief Medical Officer at Marinus Pharmaceuticals, Inc., the assignee of U.S. Application No.: 17/186,569.

2. I am a co-inventor of U.S. Application No.: 17/186,569.

3. I am familiar with U.S. Patent Application No.: 17/186,569 and the currently pending claims.

Ovid Exhibit 2007 - Page 29 of 83
Marinus v. Ovid - PGR2023-00020

7. Marinus Pharmaceuticals Inc. is investigating the use of ganaxolone for treating SE. Given the complexities of SE and difficulties in treating SE, we initially believed that a high ganaxolone exposure for a long treatment period of at least 4 days duration, would be required to break SE, *i.e.*, stop seizures and prevent seizures from rapidly returning when ganaxolone was discontinued.

Ex. 2007 at 30, ¶ 7; Ex. 2008 at 26, ¶ 7;
Patent Owner's Response at 41-42; Ex. 2014 at ¶¶ 21, 108.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Ovid Therapeutics

Epilepsia Demonstrates Claimed Doses Provide Unexpected Results

Received: 15 April 2022 | Revised: 22 June 2022 | Accepted: 22 June 2022
DOI: 10.1111/epi.17343

RESEARCH ARTICLE

Intravenous ganaxolone for the treatr status epilepticus: Results from an op phase 2 trial

Henrikas Vaitkevicius[1,2] | R. Eugene Ramsay[3] | Ch
Aatif M. Husain[5,6] | Alex Aimetti[2] | Maciej Gasior[2]

[1]Department of Neurology, Brigham and Women's Hospital, Boston, Massachusetts, USA
[2]Marinus Pharmaceuticals, Radnor, Pennsylvania, USA
[3]International Center for Epilepsy, St. Bernard Hospital, New Orleans, Louisiana, USA
[4]Carolinas Medical Center, Atrium Health, Charlotte, North Carolina, USA
[5]Department of Neurology, Duke University, Durham, North Carolina, USA
[6]Neurodiagnostic Center, Veterans Affairs Medical Center, Durham, North Carolina, USA

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Henrikas Vaitkevicius, Marinus Pharmaceuticals, Inc., 5 Radnor Corporate Center, 100 Matsonford Rd., Suite 500, Radnor, PA 19087, USA.
Email: hvaitkevicius@marinuspharma.com

Funding information
This trial was sponsored and supported by Marinus Pharmaceuticals, Inc. Marinus Pharmaceuticals, Inc., in collaboration with the steering committee, contributed to the design of the trial, data collection, data analysis and interpretation, and writing of this report. Authors had full access to all study data, and the corresponding author had the responsibility to submit this report for publication.

Abstract
Objective: Patients with refractory s
with benzodiazepines and ≥1 secon
tion (ASM). Guidelines recommend
failed, but potential harms can outwe
to stop and durably control RSE with
is an investigational neuroactive ste
study's objective was to determine t
RSE and obtain a preliminary assess
Methods: This was an open-label,
2018 to September 18, 2019, at thr
aged ≥12 years, had convulsive or n
≥1 second-line IV ASM. Twenty-on
Patients received IV ganaxolone ad
infusion was initiated as an IV bolu
decreasing infusion rates for 48–96 h
ganaxolone dosing cohorts: low, 50
713 mg/day. The primary end point v
calation to IV anesthetic treatment w
Results: Most of the 17 enrolled pat
failed a median of three prior ASM
second-line IV ASM therapy. Media
initiation was 5 min. No patient req
during the 24-h period following ganaxolone initiation. Two treatment-related
serious adverse events (sedation) were reported. Of the three deaths, none

Henrikas Vaitkevicius's was affiliated with 1 at the time the trial was conducted.

Clinical Trial Registration: NCT03350035.

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Ovid Exhibit 2003 - Page 1 of 11
Marinus v. Ovid - PGR2023-00020

TABLE 2 Onset and durability of response to ganaxolone

	Ganaxolone dose cohort		
	High (713 mg/day) ($n = 8$)	Medium (650 mg/day) ($n = 4$)	Low (500 mg/day) ($n = 5$)
No escalation to third-line IV anesthetics during 24 h following infusion initiation (primary endpoint), *n* (%)	8 (100)	4 (100)	5 (100)
Status-free during 24 h following infusion initiation (investigator determined), *n* (%)	7 (88)[a]	4 (100)	5 (100)
No escalation to additional IV ASMs or to third-line IV anesthetics for status relapse during 24 h following infusion completion, *n* (%)	8 (100)	3 (75)[b]	3 (60)[c]

Abbreviations: ASM, anti-seizure medication; IV, intravenous.
[a]One patient had status relapse on day 1, which resolved during ganaxolone infusion without treatment escalation.
[b]One patient escalated to additional IV ASM on day 1 for seizure relapse.
[c]Two patients escalated to third-line IV anesthetics for seizure relapse on day 3.

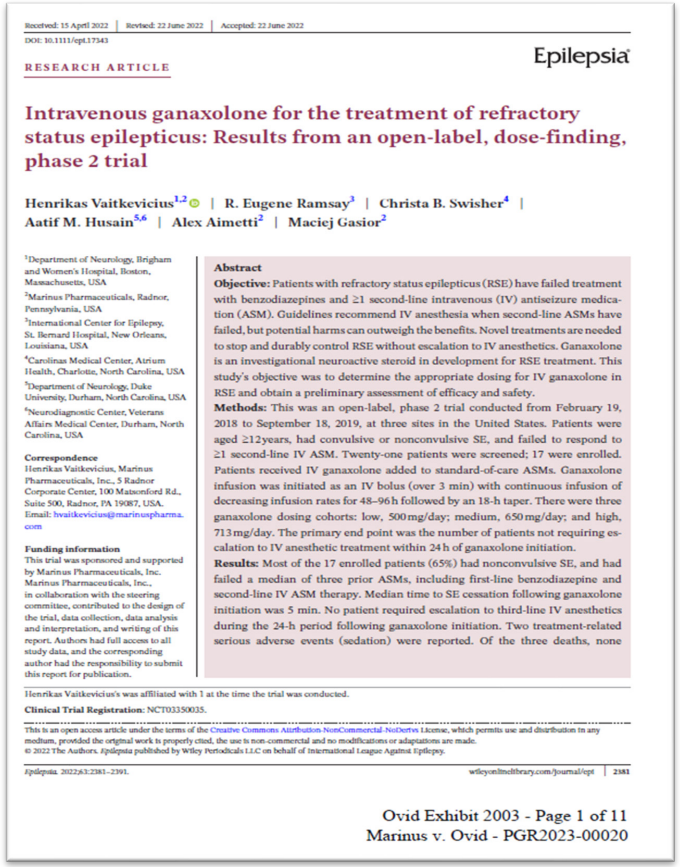
Ex. 2003 at 2386; Patent Owner's Response at 41-42;
Ex. 2014 at ¶¶ 109-111.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Ovid Therapeutics

Ovid Exhibit 2026 - Page 53 of 121
Marinus v. Ovid - PGR2023-00020

Epilepsia Demonstrates Claimed Doses Provide Unexpected Results



Received: 15 April 2022 | Revised: 22 June 2022 | Accepted: 22 June 2022
DOI: 10.1111/epi.17343

Epilepsia

RESEARCH ARTICLE

Intravenous ganaxolone for the treatment of refractory status epilepticus: Results from an open-label, dose-finding, phase 2 trial

Henrikas Vaitkevicius[1,2] | R. Eugene Ramsay[3] | Christa B. Swisher[4] | Aatif M. Husain[5,6] | Alex Aimetti[2] | Maciej Gasior[2]

[1]Department of Neurology, Brigham and Women's Hospital, Boston, Massachusetts, USA
[2]Marinus Pharmaceuticals, Radnor, Pennsylvania, USA
[3]International Center for Epilepsy, St. Bernard Hospital, New Orleans, Louisiana, USA
[4]Carolinas Medical Center, Atrium Health, Charlotte, North Carolina, USA
[5]Department of Neurology, Duke University, Durham, North Carolina, USA
[6]Neurodiagnostic Center, Veterans Affairs Medical Center, Durham, North Carolina, USA

Correspondence
Henrikas Vaitkevicius, Marinus Pharmaceuticals, Inc., 5 Radnor Corporate Center, 100 Matsonford Rd., Suite 500, Radnor, PA 19087, USA.
Email: hvaitkevicius@marinuspharma.com

Funding information
This trial was sponsored and supported by Marinus Pharmaceuticals, Inc. Marinus Pharmaceuticals, Inc., in collaboration with the steering committee, contributed to the design of the trial, data collection, data analysis and interpretation, and writing of this report. Authors had full access to all study data, and the corresponding author had the responsibility to submit this report for publication.

Abstract

Objective: Patients with refractory status epilepticus (RSE) have failed treatment with benzodiazepines and ≥1 second-line intravenous (IV) antiseizure medication (ASM). Guidelines recommend IV anesthesia when second-line ASMs have failed, but potential harms can outweigh the benefits. Novel treatments are needed to stop and durably control RSE without escalation to IV anesthetics. Ganaxolone is an investigational neuroactive steroid in development for RSE treatment. This study's objective was to determine the appropriate dosing for IV ganaxolone in RSE and obtain a preliminary assessment of efficacy and safety.

Methods: This was an open-label, phase 2 trial conducted from February 19, 2018 to September 18, 2019, at three sites in the United States. Patients were aged ≥12 years, had convulsive or nonconvulsive SE, and failed to respond to ≥1 second-line IV ASM. Twenty-one patients were screened; 17 were enrolled. Patients received IV ganaxolone added to standard-of-care ASMs. Ganaxolone infusion was initiated as an IV bolus (over 3 min) with continuous infusion of decreasing infusion rates for 48–96 h followed by an 18-h taper. There were three ganaxolone dosing cohorts: low, 500 mg/day; medium, 650 mg/day; and high, 713 mg/day. The primary end point was the number of patients not requiring escalation to IV anesthetic treatment within 24 h of ganaxolone initiation.

Results: Most of the 17 enrolled patients (65%) had nonconvulsive SE, and had failed a median of three prior ASMs, including first-line benzodiazepine and second-line IV ASM therapy. Median time to SE cessation following ganaxolone initiation was 5 min. No patient required escalation to third-line IV anesthetics during the 24-h period following ganaxolone initiation. Two treatment-related serious adverse events (sedation) were reported. Of the three deaths, none

Henrikas Vaitkevicius's was affiliated with 1 at the time the trial was conducted.

Clinical Trial Registration: NCT03350035.

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Marinus v. Ovid - PGR2023-00020

Reductions in seizure burden occurred rapidly in all three ganaxolone dose cohorts. Patients in the high-dose cohort maintained ganaxolone plasma concentrations ≥500 ng/ml for 8 h following treatment initiation and demonstrated the most durable reductions in seizure burden. Although not studied in the present trial, maintaining ganaxolone levels ≥500 ng/ml for durations longer than 8 h may offer additional benefit and will be evaluated in future clinical studies.

Sixteen patients (94%) achieved and maintained SE cessation for 24 h following ganaxolone initiation as determined by trial-site investigator assessment (Table 2). The follow-up period after ganaxolone discontinuations was up to 4 weeks; during this period, 85% of evaluable patients did not have SE relapse ($N = 13$; 1 subject in the Low Cohort and 1 subject in the Medium Cohort had SE relapse). EEG data, reviewed by the trial site investigator,

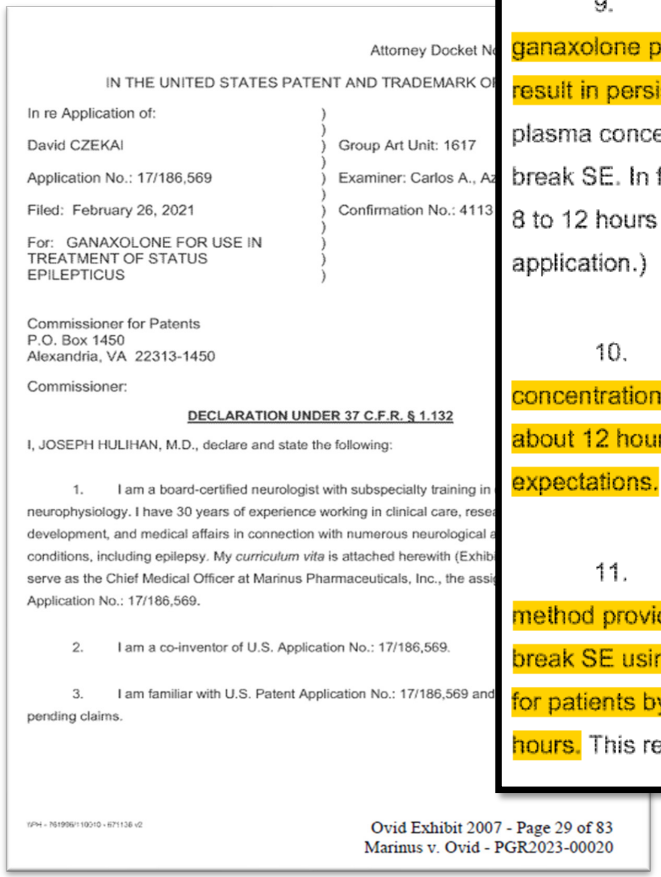
Fourteen patients (82%) did not require treatment for SE with additional second-line IV ASMs or IV anesthetics through 24 h following completion of the ganaxolone infusion (Table 2). Of the three patients who did not

Ex. 2003 at 2386, 2388; Patent Owner's Response at 42-46; Ex. 2014 at ¶¶ 109-111.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Ovid Therapeutics

Epilepsia Results Contrary to Petitioner's POSA's Expectations



Attorney Docket N

IN THE UNITED STATES PATENT AND TRADEMARK O

In re Application of:
David CZEKAI
Application No.: 17/186,569
Filed: February 26, 2021
For: GANAXOLONE FOR USE IN TREATMENT OF STATUS EPILEPTICUS

Group Art Unit: 1617
Examiner: Carlos A., Az
Confirmation No.: 4113

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

DECLARATION UNDER 37 C.F.R. § 1.132

I, JOSEPH HULIHAN, M.D., declare and state the following:

1. I am a board-certified neurologist with subspecialty training in neurophysiology. I have 30 years of experience working in clinical care, resea development, and medical affairs in connection with numerous neurological a conditions, including epilepsy. My *curriculum vita* is attached herewith (Exhib serve as the Chief Medical Officer at Marinus Pharmaceuticals, Inc., the assi Application No.: 17/186,569.

2. I am a co-inventor of U.S. Application No.: 17/186,569.

3. I am familiar with U.S. Patent Application No.: 17/186,569 and pending claims.

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Marinus v. Ovid - PGR2023-00020

9. Our investigations also surprisingly revealed that targeting a transient ganaxolone plasma concentration of about 500 ng/ml to about 1000 ng/ml was not enough to result in persistent suppression of SE. We found that it is important to maintain that ganaxolone plasma concentration for about 8 to about 12 hours to achieve persistent suppression, *i.e.*, to break SE. In fact, when the plasma concentration dropped below 500 ng/ml prior to completing 8 to 12 hours of treatment, seizures rapidly recurred. (See, FIGS. 3, 5, 7, 9 and 15 of the patent application.)

10. It was completely unexpected that providing ganaxolone at a serum concentration of about 500 ng/ml to about 1000 ng/ml for a short duration of only about 8 to about 12 hours, resulted in persistent SE suppression. In fact, it was completely contrary to our expectations.

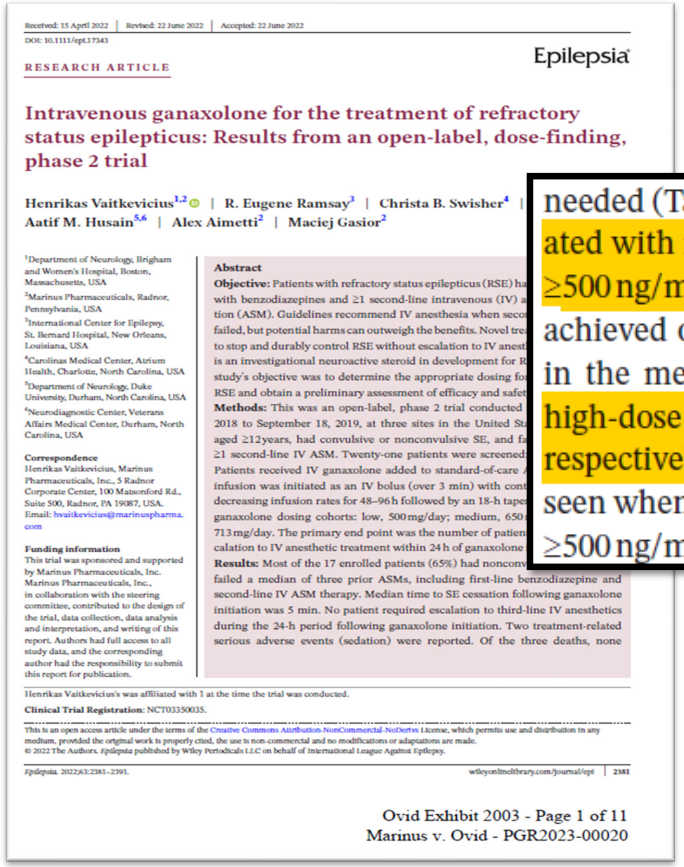
11. Importantly, this surprising and unexpected discovery and the claimed treatment method provide significant clinical advantages for patients. First, a method that can effectively break SE using ganaxolone is now available. In addition, the method provides enhanced safety for patients by limiting the duration of exposure to high drug levels to only about 8 to about 12 hours. This reduction in drug exposure lessens the risk of unwanted adverse events.

Ex. 2007 at 31, ¶¶ 9-11; Ex. 2008 at 27, ¶¶ 9-11;
Patent Owner's Response at 45-46; Ex. 2014 at ¶¶ 111-115.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Ovid Therapeutics

Unexpected Results Particularly Strong for Claim 30 (700-725 mg/day)



Received: 15 April 2022 | Revised: 22 June 2022 | Accepted: 22 June 2022
DOI: 10.1111/epi.17343

Epilepsia

RESEARCH ARTICLE

Intravenous ganaxolone for the treatment of refractory status epilepticus: Results from an open-label, dose-finding, phase 2 trial

Henrikas Vaitkevicius[1,2] | R. Eugene Ramsay[3] | Christa B. Swisher[4] | Aatif M. Husain[5,6] | Alex Aimetti[2] | Maciej Gasior[2]

[1]Department of Neurology, Brigham and Women's Hospital, Boston, Massachusetts, USA
[2]Marinus Pharmaceuticals, Radnor, Pennsylvania, USA
[3]International Center for Epilepsy, St. Bernard Hospital, New Orleans, Louisiana, USA
[4]Carolinas Medical Center, Atrium Health, Charlotte, North Carolina, USA
[5]Department of Neurology, Duke University, Durham, North Carolina, USA
[6]Neurodiagnostic Center, Veterans Affairs Medical Center, Durham, North Carolina, USA

Correspondence
Henrikas Vaitkevicius, Marinus Pharmaceuticals, Inc., 5 Radnor Corporate Center, 100 Matsonford Rd., Suite 500, Radnor, PA 19087, USA.
Email: hvaitkevicius@marinuspharma.com

Funding information
This trial was sponsored and supported by Marinus Pharmaceuticals, Inc. Marinus Pharmaceuticals, Inc., in collaboration with the steering committee, contributed to the design of the trial, data collection, data analysis and interpretation, and writing of this report. Authors had full access to all study data, and the corresponding author had the responsibility to submit this report for publication.

Abstract

Objective: Patients with refractory status epilepticus (RSE) ha
with benzodiazepines and ≥1 second-line intravenous (IV) a
tion (ASM). Guidelines recommend IV anesthesia when seco
failed, but potential harms can outweigh the benefits. Novel tre
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Henrikas Vaitkevicius's was affiliated with 1 at the time the trial was conducted.

Clinical Trial Registration: NCT03350035.

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Marinus v. Ovid - PGR2023-00020

needed (Table S1). Sustained clinical response was associated with maintaining ganaxolone plasma concentrations ≥500 ng/ml. Ganaxolone plasma levels ≥500 ng/ml 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. The greatest decrease in seizure burden was seen when ganaxolone concentrations were maintained at ≥500 ng/m for at least 8 h.

Ex. 2003 at 2386; Patent Owner's Response at 46
Ex. 2014 at ¶ 116.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

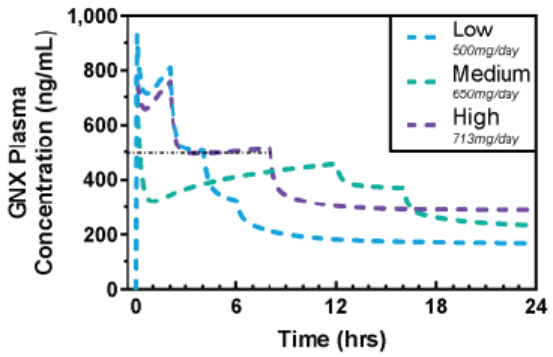
Ovid Therapeutics

Unexpected Results Particularly Strong for Claim 30 (700-725 mg/day)

MARINUS

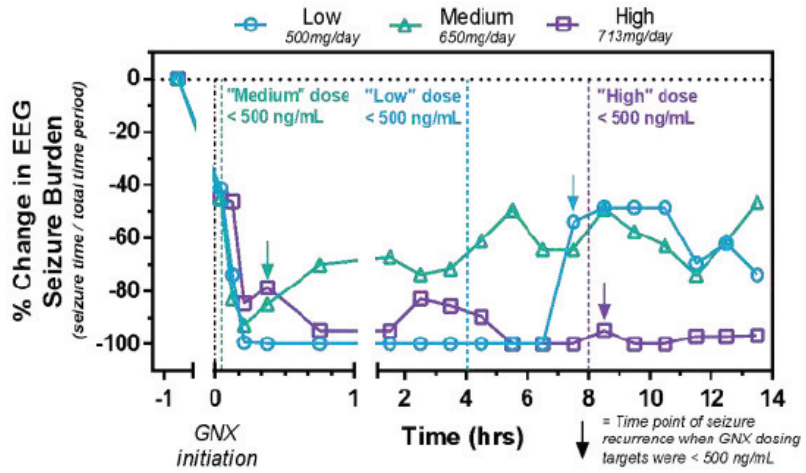
Data presented at AES 2019
PK: Pharmacokinetics / PD: Pharmadynamic

Modeled PK Curves for All Dose Groups



High Dose Achieved Target Range
≥ 500 ng/mL for ~8 hours

Seizure Burden Reduction Occurred Rapidly in All Dose Groups



Only **High Dose** Provided Sustained Reduction
(>80%) Throughout Entire Analysis Window

Ex. 2002 at 27; Patent Owner's Response at 46-48.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Ovid Therapeutics

Commensurate in Scope

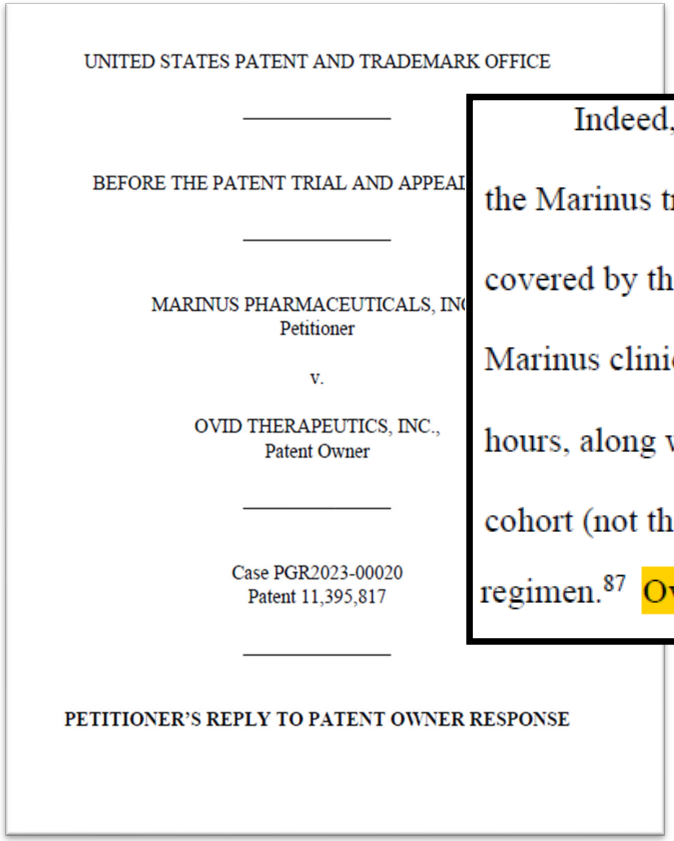


"While we have held that unexpected results must be commensurate in scope with the claims, we have not required absolute identity of scope; rather, we have rejected unexpected results where the evidence was plainly disproportionate to the scope of the claim."

Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc., 655 F.3d 1291, 1308-09 (Fed. Cir. 2011).

Patent Owner's Sur-Reply at 13.

Petitioner Admits *Epilepsia* Dosing Encompassed by Claims



UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL

MARINUS PHARMACEUTICALS, INC.
Petitioner

v.

OVID THERAPEUTICS, INC.,
Patent Owner

Case PGR2023-00020
Patent 11,395,817

PETITIONER'S REPLY TO PATENT OWNER RESPONSE

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

Petitioner's Reply at 24-25; Patent Owner's Sur-Reply at 12.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Petitioner Admits *Epilepsia* Results Tied to Claimed Doses

MARINUS

Data presented at AES 2019
PK: Pharmacokinetics / PD: Pharmadynamic

Phase 2 Trial Results Demonstrated Rapid Onset And Durability of Effect

Trial data published in *Epilepsia*

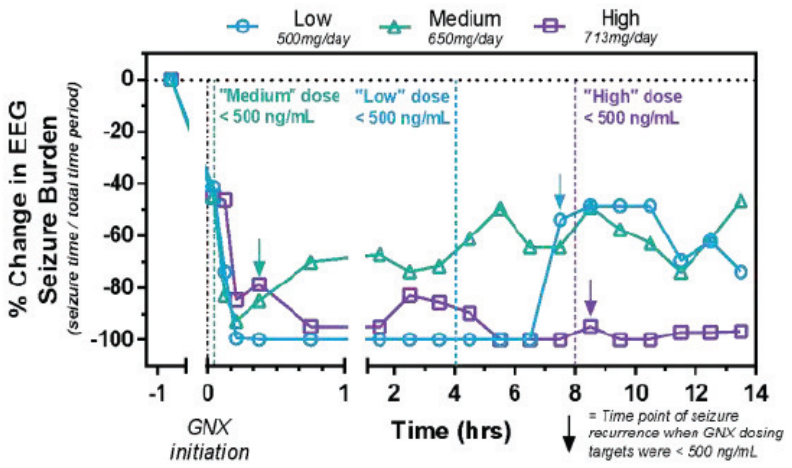
Cohort	No escalation to IV anesthetics within 24 hours from infusion initiation (Primary Endpoint)	Status-free through 24 hours from infusion initiation (investigator determination)	No escalation to additional IV AEDs or IV anesthetics for status relapse at any time through 24 hours after ganaxolone discontinuation	No SE Relapse at anytime during the 4-wk follow up period
High (713 mg/day) (n=8)	100% (8 of 8)	88% (7 of 8)	100% (8 of 8)	100% (6 of 6) (1ET, 1 died)
Medium (650 mg/day) (n=4)	100% (4 of 4)	100% (4 of 4)	75% (3 of 4)	67% (2 of 3) (1 ET)
Low (500 mg/day) (n=5)	100% (5 of 5)	100% (5 of 5)	60% (3 of 5)	50% (1 of 2) (1 died)

Immediate Prior AED Administered 4 Hours (mean) to ganaxolone treatment

SE Cessation Occurred Rapidly in All Dose Groups (median = 5 minutes)

Safety Summary:
- 2 treatment emergent serious adverse events noted as severe sedation
- 13 treatment emergent adverse events: 5 moderate (4 somnolence; 1 hypercarbia); 6 mild (2 hypotension, 2 somnolence, 1 urinary retention, 1 hypercarbia)

Seizure Burden Reduction Occurred Rapidly in All Dose Groups



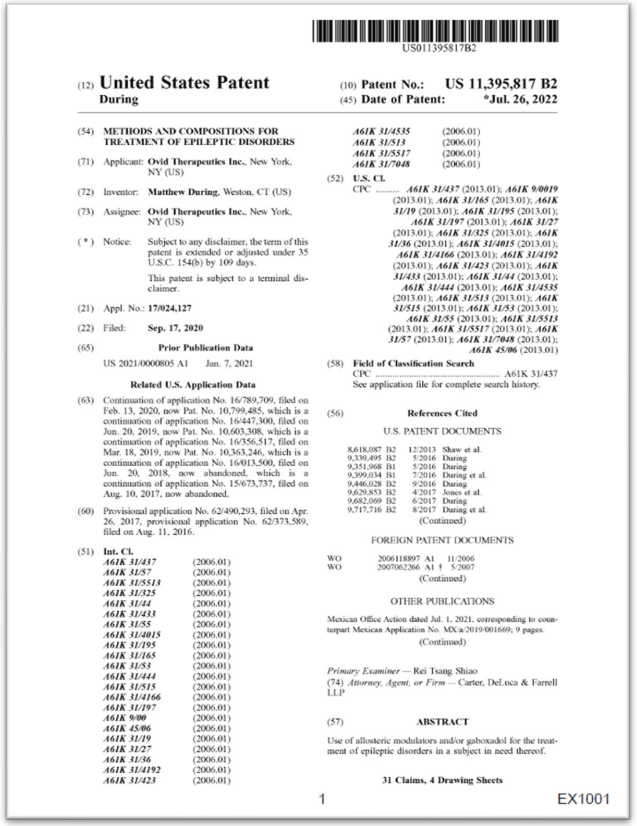
Only **High Dose** Provided Sustained Reduction (>80%) Throughout Entire Analysis Window

Ex. 2002 at 26-27; Patent Owner's Sur-Reply at 12-13.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Ovid Therapeutics

Claims Do Not Recite Specific Mode of Administration



US011395817B2

(12) **United States Patent**
During

(10) **Patent No.: US 11,395,817 B2**
(45) **Date of Patent: *Jul. 26, 2022**

(54) **METHODS AND COMPOSITIONS FOR TREATMENT OF EPILEPTIC DISORDERS**

(71) Applicant: **Ovid Therapeutics Inc.**, New York, NY (US)

(72) Inventor: **Matthew During**, Weston, CT (US)

(73) Assignee: **Ovid Therapeutics Inc.**, New York, NY (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 109 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **17/024,127**

(22) Filed: **Sep. 17, 2020**

(65) **Prior Publication Data**

US 2021/0000805 A1 Jan. 7, 2021

Related U.S. Application Data

(63) Continuation of application No. 16/789,709, filed on Feb. 13, 2020, now Pat. No. 10,799,485, which is a continuation of application No. 16/447,300, filed on Jun. 20, 2019, now Pat. No. 10,603,308, which is a continuation of application No. 16/356,517, filed on Mar. 18, 2019, now Pat. No. 10,363,246, which is a continuation of application No. 16/013,500, filed on Jun. 20, 2018, now abandoned, which is a continuation of application No. 15/673,737, filed on Aug. 10, 2017, now abandoned.

(60) Provisional application No. 62/490,293, filed on Apr. 26, 2017, provisional application No. 62/373,589, filed on Aug. 11, 2016.

(51) **Int. Cl.**

A61K 31/437	(2006.01)
A61K 31/57	(2006.01)
A61K 31/5513	(2006.01)
A61K 31/325	(2006.01)
A61K 31/44	(2006.01)
A61K 31/433	(2006.01)
A61K 31/55	(2006.01)
A61K 31/4015	(2006.01)
A61K 31/795	(2006.01)
A61K 31/165	(2006.01)
A61K 31/53	(2006.01)
A61K 31/444	(2006.01)
A61K 31/515	(2006.01)
A61K 31/4166	(2006.01)
A61K 31/197	(2006.01)
A61K 9/00	(2006.01)
A61K 45/06	(2006.01)
A61K 31/19	(2006.01)
A61K 31/27	(2006.01)
A61K 31/36	(2006.01)
A61K 31/4192	(2006.01)
A61K 31/423	(2006.01)
A61K 31/4535	(2006.01)
A61K 31/513	(2006.01)
A61K 31/5517	(2006.01)
A61K 31/7048	(2006.01)

(52) **U.S. Cl.**
CPC ***A61K 31/437*** (2013.01); ***A61K 9/0019*** (2013.01); ***A61K 31/165*** (2013.01); ***A61K 31/19*** (2013.01); ***A61K 31/195*** (2013.01); ***A61K 31/197*** (2013.01); ***A61K 31/27*** (2013.01); ***A61K 31/325*** (2013.01); ***A61K 31/36*** (2013.01); ***A61K 31/4015*** (2013.01); ***A61K 31/4166*** (2013.01); ***A61K 31/4192*** (2013.01); ***A61K 31/423*** (2013.01); ***A61K 31/433*** (2013.01); ***A61K 31/44*** (2013.01); ***A61K 31/444*** (2013.01); ***A61K 31/4535*** (2013.01); ***A61K 31/513*** (2013.01); ***A61K 31/515*** (2013.01); ***A61K 31/53*** (2013.01); ***A61K 31/55*** (2013.01); ***A61K 31/5513*** (2013.01); ***A61K 31/5517*** (2013.01); ***A61K 31/57*** (2013.01); ***A61K 31/7048*** (2013.01); ***A61K 45/06*** (2013.01)

(58) **Field of Classification Search**
CPC A61K 31/437
See application file for complete search history.

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(Continued)

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(Continued)

Primary Examiner — Rei Tsang Shiao
(74) *Attorney, Agent, or Firm* — Carter, DeLuca & Farrell LLP

(57) **ABSTRACT**

Use of allosteric modulators and/or gaboxadol for the treatment of epileptic disorders in a subject in need thereof.

31 Claims, 4 Drawing Sheets

1 EX1001

21. 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.

22. The method of claim **21** wherein the pharmaceutical composition provides improvement to the patient after administration for more than 8 hours.

25. The method of claim **21** wherein the patient is administered about 500 mg to 1000 mg/day ganaxolone.

26. The method of claim **21** wherein the patient is administered about 625 mg to 650 mg/day ganaxolone.

27. The method of claim **21** wherein the patient is administered about 650 mg to 675 mg/day ganaxolone.

28. The method of claim **21** wherein the patient is administered about 675 mg to 700 mg/day ganaxolone.

29. The method of claim **21** wherein the patient is administered about 625 mg to 700 mg/day ganaxolone.

30. The method of claim **21** wherein the patient is administered about 700 mg to 725 mg/day ganaxolone.

31. The method of claim **21** wherein the patient is administered about 1025 mg to 1050 mg ganaxolone.

Ex. 1001 at 40:8-33; Patent Owner's Sur-Reply at 14.

Marinus Does Not Meet Burden of Persuasion

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.

"Our precedent is clear that ***the burden of persuasion remains with the challenger during litigation*** because every issued patent is entitled to a presumption of validity. While this burden of persuasion remains with the challenger, a patentee bears the burden of production with respect to evidence of secondary considerations of nonobviousness."

ZUP, LLC v. Nash Mfg., Inc., 896 F.3d 1365, 1373 (Fed. Cir. 2018) (emphasis added) (internal citations and quotations omitted).

Patent Owner's Sur-Reply at 14-15.

It Is Common to Use Bolus + Continuous Infusion to Treat SE



Raman Sankar, M.D., Ph.D.

Q. What do you understand when it talks about the "rapid loading of ganaxolone"?

A. It's to achieving a therapeutic level promptly.

Q. And why is that important?

A. Because status is an emergency. You want to gain control of it.

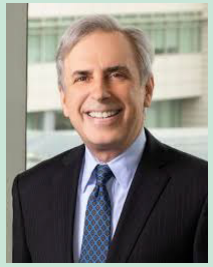
Q. And is that why it's important to use the three-minute bolus?

A. Yes. You want to achieve the blood level quickly and then you try to maintain the drip rate.

Ex. 1042 at 53:24-54:9; Patent Owner's Sur-Reply at 15.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

It Is Common to Use Bolus + Continuous Infusion to Treat SE



Michael A. Rogawski, Ph.D., M.D.

Q. Is the rapid control of seizures one goal of treating SE?

A. It is.

Q. And is it common to use a bolus dose to rapidly administer a medication?

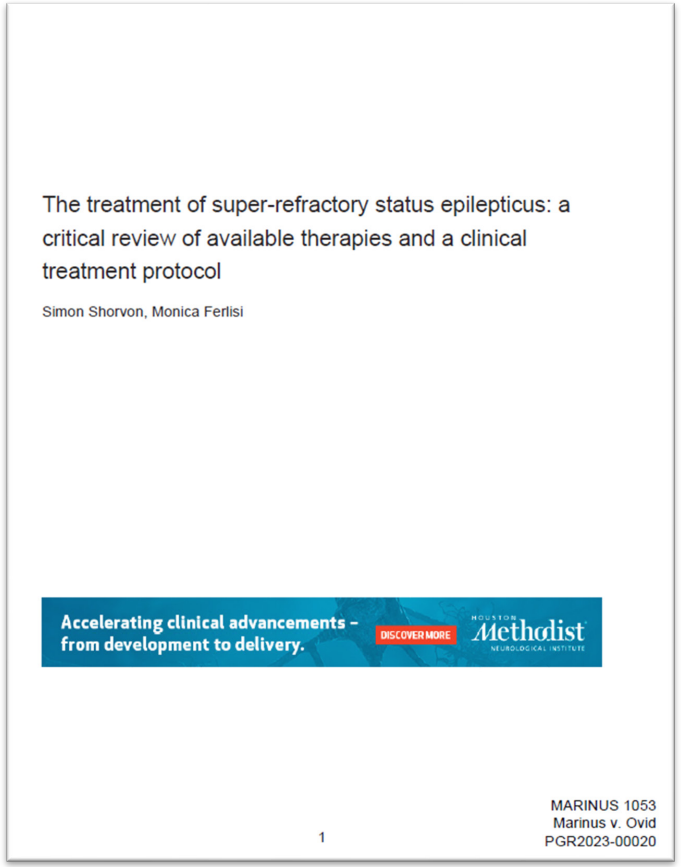
A. It really depends on the -- on the kind of medication and its pharmacokinetic properties.

Q. But is it common to use a bolus dose to achieve rapid --

A. It is common, yes.

Ex. 2024 at 18:7-19:8; Patent Owner's Sur-Reply at 15.

It Is Common to Use Bolus + Continuous Infusion to Treat SE



The treatment of super-refractory status epilepticus: a critical review of available therapies and a clinical treatment protocol

Simon Shorvon, Monica Ferlisi

Accelerating clinical advancements – from development to delivery. DISCOVER MORE Houston Methodist Neurological Institute

MARINUS 1053
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Table 2 Anaesthetic therapies

Treatment	Dose recommended		Range of doses used (from the literature review)		Main advantages	Main disadvantages
	Children	Adult	Children	Adult		
Thiopental/ pentobarbital	Bolus: 5 mg/kg Infusion: 5 mg/kg/h	Bolus: 2–3 mg/kg Infusion: 3–5 mg/kg/h	Bolus: 4–5 mg/kg Infusion: 0.5–12 mg/kg/h	Bolus: 1–19 mg/kg Infusion: 0.5–20 mg/kg/h	Strong anti-epileptic action, potential neuroprotective action, reduces intracranial pressure, long experience of its use	Zero order pharmacokinetics, strong tendency to accumulate and thus prolonged recovery phase, acute tolerance, cardiorespiratory depression, hypotension, drug inter-actions, toxicity
Midazolam	Bolus: 0.1–0.2 mg/kg Infusion: 0.05–0.23 mg/kg/h[a]	Bolus: 0.2 mg/kg Infusion: 0.1–0.4 mg/kg/h	Bolus: 0.06–0.6 mg/kg Infusion: 0.036–1.2 mg/kg/h	Bolus: 0.03–0.5 mg/kg Infusion: 0.02–1.2 mg/kg/h	Strong anti-epileptic action, less tendency to accumulate than barbiturate or other benzodiazepines	Tendency for acute tolerance to develop resulting in breakthrough seizures, hypotension and cardiorespiratory depression, hepatic metabolism
Propofol	Bolus: 1–2 mg/kg Infusion: 1–7 mg/kg/h	Bolus: 3–5 mg/kg Infusion: 5–10 mg/kg/h	Bolus: 1–3 mg/kg Infusion: 0.6–26.94 mg/kg/h	Bolus: 1–3 mg/kg Infusion: 0.1–24 mg/kg/h	Excellent pharmacokinetics, ease of use. responsive anaesthetic agent, pharmacology extensively studied	PRIS, pain at the injection side, involuntary movements, no intrinsic anti-epileptic action
Ketamine	NK	Bolus: 0.5–4.5 mg/kg Infusion: up to 5 mg/kg/h	NK	Bolus: 0.5–3 mg/kg Infusion: 0.3–7.5 mg/kg/h	Lack of cardiorespiratory depression and drug-induced hypotension. *N*-methyl-D-aspartate blockade and therefore potential neuroprotective action	Potential for neurotoxicity, hypertension

a = the rate of 2 mg/kg/h (children) is recommended by Abend & Dlugos 2008.
NK = not known.

Ex. 1053 at 2812 (Table 2); Ex. 1042, 53:24-24:9; Patent Owner's Sur-Reply at 15.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Ovid Therapeutics

Dr. Baughman's Declaration (Exs. 1058 and 1060) Is Irrelevant

UNITED STATES PATENT AND TRADEMARK OFFICE

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MARINUS PHARMACEUTICALS, INC.,
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v.

OVID THERAPEUTICS, INC.,
Patent Owner

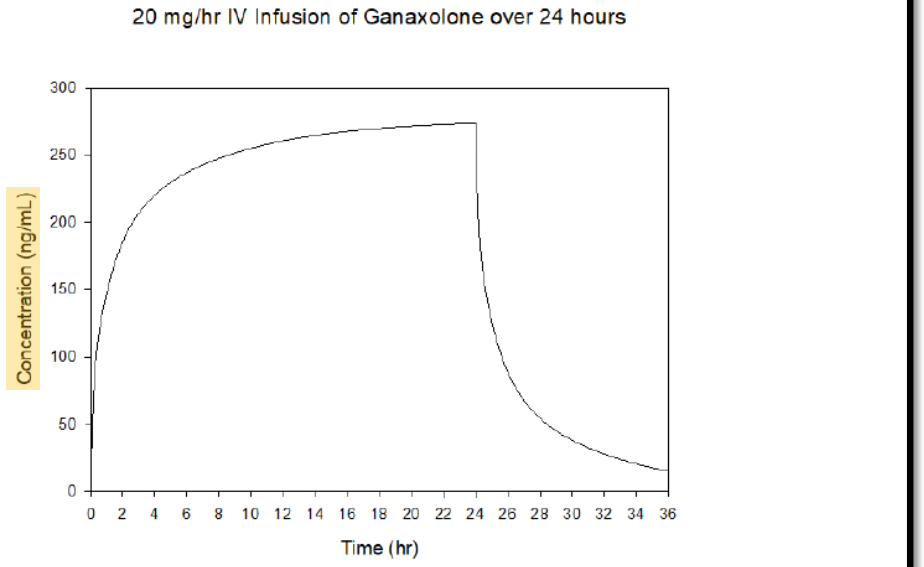
Case PGR2023-00020
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'PPLEMENTAL DECLARATION OF SHARON BAUGHMAN, Ph.D.

MARINUS 1060
Marinus v. Ovid

1

18. The modeled results for the 20 mg continuous infusion simulation are shown below (linear, semi-log):

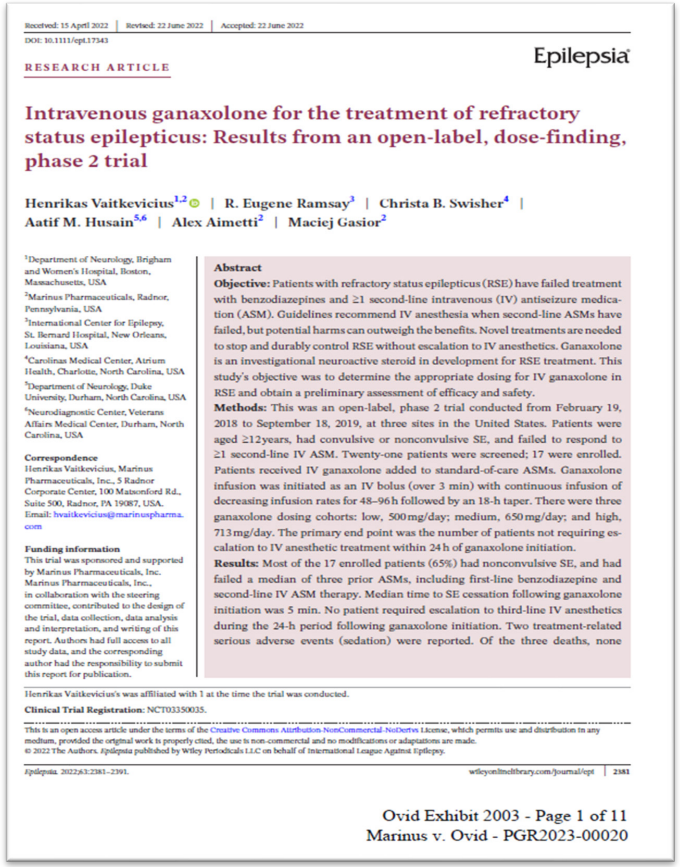


Ex. 1060 at ¶¶ 18-22; Patent Owner's Sur-Reply at 16-17.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Ovid Therapeutics

All Dose Cohorts Achieved Primary and Secondary Endpoints



Received: 15 April 2022 | Revised: 22 June 2022 | Accepted: 22 June 2022
DOI: 10.1111/epi.17343

Epilepsia

RESEARCH ARTICLE

Intravenous ganaxolone for the treatment of refractory status epilepticus: Results from an open-label, dose-finding, phase 2 trial

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[4]Carolinas Medical Center, Atrium Health, Charlotte, North Carolina, USA
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[6]Neurodiagnostic Center, Veterans Affairs Medical Center, Durham, North Carolina, USA

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Funding information
This trial was sponsored and supported by Marinus Pharmaceuticals, Inc. Marinus Pharmaceuticals, Inc., in collaboration with the steering committee, contributed to the design of the trial, data collection, data analysis and interpretation, and writing of this report. Authors had full access to all study data, and the corresponding author had the responsibility to submit this report for publication.

Abstract

Objective: Patients with refractory status epilepticus (RSE) have failed treatment with benzodiazepines and ≥1 second-line intravenous (IV) antiseizure medication (ASM). Guidelines recommend IV anesthesia when second-line ASMs have failed, but potential harms can outweigh the benefits. Novel treatments are needed to stop and durably control RSE without escalation to IV anesthetics. Ganaxolone is an investigational neuroactive steroid in development for RSE treatment. This study's objective was to determine the appropriate dosing for IV ganaxolone in RSE and obtain a preliminary assessment of efficacy and safety.

Methods: This was an open-label, phase 2 trial conducted from February 19, 2018 to September 18, 2019, at three sites in the United States. Patients were aged ≥12 years, had convulsive or nonconvulsive SE, and failed to respond to ≥1 second-line IV ASM. Twenty-one patients were screened; 17 were enrolled. Patients received IV ganaxolone added to standard-of-care ASMs. Ganaxolone infusion was initiated as an IV bolus (over 3 min) with continuous infusion of decreasing infusion rates for 48–96 h followed by an 18-h taper. There were three ganaxolone dosing cohorts: low, 500 mg/day; medium, 650 mg/day; and high, 713 mg/day. The primary end point was the number of patients not requiring escalation to IV anesthetic treatment within 24 h of ganaxolone initiation.

Results: Most of the 17 enrolled patients (65%) had nonconvulsive SE, and had failed a median of three prior ASMs, including first-line benzodiazepine and second-line IV ASM therapy. Median time to SE cessation following ganaxolone initiation was 5 min. No patient required escalation to third-line IV anesthetics during the 24-h period following ganaxolone initiation. Two treatment-related serious adverse events (sedation) were reported. Of the three deaths, none

Henrikas Vaitkevicius's was affiliated with 1 at the time the trial was conducted.

Clinical Trial Registration: NCT03350035.

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Reductions in seizure burden occurred rapidly in all three ganaxolone dose cohorts. Patients in the high-dose cohort maintained ganaxolone plasma concentrations ≥500 ng/ml for 8 h following treatment initiation and demonstrated the most durable reductions in seizure burden. Although not studied in the present trial, maintaining ganaxolone levels ≥500 ng/ml for durations longer than 8 h may offer additional benefit and will be evaluated in future clinical studies.

Sixteen patients (94%) achieved and maintained SE cessation for 24 h following ganaxolone initiation as determined by trial-site investigator assessment (Table 2). The follow-up period after ganaxolone discontinuations was up to 4 weeks; during this period, 85% of evaluable patients did not have SE relapse ($N = 13$; 1 subject in the Low Cohort and 1 subject in the Medium Cohort had SE relapse). EEG data, reviewed by the trial site investigator,

Fourteen patients (82%) did not require treatment for SE with additional second-line IV ASMs or IV anesthetics through 24 h following completion of the ganaxolone infusion (Table 2). Of the three patients who did not

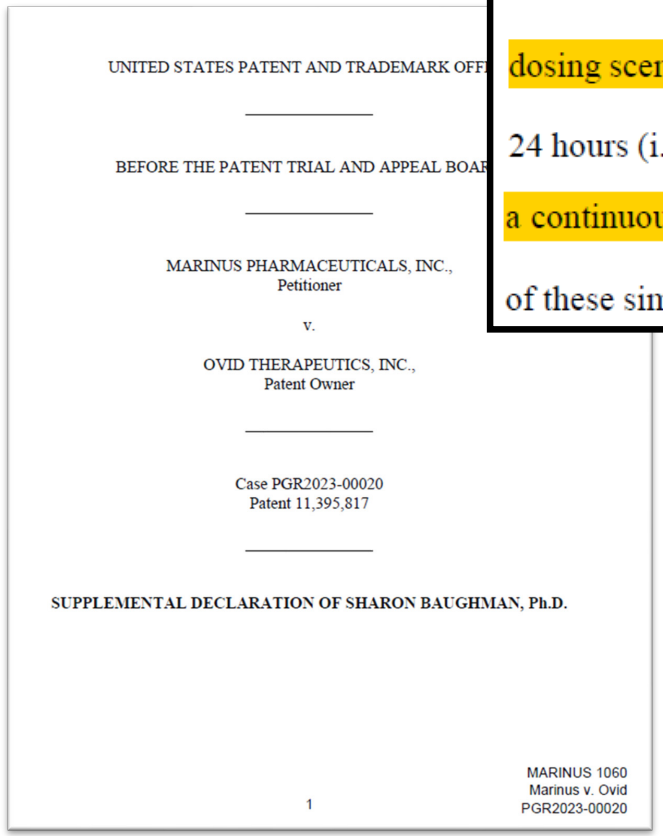
Ex. 2003 at 2386, 2388; Patent Owner's Sur-Reply at 16-17.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Ovid Therapeutics

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Dr. Baughman's Declaration (Exs. 1058 and 1060) Is Irrelevant



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Case PGR2023-00020
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SUPPLEMENTAL DECLARATION OF SHARON BAUGHMAN, Ph.D.

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17. In particular, I used the WinNonlin modeling to simulate two potential dosing scenarios: (1) 20 mg/hr of ganaxolone given as a continuous IV infusion over 24 hours (i.e., 480 mg total over 24 hours), and (2) 30 mg/hr of ganaxolone given as a continuous IV infusion over 24 hours (i.e., 720 mg total over 24 hours). Neither of these simulated scenarios include a bolus dose of ganaxolone.

Sharon Baughman, Ph.D

So whether or not the regimen included a bolus dose was not important to your modeling?

A. I was asked to -- if I could replicate the -- or bracket those dosing regimens, 500 mgs per day, 713 mgs per day. The simplest replication is a continuous infusion.

Q. Who asked you to bracket those doses?

A. Counsel.

Ex. 1060 at ¶ 17; Ex. 2025 at 24:15-25:13 Patent Owner's Sur-Reply at 17.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Ovid Therapeutics

Ground 2: Zhang Does Not Render Claims 22 and 25-31 Obvious

Claim 22: No Motivation to Combine Zhang ¶ [0074] with Example 8

[0074] Methods of treatment include treating a patient suffering from seizures, traumatic brain injury, or stroke by administering a single injection (bolus dose) of a substituted β-cyclodextrin-ganaxolone injectable formulation. The single injection may be administered intramuscularly or intravenously. The dose of the single injection may be from about 1 mg/ kg to about 20 mg/ kg, from about 2 mg/ kg to about 15 mg/ kg, from about 2 mg/ kg to about 10 mg/ kg, or about 2 mg/ kg to about 8 mg/ kg. Methods of treatment also include administering multiple injections of the β-cyclodextrin-ganaxolone injectable formulation over a period of 1 to 10 days. The injections may be given at intervals of 1 to 24 hours. Dosing schedules in which the substituted β-cyclodextrin-ganaxolone injectable formulation is injected every 1 hr, 2 hrs, 4 hrs, 6 hrs, 8 hrs, 12 hrs, or 24 hours are included herein. Dosing schedules in which the substituted β-cyclodextrin-ganaxolone injectable formulation is injected for 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 days are included herein.

EXAMPLE 8. GANAXOLONE EFFECT ON PILOCARPINE-INDUCED STATUS EPILEPTICUS IN RATS

[0117] This study was designed to determine the ability of a CAPTISOL-ganaxolone (GNX) formulation administered intravenously (IV) at 12 and 15 mg/kg to inhibit pilocarpine induced status epilepticus (SE). Allopregnanolone (Allo) (15 mg/kg; IV) was also evaluated for comparison. In this study, test drugs were administered either 15 or 60 minutes after onset of SE and compared to vehicle (30% Captisol).



"In appropriate circumstances, a single prior art reference can render a claim obvious. However, there must be a showing of a suggestion or motivation to modify the teachings of that reference to the claimed invention in order to support the obviousness conclusion."

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

Ex. 1009 at ¶ [0074], [0117]; Patent Owner's Response at 52-53; Patent Owner's Sur-Reply at 20-21; Ex. 2014 at ¶¶ 91-92.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Ovid Therapeutics

Claim 22: Insufficient Basis for Use of Common Knowledge

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



"[O]ur cases repeatedly warn that references to "common sense"—whether to supply a motivation to combine or a missing limitation—cannot be used as a wholesale substitute for reasoned analysis and evidentiary support, especially when dealing with a limitation missing from the prior art references specified."

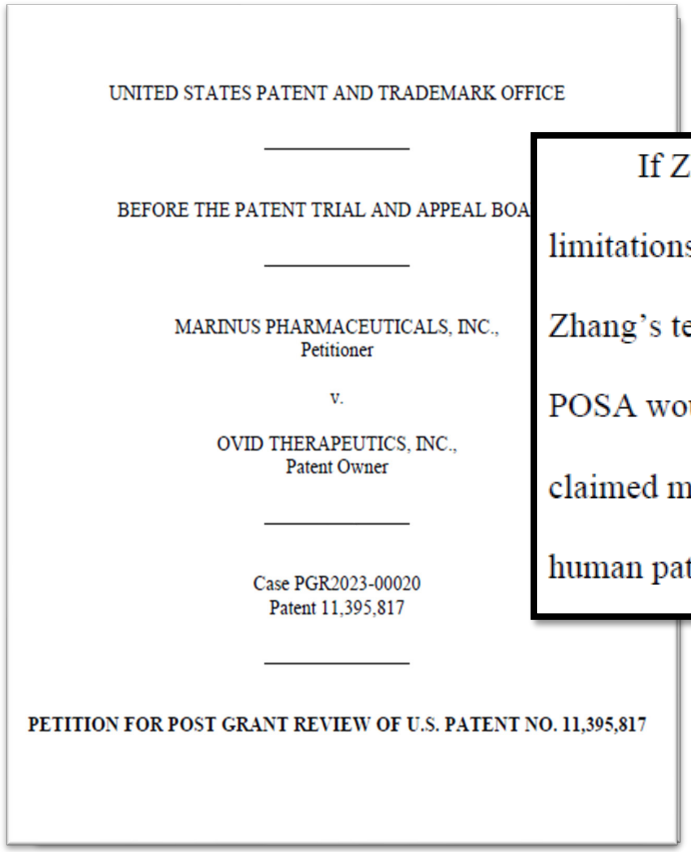
Arendi S.A.R.L. v. Apple Inc., 832 F.3d 1355, 1362 (Fed. Cir. 2016).

Petition at 48; Patent Owner's Response at 53.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Ovid Therapeutics

Claims 22: Reasonable Expectation of Success = Attorney Argument



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Patent 11,395,817

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

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

Petition at 49; Patent Owner's Response at 55.

Claim 22: Zhang Only Provides Data up to 5 Hours

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MARINUS PHARMACEUTICALS, INC.,
Petitioner

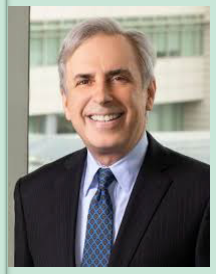
v.

OVID THERAPEUTICS, INC.,
Patent Owner

Case PGR2023-00020
Patent 11,395,817

DECLARATION OF DR. MICHAEL A. ROGAWSKI

1 EX1003



Michael A. Rogawski, Ph.D., M.D.

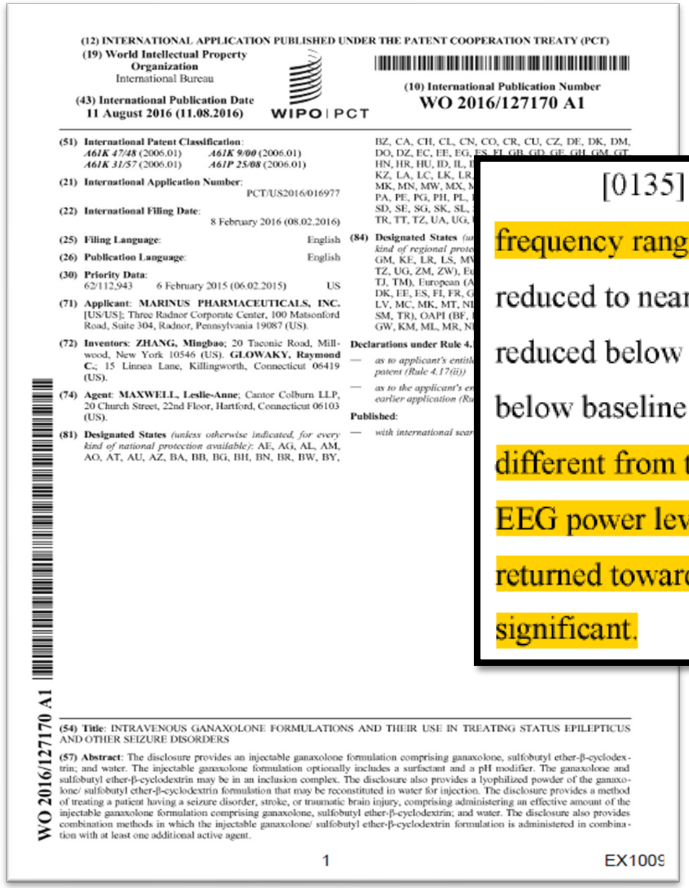
93. Zhang does not expressly state the composition provides improvement for more than 8 hours after administration. In Zhang's Example 8, the rats experiencing SE were sacrificed after 5 hours and, so, even though some effects of ganaxolone were sustained for the entire 5 hours, because the experiment was stopped at 5 hours, there is no data demonstrating a response "for more than 8 hours."[1] To the extent that improvement to the patient were to occur after that time period, however, it would be the natural result of administering the ganaxolone formulations in the manner taught in Zhang.

Ex. 1003 at ¶ 93; Patent Owner's Response at 54
Patent Owner's Sur-Reply at 21-22; Ex. 2014 at ¶ 94.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Ovid Therapeutics

Claim 22: Effect of Ganaxolone Diminishes by 5 Hours



(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
11 August 2016 (11.08.2016)

WIPO | PCT

(10) International Publication Number
WO 2016/127170 A1

(51) International Patent Classification:
A61K 47/48 (2006.01) *A61K 9/00* (2006.01)
A61K 31/57 (2006.01) *A61P 25/08* (2006.01)

(21) International Application Number:
PCT/US2016/016977

(22) International Filing Date:
8 February 2016 (08.02.2016)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/112,943 6 February 2015 (06.02.2015) US

(71) Applicant: **MARINUS PHARMACEUTICALS, INC.** [US/US]; Three Radnor Corporate Center, 100 Matsonford Road, Suite 304, Radnor, Pennsylvania 19087 (US).

(72) Inventors: **ZHANG, Mingbao**; 20 Taconic Road, Millwood, New York 10546 (US). **GLOWAKY, Raymond C.**; 15 Linnea Lane, Killingworth, Connecticut 06419 (US).

(74) Agent: **MAXWELL, Leslie-Anne**; Cantor Colburn LLP, 20 Church Street, 22nd Floor, Hartford, Connecticut 06103 (US).

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(84) Designated States (kind of regional protection available): GM, KE, LR, LS, MW, TZ, UG, ZM, ZW), Eurasian (TJ, TM), European (AL, DK, EE, ES, FI, FR, LV, MC, MK, MT, NL, SM, TR), OAPI (BF, GW, KM, ML, MR,

Declarations under Rule 4.
— as to applicant's entitl
patent (Rule 4.17(ii))
— as to the applicant's e
earlier application (Ru

Published:
— with international sear

(54) Title: INTRAVENOUS GANAXOLONE FORMULATIONS AND THEIR USE IN TREATING STATUS EPILEPTICUS AND OTHER SEIZURE DISORDERS

(57) Abstract: The disclosure provides an injectable ganaxolone formulation comprising ganaxolone, sulfobutyl ether-β-cyclodextrin; and water. The injectable ganaxolone formulation optionally includes a surfactant and a pH modifier. The ganaxolone and sulfobutyl ether-β-cyclodextrin may be in an inclusion complex. The disclosure also provides a lyophilized powder of the ganaxolone/ sulfobutyl ether-β-cyclodextrin formulation that may be reconstituted in water for injection. The disclosure provides a method of treating a patient having a seizure disorder, stroke, or traumatic brain injury, comprising administering an effective amount of the injectable ganaxolone formulation comprising ganaxolone, sulfobutyl ether-β-cyclodextrin; and water. The disclosure also provides combination methods in which the injectable ganaxolone/ sulfobutyl ether-β-cyclodextrin formulation is administered in combination with at least one additional active agent.

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EX1009

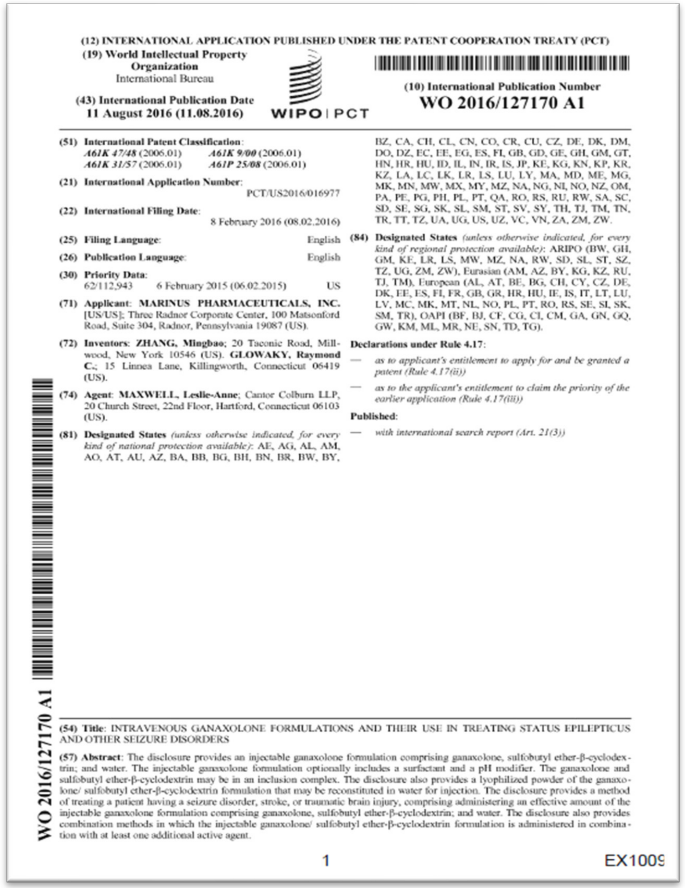
[0135] When dosed 15 minutes after SE-onset, GNX reduced EEG power across all frequency ranges to levels at or below baseline for at up to 5 h. From 5-70 Hz, EEG power was reduced to near the baseline level and remained there for 5 h post dosing. At 0-5 Hz, EEG power was reduced below the baseline level for approximately 90 min, and at 70-96 Hz, EEG power remained below baseline for the entire 5 h. However, between 2 to 5 h, EEG power above 30 Hz was not different from the vehicle group, indicating it was also not significantly different from the baseline EEG power level. Note also that at the higher frequency ranges, EEG power in the vehicle groups returned towards baseline after 2 h, so that differences between the GNX and vehicle groups were not significant.

Ex. 1009 at ¶ [0135]; Patent Owner's Response at 54-56; Patent Owner's Sur-Reply at 21-22; Ex. 2014 at ¶ 94.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Ovid Therapeutics

Claim 22: Effect of Ganaxolone Diminishes by 5 Hours



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Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:
— *with international search report (Art. 21(3))*

(54) Title: INTRAVENOUS GANAXOLONE FORMULATIONS AND THEIR USE IN TREATING STATUS EPILEPTICUS AND OTHER SEIZURE DISORDERS

(57) Abstract: The disclosure provides an injectable ganaxolone formulation comprising ganaxolone, sulfobutyl ether-β-cyclodextrin; and water. The injectable ganaxolone formulation optionally includes a surfactant and a pH modifier. The ganaxolone and sulfobutyl ether-β-cyclodextrin may be in an inclusion complex. The disclosure also provides a lyophilized powder of the ganaxolone/ sulfobutyl ether-β-cyclodextrin formulation that may be reconstituted in water for injection. The disclosure provides a method of treating a patient having a seizure disorder, stroke, or traumatic brain injury, comprising administering an effective amount of the injectable ganaxolone formulation comprising ganaxolone, sulfobutyl ether-β-cyclodextrin; and water. The disclosure also provides combination methods in which the injectable ganaxolone/ sulfobutyl ether-β-cyclodextrin formulation is administered in combination with at least one additional active agent.

WO 2016/127170 A1

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EX1009

TABLE 6 - Treatment Effects, Rats Treated 15 minutes post SE onset

		Significance, Time post drug administration					
Comparison	Frequency	0-15 min.	15-30	30-60	1-2 hrs	2-3 hrs	3-5 hrs
Vehicle vs. Allo.(15 mg/ml), both administered 15' post SE onset	0-5 Hz	****	****	****	***	*	ns
	5-10 Hz	****	****	****	***	ns	ns
	10-30 Hz	****	****	***	**	ns	ns
	30-50 Hz	****	****	***	ns	ns	ns
	50-70 Hz	***	***	**	ns	ns	ns
	70-96 Hz	***	***	**	ns	ns	ns
Vehicle vs GNX (12 mg/ml) both administered 15 minutes post SE onset	0-5 Hz	****	****	****	****	***	**
	5-10 Hz	****	****	***	**	*	ns
	10-30 Hz	***	****	**	*	ns	ns
	30-50 Hz	***	***	**	*	ns	ns
	50-70 Hz	**	**	*	**	ns	ns
	70-96 Hz	**	**	*	**	ns	ns
Vehicle vs GNX (15 mg/ml) both administered 15 minutes post SE onset	0-5 Hz	****	****	****	****	****	***
	5-10 Hz	****	****	****	****	***	ns
	10-30 Hz	****	****	****	**	*	ns
	30-50 Hz	***	***	***	**	ns	ns
	50-70 Hz	**	**	**	**	ns	ns
	70-96 Hz	**	***	**	**	ns	ns

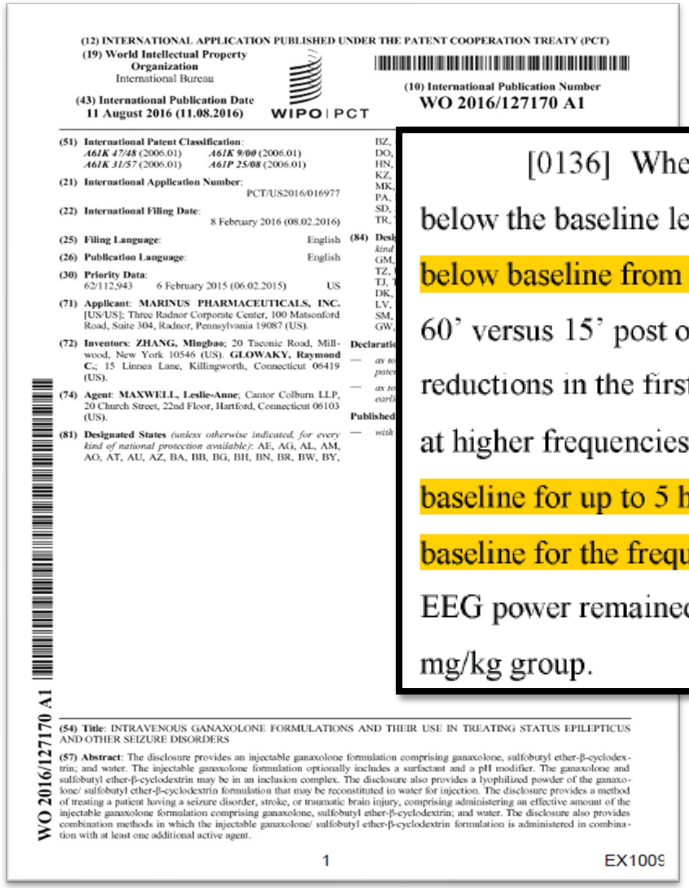
* P < 0.05; ** P < 0.01; *** P < 0.001; **** P < 0.0001, ns = not significant CLAIMS

Ex. 1009 at Table 6; Patent Owner's Response at 54-56; Patent Owner's Sur-Reply at 21-22; Ex. 2014 at ¶ 94.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Ovid Therapeutics

Claim 22: Effect of Ganaxolone Diminishes by 5 Hours



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WO 2016/127170 A1

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EX1009

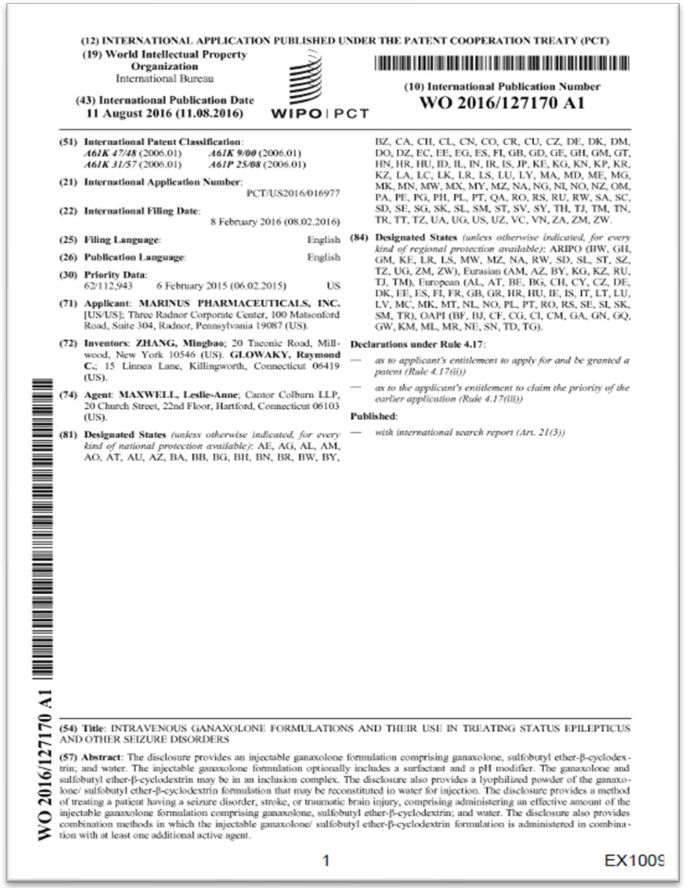
[0136] When dosed at 60' post SE-onset, EEG power was also strongly reduced, but not below the baseline level for frequencies up to 70 Hz. From 70-96 Hz, EEG power appeared to drop below baseline from 1 to 4 h post dosing. The principal difference between effects of GNX dosed at 60' versus 15' post onset were (1) at higher frequencies (> 30 Hz), there were no significant reductions in the first 15' post dosing, and (2) the activity the drug appeared to be stronger especially at higher frequencies at the 2-3 h time point. Again, the EEG power levels were maintained at baseline for up to 5 h post dosing, however, the EEG levels of the vehicle group also returned to baseline for the frequency ranges above 30 Hz so the drug showed no effect. In contrast, at 0-5 Hz, EEG power remained high in the vehicle group, and GNX showed a significant reduction in the 12 mg/kg group.

Ex. 1009 at ¶ [0136]; Patent Owner's Response at 54-56; Patent Owner's Sur-Reply at 21-22; Ex. 2014 at ¶ 94.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Ovid Therapeutics

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Published:
— *with international search report (Art. 21(3))*

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1 EX1009

TABLE 7 - Treatment Effects, Rats Treated 60 minutes post SE onset

		Significance, Time post drug administration					
Comparison	Frequency	0-15 min.	15-30	30-60	1-2 hrs	2-3 hrs	3-5 hrs
Vehicle vs. Allo.(15 mg/ml), both administered 15' post SE onset	0-5 Hz	**	ns	Ns	ns	ns	ns
	5-10 Hz	**	ns	Ns	ns	ns	ns
	10-30 Hz	ns	ns	Ns	ns	ns	ns
	30-50 Hz	ns	ns	Ns	ns	ns	ns
	50-70 Hz	ns	ns	Ns	ns	ns	ns
	70-96 Hz	ns	ns	Ns	ns	ns	ns
Vehicle vs GNX (12 mg/ml) both administered 15 minutes post SE onset	0-5 Hz	***	****	****	****	***	**
	5-10 Hz	****	****	****	***	**	ns
	10-30 Hz	*	**	**	**	*	ns
	30-50 Hz	ns	ns	*	**	*	ns
	50-70 Hz	ns	*	**	**	*	ns
	70-96 Hz	ns	**	***	***	**	ns

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	5-10 Hz	**	****	****	**	**	ns
	10-30 Hz	ns	ns	*	**	*	ns
	30-50 Hz	ns	ns	*	*	ns	ns
	50-70 Hz	ns	ns	*	**	ns	ns
	70-96 Hz	ns	*	**	**	*	ns

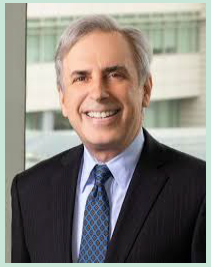
* P < 0.05; ** P < 0.01; *** P < 0.001; **** P < 0.0001, ns = not significant CLAIMS

Ex. 1009 at Table 7; Patent Owner's Response at 54-56; Patent Owner's Sur-Reply at 21-22; Ex. 2014 at ¶ 94.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Ovid Therapeutics

Claim 22: Improvement Not Expected After 5 Hours in Zhang



Michael A. Rogawski, Ph.D., M.D.

Q. When you say that to the extent that improvement to the patient were to occur after that time period, are you acknowledging that it's possible that the improvement may not be occurring after that time period?

A. I think 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 at 154:16:7-16; Patent Owner's Response at 54.

Reasonable Expectation of Success

"[W]e held that it was not enough for the [patent challenger] to have shown that a skilled artisan would have pursued the claimed method as a treatment option, but the [patent challenger] also had to show that the skilled artisan would have reasonably expected to achieve success in the treatment."

Eli Lilly & Co. v. Teva Pharms. Int'l GmbH, 8 F.4th 1331, 1344 (Fed. Cir. 2021).

"[P]rior art fails to provide the requisite 'reasonable expectation' of success where it teaches merely to pursue a 'general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.'"

Medichem, S.A. v. Rolabo, S.L., 437 F.3d 1157, 1165 (Fed. Cir. 2006).

Patent Owner's Response at 60; Patent Owner's Sur-reply at 19-20.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Claims 25-31: Animal Models Only Identify "Potential Treatments"

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

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Petitioner

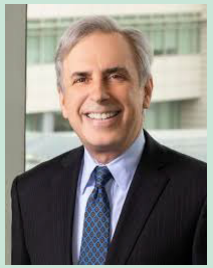
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Patent Owner

Case PGR2023-00020
Patent 11,395,817

DECLARATION OF DR. MICHAEL A. ROGAWSKI

1 EX1003



Michael A. Rogawski, Ph.D., M.D.

25. Researchers often use animal models to identify treatments that may be effective in terminating SE in humans. When such a potential treatment is identified, it may be advanced to human clinical trials, which are required for regulatory approval before the treatment becomes available for use in medical practice. (Imtiyaz, Ex. 1006, at 1.)

27. One animal model used to evaluate potential treatments for SE is the rat pilocarpine model, which was developed in the 1980s. (Turski, Ex. 1007,

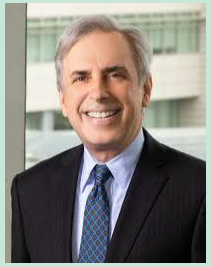
33. I have been involved in studies that have used the rat pilocarpine model to evaluate potential treatments for SE and, in my opinion, it is well-recognized in the art as satisfying the accepted criteria for a model that predicts if a therapy could be useful in the treatment of SE in humans. (*See generally, e.g.*, Kokate, Ex. 1008.)

Ex. 1003 at ¶¶ 25, 27, 33; Patent Owner's Sur-Reply at 21
Ex. 2014 at ¶¶ 104-105.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Ovid Therapeutics

Claims 25-31: Rat Models Do Not Translate Directly to Humans



Michael A. Rogawski, Ph.D., M.D.

Q. Have you done research in any other neurosteroids besides ganaxolone and allopregnanolone for treating SE?

A. I have.

Q. Which ones are those?

A. There were a variety of neuroactive steroids that we studied in the beginning of our research effort in this area many years ago -- this would be in the 1980s. And I can't recall precisely what compounds we studied. Those are listed in our publication. But they all had some degree of activity in -- in status epilepticus.

Q. And when you say there's "some degree of activity," was that in an animal model?

A. That was in an animal model, yes -- or several animal models, I should say.

Q. Okay. And did any of those other compounds advance to clinical trials in humans?

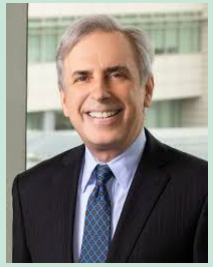
A. Not that I'm aware of, no.

Ex. 2015 at 24:14-25:7; Patent Owner's Response at 59; Patent Owner's Sur-Reply at 21;.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Ovid Therapeutics

Claims 25-31: Rat Models Do Not Translate Directly to Humans



Michael A. Rogawski, Ph.D., M.D.

Q. And what was the general kind of nature of that research?

A. We have developed a treatment based on animal research in the laboratory, and we had an opportunity to collaborate with a group of clinicians who were studying status epilepticus -- or treating status epilepticus in humans. And we provided our treatment to them, and that resulted in jointly authored publications. I believe there were three -- about three jointly authored publications that resulted from that clinical research.

Q. And what drug compound was that research done with?

A. That was with allopregnanolone.

Q. Did allopregnanolone advance to clinical trials in humans for treating SE?

A. It did.

Q. Did it receive approval for treating SE from the FDA?

A. Not that I'm aware of, no.

Q. Do you know why that was?

A. There was a clinical trial in super-refractory status epilepticus where allopregnanolone was not found to meet the predefined endpoints, and therefore the program did not progress.

Ex. 2015 at 21:10-24:13; Patent Owner's Response at 59; Patent Owner's Sur-Reply at 21.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Ground 3:
Zhang and Saporito P1 and/or Saporito P2 Do Not Render Claims 22 and 25-31 Obvious

Ovid Exhibit 2026 - Page 83 of 121
Marinus v. Ovid - PGR2023-00020

Printed Publications Must Be Publicly Accessible to Be Prior Art

"The statutory phrase 'printed publication' has been interpreted to mean that before the critical date the reference must have been sufficiently accessible to the public interested in the art; dissemination and public accessibility are the keys to the legal determination whether a prior art reference was 'published.'"

In re Cronyn, 890 F.2d 1158, 1160 (Fed. Cir. 1989).

"The determination of whether a reference is a 'printed publication' under 35 U.S.C. 102(a) involves a case-by-case inquiry into the facts and circumstances surrounding the reference's disclosure to members of the public."

In re Klopfenstein, 380 F.3d 1345, 1348 (Fed. Cir. 2004).

Patent Owner's Response at 61-62.

Dr. Saporito Unable to Confirm Number of Attendees



Michael Saporito

But did you pin down more of a specific number?

You said earlier between 50 and 100 people.

A. I didn't count them.

Q. Okay. So you have no guess or estimation?

A. No.

How many people stopped to ask questions?

A. It's hard. I can't put a specific number on the number of people who asked questions.

But as before, I think it was as well attended as the previous poster. Maybe a lot of the similar folks that stopped by the first poster stopped by the second poster.

How many people would you estimate asked questions about --

A. Same number.

Q. So every person that you interacted with asked questions?

A. Not everybody. Anybody I spoke with asked questions.

Q. But you're estimating the same number for interactions and questions?

A. I didn't say -- I said "interactions," not "questions."

Q. Well, I just asked you how many people you interacted with when you said "I interacted with many," and you said about 50.

A. Any -- it's a very rough estimate, right. It could be 50. It could have been 200. I really don't remember. It was a lot of people. It was a very busy poster session.

Ex. 2016 at 64:23-65:20, 66:17-67:23, 79:15-80:21; Patent Owner's Response at 62.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Ovid Therapeutics

Dr. Saporito Unable to Confirm Same Poster Presented



Michael Saporito

Q. Okay. Is there anything on the poster that indicates that it was presented at the 2016 AAN meeting?
Feel free to take your time and look it over.
A. There's nothing in the poster that specifically says that that was presented.

Q. Okay. Is there a date on this poster?
A. There is not.
Q. Is there anything on the poster that indicates that it was presented at the 2016 AAN meeting?
A. There is nothing on that poster that says that.

Ex. 2016 at 48:16-22; Patent Owner's Response at 63.

Dr. Saporito Unable to Confirm Same Poster Presented



Michael Saporito

Who split the full-page version into four pieces?

ATTORNEY TYREUS HUFNAL: You can answer that with a name, if you know.

THE WITNESS: I don't know. I just don't know.

Q. So it wasn't you?

A. It wasn't me.

Q. Okay. And just to confirm, the original poster was not split into four pieces; is that correct?

A. That's correct.

Ex. 2016 at 90:2:91:7; Patent Owner's Response at 63.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Ovid Therapeutics

Saporito P1 Has Different Authorship than AAN Brochure

Ganaxolone Administered Intravenously Prevents Behavioral Seizures and Promotes Survival in the Rat Lithium-Pilocarpine Model of Status Epilepticus

MARINUS PHARMACEUTICALS

Michael S. Saporito,[1] Donna Henry,[1] Melissa L. Barker-Haliski,[2] Cameron S. Metcalf,[3] Julia Tsai,[1] Albena Patroneva,[1] and Steve White.[2]
[1]Marinus Pharmaceuticals, Radnor, PA [2]University of Utah, Salt Lake City, UT [3]Neuroadjuvants, Inc. Salt Lake City, UT.

Saporito P1

P2.020 Ganaxolone Administered Intravenously Prevents Behavioral Seizures and Promotes Survival in the Rat Lithium-Pilocarpine Model of Status Epilepticus—*Michael Saporito, Julia Tsai, Albena Patroneva, Steve White, Cameron Metcalf, Melissa L. Barker-Haliski*

AAN Meeting Brochure



Michael Saporito

Q. Okay. If you compare the authors listed here to the authors listed on the poster, Donna Henry is identified on the poster but is not identified on the brochure.

Do you see that?

A. I do.

Q. Why is that?

A. I don't remember specifically why Donna wasn't included in the abstract description of it and then ultimately in the program.

Ex. 1013 at 1; Ex. 1012 at 48; Ex. 2016 at 54:3-13; Patent Owner's Response at 64.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Ovid Therapeutics

Saporito P2 Lists No Authors

Intravenous Administration of Ganaxolone Attenuates Electroencephalographic Seizures in a Diazepam Resistant Model of Status Epilepticus

MARINUS PHARMACEUTICALS

Saporito P2

P4.212 Intravenous Administration of Ganaxolone Attenuates Electroencephalographic Seizures in a Diazepam Resistant Model of Status Epilepticus —*Michael Saporito, Julia Tsai, Albena Patroneva*

AAN Meeting Brochure



Michael Saporito

9	Q. Okay. Are there authors listed on
10	this poster?
11	A. **There is not authors listed on this**
12	**poster.**
13	Q. Why are there not authors on this
14	poster?
15	A. **It was an inadvertent mistake that I**
16	**didn't catch. It was printed.**
17	Q. Okay. So it should have had authors
18	on it?
19	A. **It should have had authors on it.**

Ex. 1014 at 1; Ex. 1012 at 99; Ex. 2016 at 73:9-19; Patent Owner's Response at 64-65.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Ovid Therapeutics

No Motivation to Combine Zhang with Saporito P1 or P2

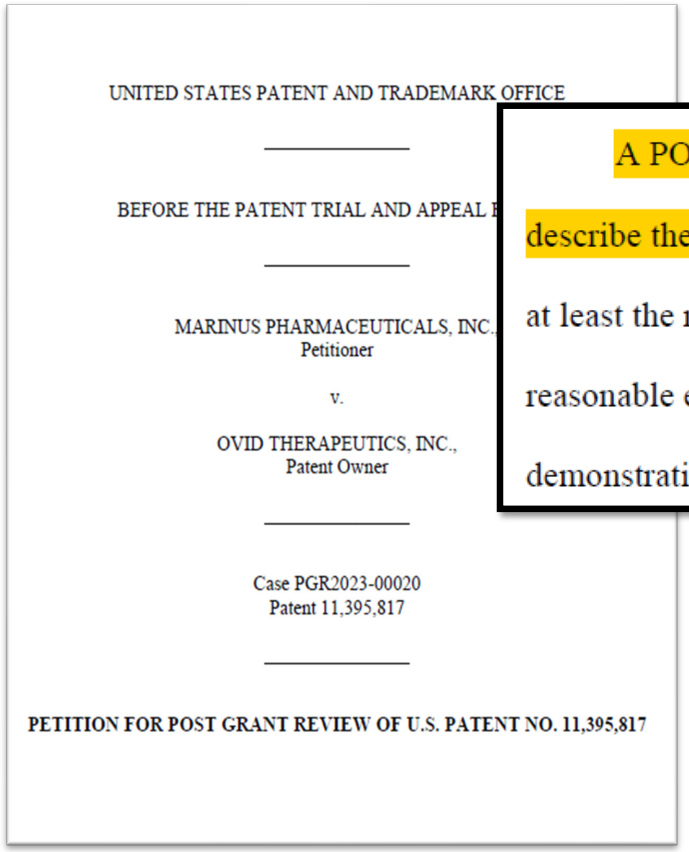
"'Mere compatibility of the references' or a showing that the references are 'analogous art or relevant to the field of endeavor of the challenged patent' is insufficient 'to establish that one of ordinary skill would have had reason to combine its teaching with other prior art in the manner set forth in the claim.'"

Johns Manville Corp. v. Knauf Insulation, Inc., IPR2018-00827, Paper 9 at 10 (PTAB Oct. 16, 2018).

Patent Owner's Response at 68.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Petitioner's Motivation to Combine Is Legally Insufficient



UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL B

MARINUS PHARMACEUTICALS, INC.,
Petitioner

v.

OVID THERAPEUTICS, INC.,
Patent Owner

Case PGR2023-00020
Patent 11,395,817

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

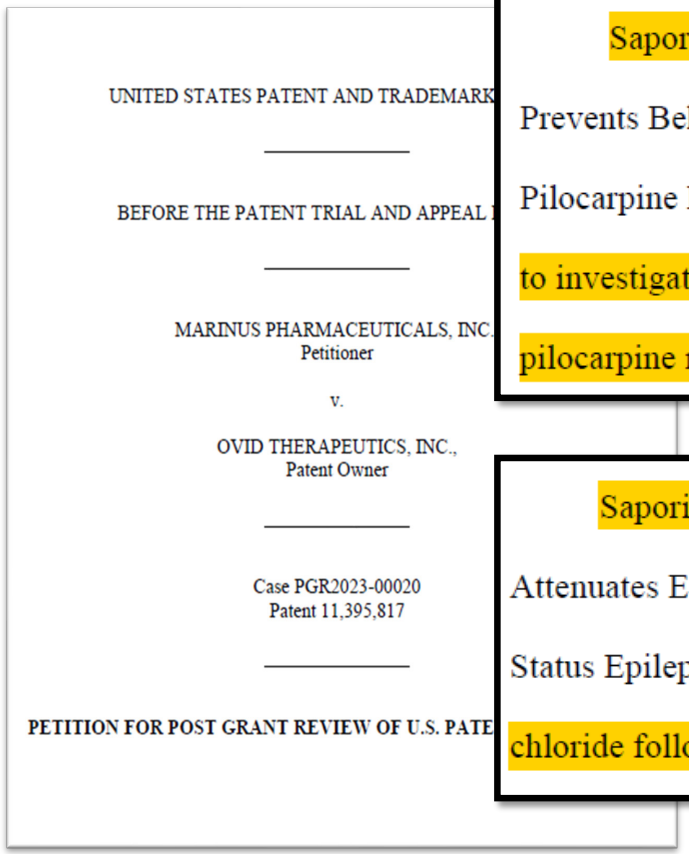
A POSA would have readily combined these references—as they both describe the same drug, the same disease, and the same animal model.[218] And, for at least the reasons described in Section VIII.B, it would have been with a reasonable expectation of success, with the posters providing additional data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

Petition at 54; Patent Owner's Response at 67-68.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Ovid Therapeutics

Saporito P1 and P2 Administer Ganaxolone to Rats Only



UNITED STATES PATENT AND TRADEMARK

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PETITION FOR POST GRANT REVIEW OF U.S. PATE

Saporito P1 (Ex. 1013), titled "Ganaxolone Administered Intravenously Prevents Behavioral Seizures and Promotes Survival in the Rat-Lithium Pilocarpine Model of Status Epilepticus," reports on a study conducted by Marinus to investigate the effects of IV-administered ganaxolone in the rat lithium-pilocarpine model.[196] In the study described on the poster, rats were administered

Saporito P2 (Ex. 1014), titled "Intravenous Administration of Ganaxolone Attenuates Electroencephalographic Seizures in a Diazepam Resistant Model of Status Epilepticus," like Saporito P1, shows that rats were administered lithium chloride followed by pilocarpine to induce SE.[207] The poster explains that "[s]tatus

Petition at 50, 52; Patent Owner's Response at 65-66
Ex. 2014 at ¶130.

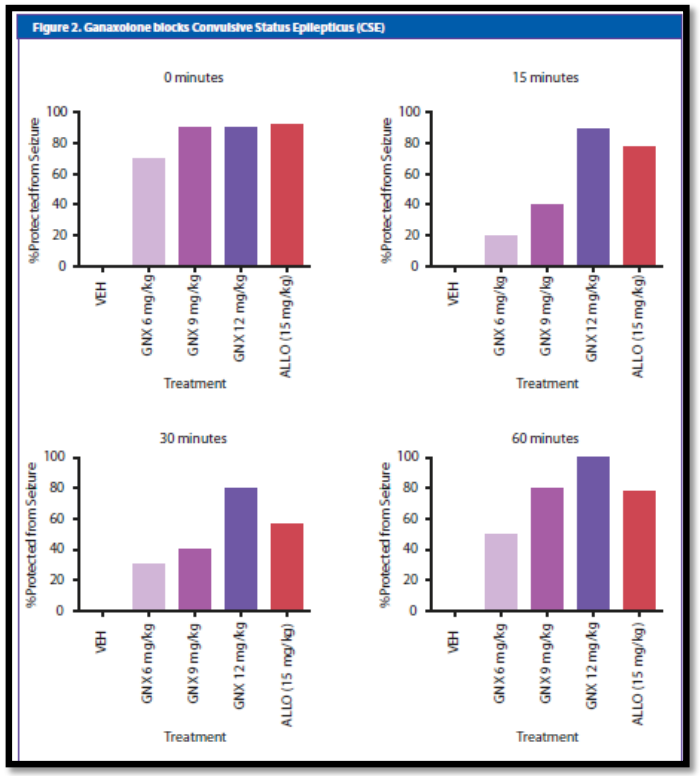
DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Claim 22: Saporito P1 Contains No Data Beyond 2 Hours

Ganaxolone Administered Intravenously Prevents Behavioral Seizures and Promotes Survival in the Rat Lithium-Pilocarpine Model of Status Epilepticus

MARINUS PHARMACEUTICALS

Michael S. Saporito,[1] Donna Henry,[1] Melissa L. Barker-Haliski,[2] Cameron S. Metcalf,[3] Julia Tsai,[1] Albena Patroneva,[1] and Steve White.[2]
[1]Marinus Pharmaceuticals, Radnor, PA [2]University of Utah, Salt Lake City, UT [3]Neuroadjuvants, Inc. Salt Lake City, UT.



- Compounds were administered via IV administration at time of CSE onset (time 0) and 15, 30, and 60 minutes after onset.
- After compound administration, animals were observed for the presence or absence of convulsive seizures (stage 3 or greater) for an additional 2 hours. Animals that did not exhibit a convulsive seizure during that time period were considered protected (**Figure 2**).

Ex. 1013 at 1; Patent Owner's Response at 69-70;
Patent Owner's Sur-Reply at 22; Ex. 2014 at ¶¶ 133-135.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Ovid Therapeutics

Claim 22: Saporito P2 Shows EEG Power Effect Diminishes by 6 Hours

Intravenous Administration of Ganaxolone Attenuates Electroencephalographic Seizures in a Diazepam Resistant Model of Status Epilepticus

MARINUS PHARMACEUTICALS

Figure 3. Ganaxolone Elicits a Durable Anti-Epileptic Effect when Administered IV 15 minutes after SE Onset

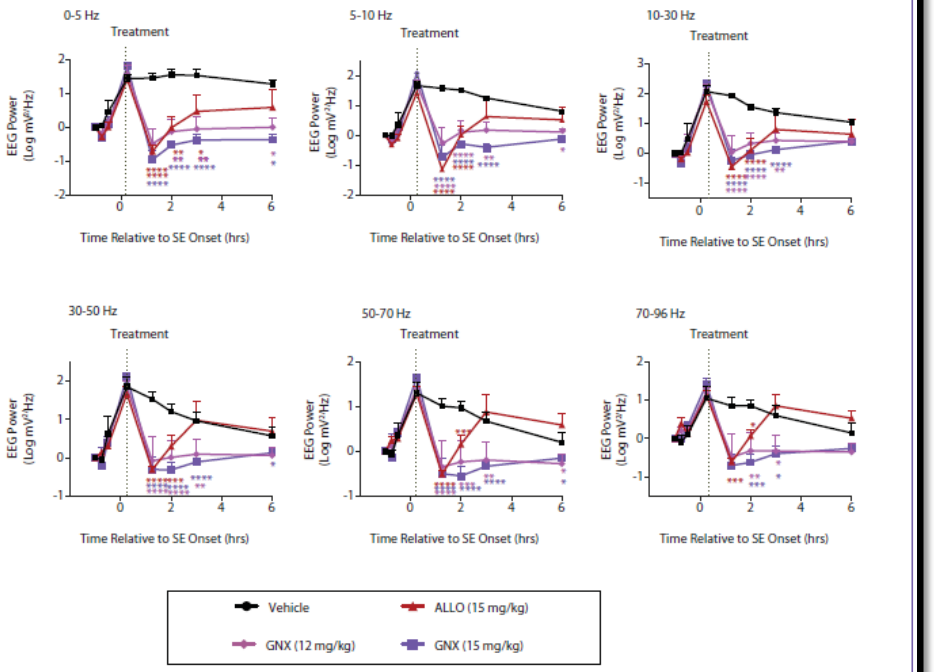
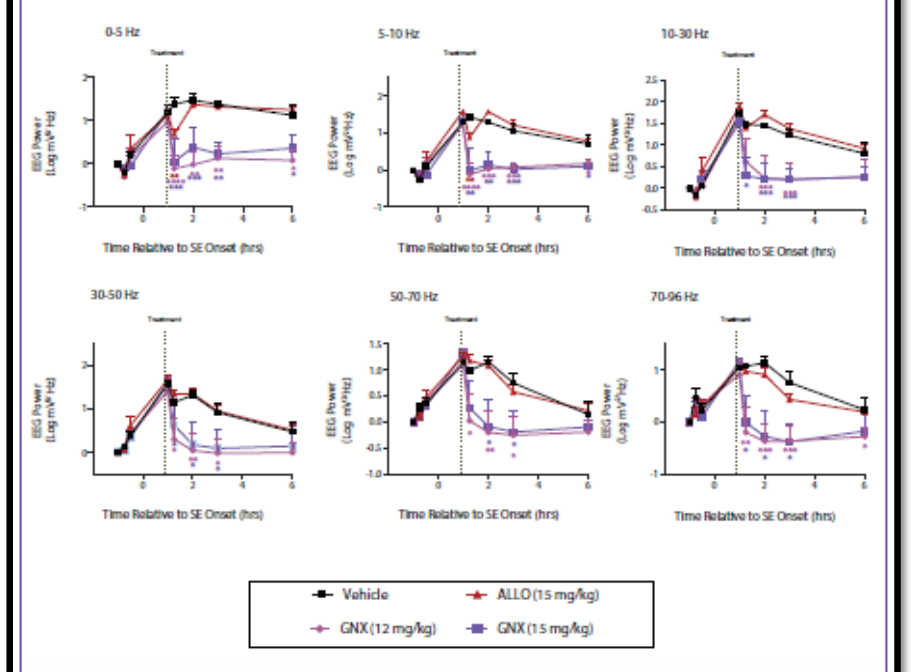


Figure 4. Ganaxolone Blocks Status Epilepticus when Administered IV 1 hr after SE Onset

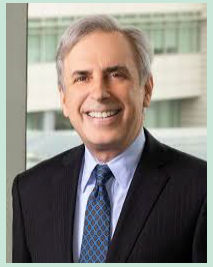


Ex. 1014 at 1; Patent Owner's Response at 69-70;
Patent Owner's Sur-Reply at 22; Ex. 2014 at ¶¶ 133-135.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Ovid Therapeutics

Claim 22: Saporito P2 Contains No Data Beyond 6 Hours



Michael A. Rogawski, Ph.D., M.D.

Q. Okay. And you would agree that the last time point at which data was taken was, in the case of Figure 3, 5 hours and 45 minutes after administration of ganaxolone; right?

A. Well, I don't know that. I -- I can say that it appears that the data presented in the graph is the last time point where the data provided in the graph is taken at, as you say, 5 hours and 45 minutes.

Q. And then for Figure 4, the last data point that's presented in the graph is -- would be five hours after administration on the ganaxolone; is that right?

A. Yes, I would agree with that.

Ex. 2015 at 115:1-14; Patent Owner's Response at 69-70; Patent Owner's Sur-Reply at 22.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Claim 22: Reliance on 24 Hours Survival = Attorney Argument

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OVID THERAPEUTICS, INC.,
Patent Owner

Case PGR2023-00020
Patent 11,395,817

PETITION FOR POST GRANT REVIEW OF U.S. PATENT NO. 1

6. Claim 22

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

[222] *Id.*

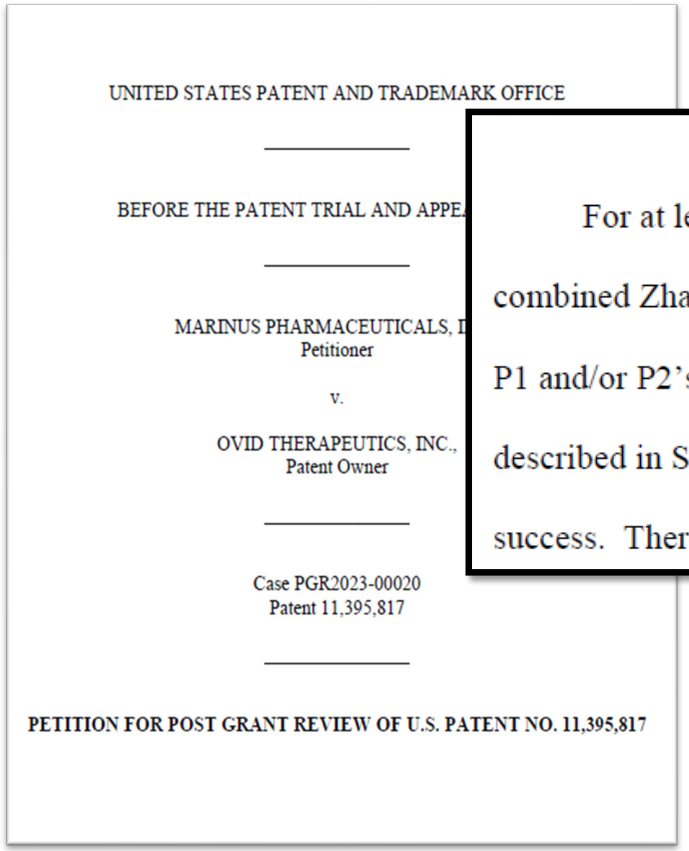
[223] *Id.*

[224] Ex. 1013 at Figure 3.

[225] *Id.*

Petition at 56 (citing Ex. 1013 at Figure 3);
Patent Owner's Response at 70.

Claims 25-31: No Arguments Specific to Claimed Doses



UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPE

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OVID THERAPEUTICS, INC.,
Patent Owner

Case PGR2023-00020
Patent 11,395,817

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

8. Claims 24–31

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

Petition at 56 (citing Ex. 1013 at Figure 3); Patent Owner's Response at 71-72; Patent Owner's Sur-Reply at 23.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Claims 25-31: Saporito P1 and P2 Do Not Teach Claimed Doses

METHODS

- Juvenile male Sprague-Dawley rats 5 weeks of age and weighing between 100 and 125 grams were used for these studies.
- CSE was induced by the administration of lithium chloride (127 mg/kg, intraperitoneal (i.p.), 24 hours prior to the study day) and pilocarpine (50 mg/kg, i.p.).
- Animals were monitored for seizure activity according to the Racine scale (Racine 1972). Any rat not showing convulsive seizure activity (stage 3 or greater) within 45 minutes of pilocarpine administration was excluded from the study prior to any administration of investigational compound or vehicle (VEH).
- GNX and ALLO were formulated to a concentration of 2.5 mg/mL in 30% Captisol. Dose volumes were adjusted so that animals received GNX dose-levels of 6, 9, 12 mg/kg and an ALLO dose-level of 15 mg/kg.

Saporito P1

METHODS

- Adult male Sprague-Dawley rats (10 weeks of age) were pre-implanted with cortical electrodes (**Figure 1**).
- Rats were administered lithium chloride (127 mg/kg) followed by pilocarpine (50 mg/kg) to induce SE. Scopolamine was administered prior to pilocarpine to dampen peripherally mediated pilocarpine actions.
- SE was first identified by presence of large amplitude slow wave EEG activity and then behaviorally using the Racine scale. Racine stage 3 seizures were used as the time-marker for SE onset and subsequent treatment.
- GNX, ALLO, or diazepam were administered via intravenous (IV) bolus injection 15 or 60 minutes after detection of SE onset.

Ganaxolone (GNX) (12 and 15 mg/kg) or allopregnanolone (ALLO) (15 mg/kg) were administered 15 minutes after status epilepticus (SE) onset and EEG seizure response measured for 5 additional hours. GNX at both dose-levels produced a durable reduction in seizure response (≥ 5 hrs). ALLO produced a shorter duration response (≤ 1 hr).

Saporito P2

Ex. 1014 at 1; Patent Owner's Response at 72;
Patent Owner's Sur-Reply at 23.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Ground 4:
Zhang and Marinus's Press Releases Do Not Render Claims 22 and 25-31 Obvious

No Motivation to Combine Zhang with Marinus Press Releases

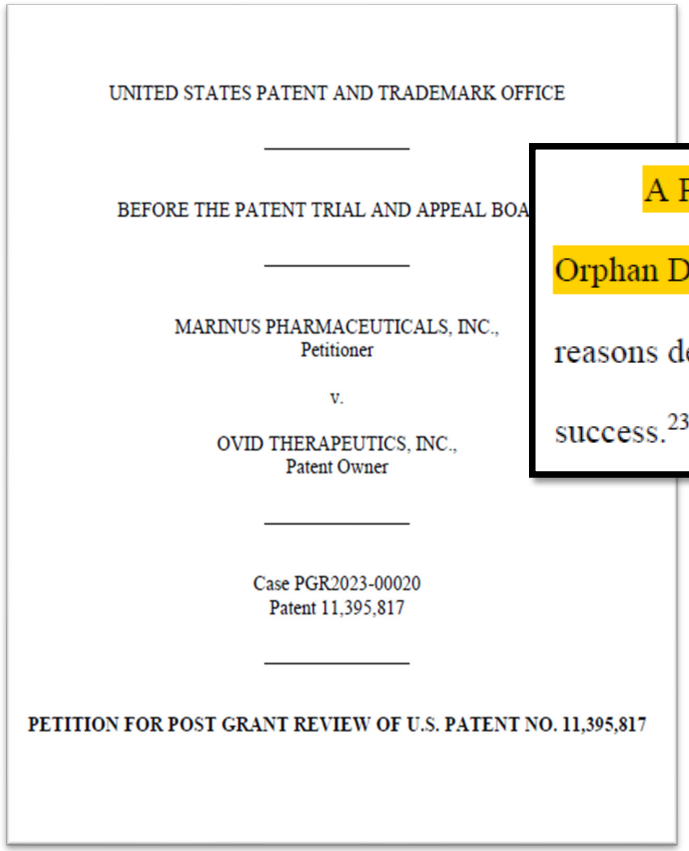


"[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness."

KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 418 (2007) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)).

Patent Owner's Response at 72-73.

Petitioner's Motivation to Combine Is Legally Insufficient



UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOA

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Case PGR2023-00020
Patent 11,395,817

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

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

Petition at 60 (citing Ex. 1003 at ¶124); Patent Owner's Response at 72-73.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Petitioner's Motivation to Combine Is Legally Insufficient

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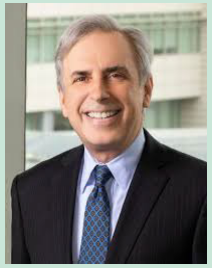
v.

OVID THERAPEUTICS, INC.,
Patent Owner

Case PGR2023-00020
Patent 11,395,817

DECLARATION OF DR. MICHAEL A. ROGAWSKI

1 EX1003



Michael A. Rogawski, Ph.D., M.D.

124. A person of skill in the art reading Zhang would have had reason to look for additional publications related to the treatment of SE by administering ganaxolone to a patient in need. Marinus's Orphan Drug and Phase I Press Releases are such publications.

Ex. 1003 at ¶ 124; Patent Owner's Response at 72-73.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Ovid Therapeutics

Reasonable Expectation of Success



"[W]e held that it was not enough for the [patent challenger] to have shown that a skilled artisan would have pursued the claimed method as a treatment option, but the [patent challenger] also had to show that the skilled artisan would have reasonably expected to achieve success in the treatment."

Eli Lilly & Co. v. Teva Pharms. Int'l GmbH, 8 F.4th 1331, 1344 (Fed. Cir. 2021).



"[P]rior art fails to provide the requisite 'reasonable expectation' of success where it teaches merely to pursue a 'general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.'"

Medichem, S.A. v. Rolabo, S.L., 437 F.3d 1157, 1165 (Fed. Cir. 2006).

Patent Owner's Response at 74-76; Patent Owner's Sur-Reply at 19-20, 23-24.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Ovid Therapeutics

Marinus's Phase 1 Press Release

Marinus Pharmaceuticals Doses First Subject in Phase 1 Clinical Trial for Ganaxolone IV

06/22/2016

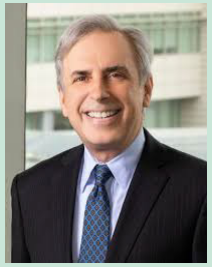
RADNOR, Pa., June 22, 2016 (GLOBE NEWSWIRE) -- Marinus Pharmaceuticals, Inc. (Nasdaq:MRNS), a biopharmaceutical company dedicated to the development of innovative therapeutics to treat epilepsy and neuropsychiatric disorders, today announced that it has dosed the first subject in its Phase 1 clinical trial of ganaxolone IV, an intravenous (IV) formulation of Marinus' CNS-selective GABAA modulator, for the treatment of status epilepticus (SE). The study is designed to evaluate the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of ganaxolone IV in healthy volunteers, with data anticipated in the second half of 2016.

Albena Patroneva, M.D., chief medical officer of Marinus Pharmaceuticals, commented, "Status epilepticus is a life-threatening medical emergency associated with high mortality and limited treatments. Typically, single or combination IV antiepileptic drugs are used in an attempt to break the seizures, however there are approximately 45,000 patients in the U.S. who do not respond to treatment and progress to established SE. Our preclinical research suggests ganaxolone IV could be a promising therapeutic in this difficult to treat seizure disorder, especially after first-line benzodiazepine treatment fails to halt the seizures. We look forward to reporting the results on this Phase 1 study later this year."

Ex. 1022 at 1; Patent Owner's Response at 74-75;
Patent Owner's Sur-Reply at 23-24; Ex. 2014 at ¶¶ 149, 158.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Marinus's Phase 1 Press Release



Michael A. Rogawski, Ph.D., M.D.

Q. Does the document state that this Phase I clinical trial evaluated the efficacy of ganaxolone IV in treating SE?

A. Well, I don't see any words to that effect here.

Q. You would agree that the last sentence of this first paragraph says that ganaxolone IV was administered to healthy volunteers in efforts Phase I clinical trials?

A. Yes.

Q. And here "healthy volunteers" means that the subjects did not have SE?

A. I think that's a fair assumption, if they used the term healthy volunteers, yes.

Ex. 2015 at 127:19-23, 128:5-13; Patent Owner's Sur-Reply at 24.

Phase 1 Dosing ≠ Reasonable Expectation



REVIEW

Issues for new antiepilepsy drug development

Michele Simonato[a,b], Jacqueline A. French[c], Aristea S. Galanopoulou[d], and Terence J. O'Brien[e,f]

Purpose of review
Preclinical research in epileptology has been very successful in producing effective drugs. Unfortunately, however, seizures are still not adequately controlled in a third of the affected individuals, and comorbidities still impose a major burden on the quality of life. New preclinical and clinical drug development strategies are needed to identify drugs that target these unmet medical needs.

Recent findings
Even in recent years, the antiseizure approach based on screenings has contributed to the identification of new drugs. Thus, it should not be abandoned. However, we propose that a radically new approach, specifically designed to tackle the existing gaps in care, should be developed to complement the traditional screening. This new approach will require integrated strategies for preclinical screening and experimental trial design. In this review, we will attempt to address some of the issues that must be resolved to engage this effort. Are there suitable models to tackle the unmet therapeutic needs in epilepsy? Are there ways to de-risk the transition from preclinical to clinical studies? Are there ways to improve the efficiency of clinical trials and to design ad hoc trials for the unmet therapeutic needs?

Summary
Development and validation of a new, integrated strategy for antiepilepsy drug development is needed to identify truly innovative drugs.

Keywords
antiepileptogenesis, antiseizure drug, biomarker, comorbidity, disease modification

INTRODUCTION

Preclinical research in epileptology has been very successful in producing effective drugs. Since the identification of phenytoin using maximal electroshock (MES) and, subsequently, of trimethadione using subcutaneous pentylenterazole (PTZ), these predictive seizure models have been used for decades, allowing the development of many effective drugs that prevent seizures in approximately 70% of the patients. However, although all epileptic syndromes share the common symptom of seizures, they dramatically differ in terms of cause, other symptomatology, natural history, and sensitivity to available drug treatments, and all available antiepileptic drugs (AEDs) are symptomatic agents that may control the seizures but do not modify the disease [1,2**]. Thus, we will avoid here the commonly used term AEDs and, to describe drug effects, we will use instead the words 'antiseizure' for symptomatic effects, 'antiepileptogenic' for prevention and cure, and 'antiepilepsy' as a general term [2**].

Screening programs based on the classic acute seizure models (MES and PTZ), more recently integrated with other models like kindling and 6 Hz electrical stimulation, continue to identify new antiseizure drugs. For example, the Anticonvulsant Screening Program (ASP) of the American National Institutes for Neurological Disorders and Stroke (NINDS) has tested more than 30 000 potential drugs, identifying or contributing to the identification of at least nine new drugs [3]. Availability of these new drugs has expanded the therapeutic armamentarium and offered alternatives in patients

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Curr Opin Neurol 2013, 26:195–200
DOI:10.1097/WCO.0b013e32835ele29

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> Another important consideration is the frequency of failures in the clinical development. The success rate of phase III clinical studies for AEDs has gradually declined to about 10%. As a result, there is increasing skepticism regarding the possibility of identifying truly transformational new drugs for epilepsy using conventional screening and concern about the high risk associated with the clinical phase, with interest of the pharmaceutical industry in embarking on the development of new AEDs reduced dramatically in the past few years.

Ex. 2020 at 2; Patent Owner's Response at 75;
Patent Owner's Sur-Reply at 24; Ex. 2014 at ¶¶ 151, 160.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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Marinus v. Ovid - PGR2023-00020

Marinus's Orphan Drug Press Release

Marinus Pharmaceuticals Receives FDA Orphan Drug Designation for Ganaxolone IV to Treat Status Epilepticus

04/15/2016

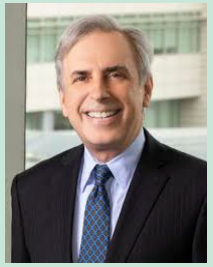
RADNOR, Pa., April 15, 2016 (GLOBE NEWSWIRE) -- Marinus Pharmaceuticals, Inc. (Nasdaq:MRNS), a biopharmaceutical company dedicated to the development of innovative therapeutics to treat epilepsy and neuropsychiatric disorders, today announced that the U.S. Food and Drug Administration (FDA) has granted Orphan Drug Designation to the intravenous (IV) formulation of its CNS-selective $GABA_A$ modulator, ganaxolone, for the treatment of status epilepticus. A Phase 1 clinical trial evaluating the safety, tolerability and pharmacokinetics of ganaxolone IV is expected to initiate in the first half of 2016.

"Status epilepticus is a life-threatening condition, associated with high mortality and if not treated immediately, can result in brain damage, cognitive impairment and death," remarked Christopher M. Cashman, Chief Executive Officer of Marinus Pharmaceuticals. "We are pleased to receive the Orphan Drug Designation for ganaxolone IV in this difficult to treat seizure disorder with limited treatment options."

Orphan Drug Designation is granted by the FDA Office of Orphan Products Development (OOPD) to novel drugs or biologics that treat a rare disease or condition affecting fewer than 200,000 patients in the U.S. The designation provides the drug developer with a seven-year period of U.S. marketing exclusivity, as well as tax credits for clinical research costs, the ability to apply for annual grant funding, clinical research trial design assistance and waiver of Prescription Drug User Fee Act (PDUFA) filing fees.

Ex. 1011 at 1; Patent Owner's Response at 74-75; Patent Owner's Sur-Reply at 24; Ex. 2014 at ¶ 149, 158.

Marinus's Orphan Drug Press Release



Michael A. Rogawski, Ph.D., M.D.

Q. This statement does not state that ganaxolone is effective for treating SE in humans, does it?

A. It states that they were granted orphan drug designation to the intravenous formulation of ganaxolone for the treatment of SE.

Q. And it does not mention that ganaxolone is effective for treating SE in humans; is that right?

A. Well, again, it indicates that they were granted orphan drug designation for the treatment of status epilepticus.

Q. And it does not say that ganaxolone is effective for treating SE in humans, does it?

A. I don't see the word "effective" in that statement that you read.

Ex. 2015 at 128:5-13; Patent Owner's Sur-Reply at 24.

Orphan Drug Designation ≠ Reasonable Expectation

Fermaglich and Miller
Orphanet Journal of Rare Diseases (2023) 18:163
https://doi.org/10.1186/s13023-023-02790-7

Orphanet Journal of Rare Diseases

RESEARCH Open Access

A comprehensive study of the rare diseases and conditions targeted by orphan drug designations and approvals over the forty years of the Orphan Drug Act

Lewis J. Fermaglich[1]* and Kathleen L. Miller[1]

Abstract

Background Rare diseases affect more than 30 million Americans. The passage of the Orphan Drug Act (ODA) in the United States in 1983 represented a launching point for a rare disease drug development revolution for these patients. Financial incentives provided by the ODA through its Orphan Drug Designation Program, in addition to remarkable scientific advances over the past 40 years, have led to hundreds of drug approvals for rare diseases. Our research examines the rare diseases that have been targeted by orphan drug designations and subsequent approvals since the law was enacted.

Methods Using an internal FDA database, we classified and analyzed all orphan drug designations and approvals from 1983 to 2022 by disease and therapeutic area.

Results Over the 40 years of the ODA, 6,340 orphan drug designations were granted, representing drug development for 1,079 rare diseases. Additionally, 882 of those designations resulted in at least one FDA approval for use in 392 rare diseases. Much of this development has been concentrated in oncology as seven of the top ten most designated and approved diseases were rare cancers.

Conclusions Researchers have estimated that there may be 7000–10,000 rare diseases that have been identified and described. Based on our study, we can conclude that around 5% of rare diseases have an FDA-approved drug and up to 15% of rare diseases have at least one drug that has been developed and shown promise in their treatment, diagnosis or prevention. Funding of basic and translational science for rare disease drug development should continue in order to bring therapies to the millions of affected patients who remain without treatment options.

Background

The Orphan Drug Act (ODA) was signed into law in the United States on January 4th, 1983 [1]. Drug development for rare diseases can be commercially risky, and prior to this legislation, only approximately two drugs per year had been approved by the US Food and Drug Administration (FDA) for rare diseases [2]. Now, four decades later, hundreds of "orphan" drugs have been approved for use in the 7000–10,000 diseases and conditions that are considered rare.[3].

In addition to establishing the Orphan Products Grants Program, the ODA created the Orphan Drug Designation Program, which was designed to provide financial incentives for companies developing drugs and biologics for rare diseases and conditions [4]. These

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BMC

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As of December 31, 2022, OOPD had granted 6340 orphan drug designations which represented 1079 diseases.

From 1983 to 2022, there were 1122 total approvals (including new molecule, indication, and formulation approvals) of orphan-designated products. There were 882 initial approvals (first approval falling under one orphan designation) representing 392 rare diseases. Fourteen percent of designations resulted in at least one orphan drug approval.

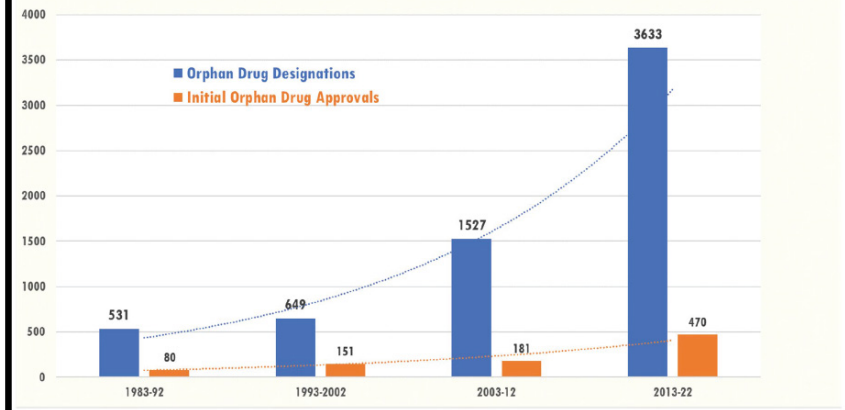


Fig. 1 Total orphan drug designations (n = 6340) and initial orphan drug approvals (n = 882) by decade, 1983–2022

Ex. 2019 at 3; Patent Owner's Response at 75;
Patent Owner's Sur-Reply at 24; Ex. 2014 at ¶¶ 150, 159.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Ovid Therapeutics

Ground 7:
Claims 22 and 25-31 Are Enabled

Reasonable Amount of Experimentation



"[A] specification may call for a reasonable amount of experimentation to make and use a patented invention. What is reasonable in any case will depend on the nature of the invention and the underlying art."

Amgen Inc. v. Sanofi, 598 U.S. 594, 612 (2023)
(citing *Minerals Separation v. Hyde*, 242 U.S. 261, 270-71 (1916)).

Patent Owner's Response at 76-77; Patent Owner's Sur-Reply at 25.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Ovid Therapeutics

Wands Factors for Determining Undue Experimentation



"Factors to be considered in determining whether a disclosure would require undue experimentation . . . include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

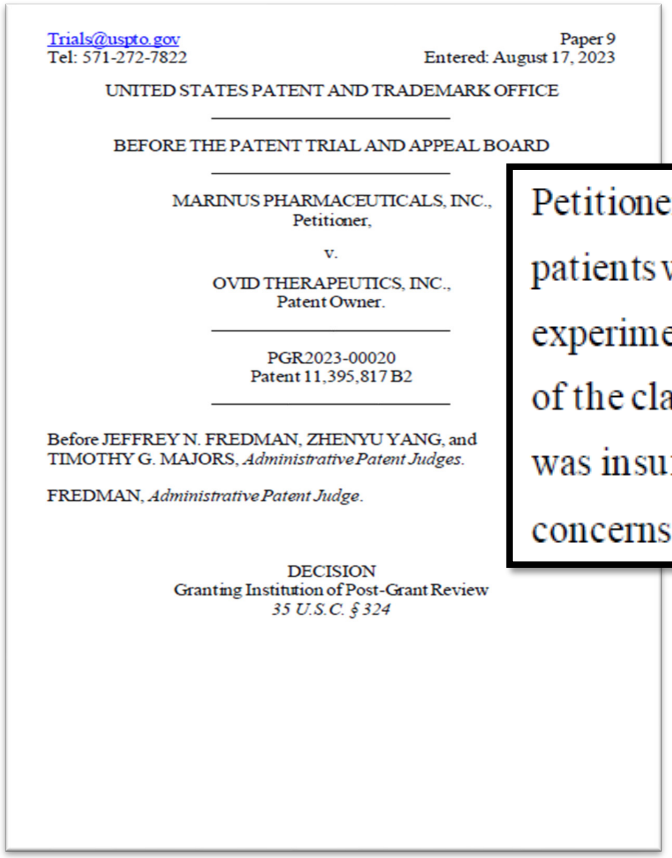
In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988).

Patent Owner's Response at 76-77.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Ovid Therapeutics

Petitioner Provides No Evidence for 7 of 8 *Wands* Factors



Trials@uspto.gov
Tel: 571-272-7822

Paper 9
Entered: August 17, 2023

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MARINUS PHARMACEUTICALS, INC.,
Petitioner,

v.

OVID THERAPEUTICS, INC.,
Patent Owner.

PGR2023-00020
Patent 11,395,817 B2

Before JEFFREY N. FREDMAN, ZHENYU YANG, and TIMOTHY G. MAJORS, *Administrative Patent Judges*.

FREDMAN, *Administrative Patent Judge*.

DECISION
Granting Institution of Post-Grant Review
35 U.S.C. § 324

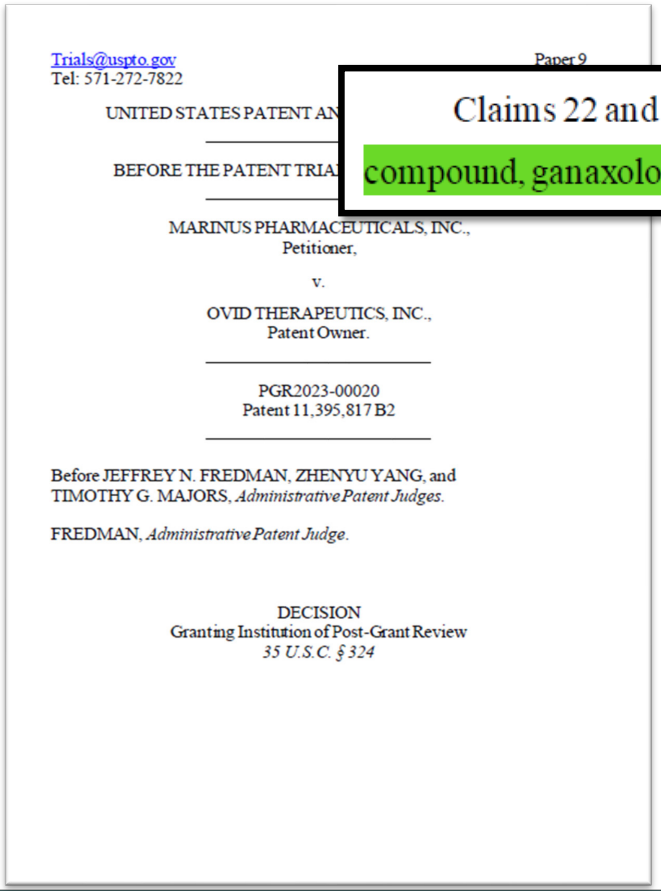
Petitioner provides no evidence that the treatment of status epilepticus patients with ganaxolone was unpredictable, that a large quantity of experimentation was necessary to show ganaxolone efficacy, that the scope of the claim was unduly broad, that the guidance of the '817 specification was insufficient guidance for the claim scope, or that the prior art established concerns regarding the claimed treatment. And while Petitioner does point

Institution Decision, Paper 9 at 47; Patent Owner's Response at 76-77; Patent Owner's Sur-Reply at 25.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Ovid Therapeutics

Claims 22 and 25-31 Are Narrowly Drawn



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Paper 9

UNITED STATES PATENT AN

BEFORE THE PATENT TRIA

MARINUS PHARMACEUTICALS, INC.,
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v.

OVID THERAPEUTICS, INC.,
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PGR2023-00020
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Before JEFFREY N. FREDMAN, ZHENYU YANG, and TIMOTHY G. MAJORS, *Administrative Patent Judges.*

FREDMAN, *Administrative Patent Judge.*

DECISION
Granting Institution of Post-Grant Review
35 U.S.C. § 324

Claims 22 and 25–31 are narrowly drawn to a particular drug compound, ganaxolone, and a particular disease, status epilepticus.

'817 Patent Claims

21. 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.

22. The method of claim **21** wherein the pharmaceutical composition provides improvement to the patient after administration for more than 8 hours.

Institution Decision, Paper 9 at 47; Ex. 1001 at 40:8-15; Patent Owner's Response at 77.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Dr. Sankar's Statements Are Not Probative of Enablement

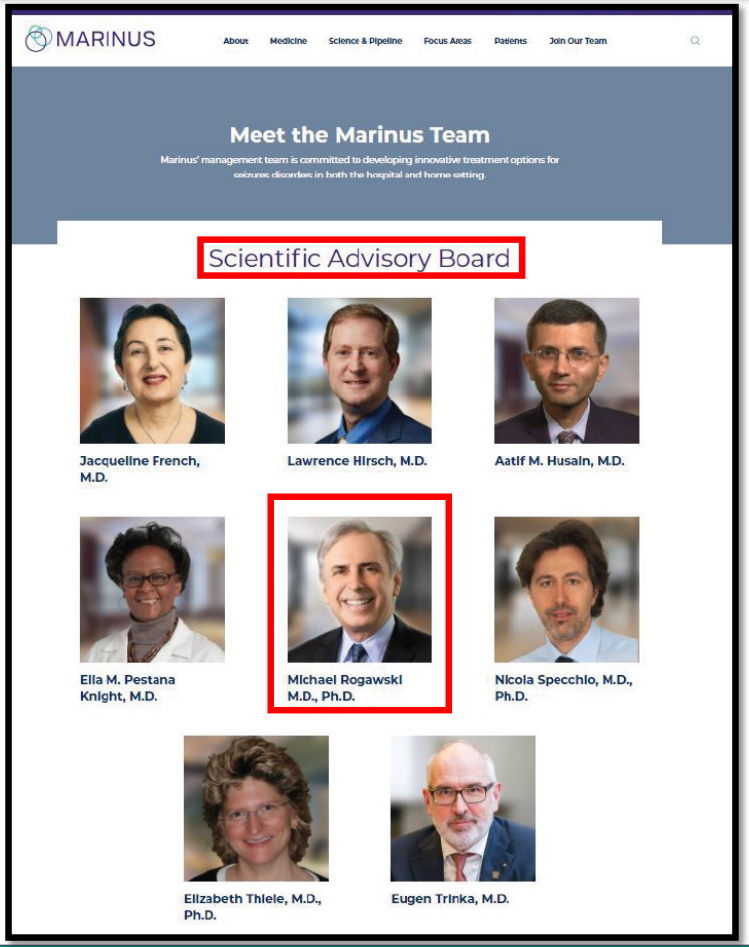


Raman Sankar, M.D., Ph.D.

19	Q.	You're not offering any opinions with
20	respect to enablement?	
21	A.	No.
22	Q.	Are you familiar with the concept of
23	enablement in patent law?	
24	A.	No. Explain that to me.

Ex. 1042, 41:19-24; Patent Owner Sur-Reply at 25.

Dr. Rogawski's Undisclosed Role with Marinus

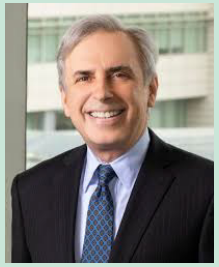


Ex. 2012 at 1; Patent Owner's Response at 13-14; Patent Owner's Sur-Reply at 2-3.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Ovid Therapeutics

Dr. Rogawski's Undisclosed Role with Marinus



Michael A. Rogawski, Ph.D., M.D.

Q. Apart from being retained by Marinus for this matter, do you do any other work for Marinus?

A. I do.

Q. And what is that other work?

A. I'm currently a member of the scientific advisory board for Marinus.

Q. And how long have you been on Marinus' scientific advisory board?

A. I don't know exactly. It's been several years.

Q. And what are your duties as a member of Marinus' scientific advisory board?

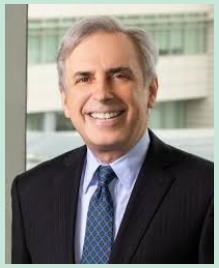
A. I participate in occasional meetings, these have generally been over Zoom recently, where the company provides updates on their research and the members of the advisory board provide commentary.

Q. And is that scientific substantive commentary?

A. Yes.

Ex. 2015 at 33:1-22; Patent Owner's Response at 13.

Dr. Rogawski's Undisclosed Role with Marinus



Michael A. Rogawski, Ph.D., M.D.

Q. Are you compensated at all for your time working on the scientific advisory board at Marinus?

A. I am.

Q. And what is that compensation?

A. I don't know exactly what it is.

Ex. 2015 at 34:6-11; Patent Owner's Response at 13.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Ovid Therapeutics

Dr. Rogawski's Undisclosed Consulting with Ovid

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MARINUS PHARMACEUTICALS, INC.,
Petitioner

v.

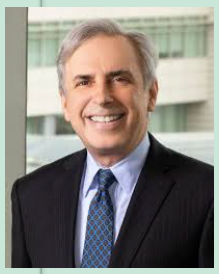
OVID THERAPEUTICS, INC.,
Patent Owner

Case PGR2023-00020
Patent 11,395,817

SUPPLEMENTAL DECLARATION OF DR. MICHAEL A. ROGAWSKI

MARINUS 1041
Marinus v. Ovid
PGR2023-00020

1



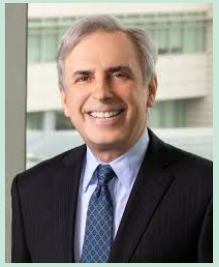
Michael A. Rogawski, Ph.D., M.D.

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.

Ex. 1041 at ¶ 16; Patent Owner's Sur-Reply at 2-3.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Dr. Rogawski's Undisclosed Consulting with Ovid



Michael A. Rogawski, Ph.D., M.D.

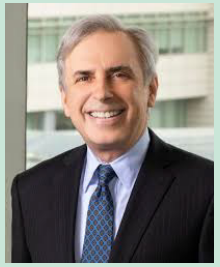
THE WITNESS: If I could maybe revise my last statement, all of my comments related to Ovid's research on ganaxolone, I want to make that very clear, that every one of the statements that I just made about Ovid being involved in research is with respect to ganaxolone for the treatment of status epilepticus. I want to make that very clear.

Q. So, in paragraph 16, where you say, "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," you're saying that's only referring to ganaxolone?

A. I'm not sure what I had in my mind at that time, but I can say now that I -- my view is that Ovid is not engaged in research on ganaxolone for the treatment of status epilepticus and never has been.

Ex. 2024 at 29:15-21; 29:23-30:7; Patent Owner's Sur-Reply at 3.

Dr. Rogawski's Undisclosed Consulting with Ovid



Michael A. Rogawski, Ph.D., M.D.

Q. Have you done any consulting work for Ovid?

A. Not any paid consulting, no.

Q. Have you been on any advisory boards for Ovid?

A. I -- oh, yes, yes. I -- I was on an advisory board for Ovid.

Q. And what did that advisory board relate to?

A. That did relate to -- yes, that did relate to status epilepticus, but not with ganaxolone.

Q. And you don't mention this work that you did with Ovid related to status epilepticus in your supplemental declaration; is that correct?

A. I don't, no.

Ex. 2024 at 31:1-12; Patent Owner's Sur-Reply at 3.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE