PATENT
Attorney Docket No. 761996.110010

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	
	)	
David CZEKAI	)	Group Art Unit: To Be Assigned
	)	
Application No.: To Be Assigned	)	Examiner: To Be Assigned
	)	
Filed: Herewith	)	Confirmation No.: To Be Assigned
	)	
For: GANAXOLONE FOR USE IN TREATMENT OF STATUS EPILEPTICUS	)	

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

Commissioner:

PRELIMINARY AMENDMENT

Amendments to the Specification begin on page 2 of this paper.

Amendments to the Claims begin on page 3 of this paper.

Remarks/Arguments begin after the Amendments.

AMENDMENTS TO THE SPECIFICATION

Please amend the related applications paragraph at paragraph [0001] as follows:

The present application is a Continuation of International Patent Application No.: PCT/US2020/044843, filed on August 4, 2020, which claims the benefit of U.S. Provisional Application No. 62/882,648 filed on August 5, 2019, ~~the entire contents~~ each of which are incorporated herein by reference in their entirety.

AMENDMENT TO THE CLAIMS

1-54. (Cancelled)

55. (New) A method of treating status epilepticus (SE), comprising administering to a subject in need thereof an effective amount of ganaxolone to suppress SE for a period of at least 8 hours, wherein the effective amount of ganaxolone is administered as an intravenous bolus plus continuous infusion to produce and maintain a ganaxolone plasma concentration of at least about 500 ng/ml for at least about 8 hours.

56. (New) The method of claim 55, wherein the intravenous bolus comprises about 5 mg to about 40 mg of ganaxolone.

57. (New) The method of claim 56, wherein the intravenous bolus comprises about 30 mg of ganaxolone.

58. (New) The method of claim 55, wherein the continuous intravenous infusion comprises infusion of about 20 mg of ganaxolone per hour to about 80 mg of ganaxolone per hour.

59. (New) The method of claim 58, wherein about 80 mg of ganaxolone per hour are infused into the subject at the initiation of the continuous intravenous infusion and for at least about 2 hours thereafter.

60. (New) The method of claim 59, wherein the amount of ganaxolone infused into the subject by the continuous intravenous infusion is decreased from about 80 mg per hour to about 40 mg per hour after about 2 hours.

61. (New) The method of claim 60, wherein the 40 mg per continuous intravenous infusion is administered for about 6 hours to about 10 hours.

62. (New) The method of claim 61, wherein the amount of ganaxolone infused into the subject by the continuous intravenous infusion is then decreased from about 40 mg per hour to about 20 mg per hour.

63. (New) The method of claim 62, wherein the 20 mg per hour continuous intravenous infusion is administered for about 12 hours to about 24 hours.

64. (New) The method of claim 55, wherein a continuous intravenous infusion of ganaxolone is initiated periprocedurally with the intravenous bolus and the continuous intravenous infusion comprises: a) an infusion of about 80 mg ganaxolone per hour for about 2 hours, then b) an infusion of about 40 mg ganaxolone per hour for about 6 hours to about 10 hours, then c) an infusion of about 20 mg ganaxolone per hour for about 12 hours to about 24 hours, and optionally wherein the 20 mg per hour infusion is increased to up to 45 mg per hour starting at about 24 hours after initiating the continuous intravenous infusion for up to about 12 hours.

65. (New) The method of claim 55, wherein the intravenous bolus produces a ganaxolone plasma concentration in the subject of at least about 500 ng/ml to about 1000 ng/ml.

66. (New) The method of claim 55, wherein the continuous intravenous infusion produces a ganaxolone plasma concentration in the subject of at least about 500 ng/ml to about 1000 ng/ml for at least about 8 hours.

67. (New) The method of claim 55, wherein the intravenous bolus is administered to the subject for about 1 minute to about 5 minutes.

68. (New) The method of claim 64, wherein the continuous intravenous infusion is administered for at least about 8 hours to about 36 hours after the initiation of the continuous intravenous infusion.

69. (New) The method of claim 68, wherein the treatment period is about 36 hours after the initiation of the continuous intravenous infusion.

70. (New) The method of claim 64, further comprising a taper period for about 12 hours, wherein the taper period starts at about 36 hours from the initiation of the continuous intravenous infusion.

71. (New) The method of claim 55, wherein the intravenous bolus plus continuous infusion produces and maintains a ganaxolone plasma concentration of at least about 500 ng/ml for at least about 8 hours to about 12 hours.

72. (New) The method of claim 55, wherein the subject as refractory status epilepticus.

73. (New) The method of claim 55, wherein the bolus plus the continuous infusion results is a reduction of seizure burden to about 20% or less, or a reduction of seizure burden of at least about 50% relative to the seizure burden during the 30 minutes immediately prior to administration of the bolus.

74. (New) The method of claim 73, wherein the reduction of seizure burden persist for at least about 8 hours to about 12 hours.

REMARKS

The specification has been amended to update the Related Applications paragraph.

Claims 1-54 have been cancelled. New claims 55-74 have been added.

Applicant submits herewith a Request for Prioritized Examination under 37 C.F.R. § 1.102(e) and a Request for First Action Interview.

Although Applicant does not believe any fees are due, the Commissioner is hereby authorized to charge any deficiency in the fees filed, asserted to be filed, or which should have been filed herewith to our Deposit Account No. 50-1349.

Respectfully submitted,
HOGAN LOVELLS US LLP

/Robert H. Underwood, Reg. No. 45,170/

Robert H. Underwood
Registration No. 45,170

Date: February 26, 2021

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/186,569	02/26/2021	David CZEKAI	761996.110010	4113

24633 7590 04/20/2021

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WASHINGTON, DC 20004

EXAMINER	
AZPURU, CARLOS A	

ART UNIT	PAPER NUMBER
1617	

NOTIFICATION DATE	DELIVERY MODE
04/20/2021	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

HLUSDocketing@hoganlovells.com
dcptopatent@hoganlovells.com

Office Action Summary	Application No. 17/186,569	Applicant(s) CZEKAI et al.	
	Examiner CARLOS A AZPURU	Art Unit 1617	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL.** 2b) ☑ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 55-74 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 55-74 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☑ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date 04012021.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

DETAILED ACTION

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

A preliminary amendment was filed on 02/26/2021.

Information Disclosure Statement

An information disclosure statement was filed on 04/01/2021.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112(a):

> (a) IN GENERAL.—The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor or joint inventor of carrying out the invention.

The following is a quotation of the first paragraph of pre-AIA 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 55-64, 67-74 are rejected under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph, because the specification, while being enabling for a bolus administration up to 1000 ng/mL, does not reasonably provide enablement for all doses above 500 ng/mL. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The specification is clear that plasma levels above 1000 ng/ML should be avoided because they cause anesthesia (see page 5, [0012]). Correction is requested.

The following is a quotation of 35 U.S.C. 112(b):
(b) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 72 is rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor (or for applications subject to pre-AIA 35 U.S.C. 112, the applicant), regards as the invention.

Claim 72 appears to be missing a word or two, and is indefinite because it is unclear what is intended. Correction is requested.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

Claim 55-74 is/are rejected under 35 U.S.C. 103 as being unpatentable over US 2016/0228454 A1 (Marimus).

Marimus teaches a method for treating status epilepticus as well as other types of seizure disorders [0070]. An injectable ganaxolone formulation also comprising sulfobutylether-Beta-cyclodextrin and water [0076] and [0022] is administered as one or more bolus injections. The method of treatment maintains a plasma concentration of ganaxolone from about 50 ng to about 3500 ng/ml [0090]. Cmax for the treatment is 100 ng/mL to about 1000 ng/mL, after which an infusion is administered over time giving a constant dose sufficient to provide a plasma concentration which is 40% of Cmax for a period of time between 30 mins and 120 hours (5 days) [0089]. This infusion process lasts much longer than the bolus administration, and eliminates or suppresses seizure activity [0070] and [0089]. The plasma concentration range of ganaxolone includes values from 500 ng/mL to 3500 ng/mL (5 grams/mL to 35 grams/mL). The dosage for the infusion is 40% of Cmax which translates to 4 mg/mL to 40 mg/mL. Various forms of status epilepticus such as refractory status epilepticus are recited at [0089]. While Marimus does not recite the same periods of time for bolus or infusion, Marimus is clear in its teaching that ganaxolone is used for treatment of various forms status epilepticus by administering a bolus injection, followed by a continuous infusion of ganaxolone which maintains a therapeutic level which suppresses or eliminates seizure activity. Regarding the tapering period, any infusion will have this feature since the amount left becomes smaller and smaller until all the infusion solution is used up. Therefore a tapering period is inherent to any infuion treatment. Marimus is silent as to the percentage of suppression as well. However, since Marimus clearly teaches the method of treatment which attains a therapeutically effective amount in the plasma, therapeutic protocols as to duration of both bolus and infusion, as well as exact dosage would be parameters well recognized by the ordinary medical practitioner. Further, since Marimus teaches the claimed method of treatment, the ordinary practitioner would further have a reasonable expectation of similar suppression or elimination of seizure activity. As such, the instantly claimed method of treating status epilepticus would have been obvious to one of ordinary skill in the art at the time of filing given the teachings of Marimus.

Conclusion

No claims are allowed.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CARLOS A AZPURU whose telephone number is (571)272-0588. The examiner can normally be reached on 9 am- 3 pm, 4 pm-8pm.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann R Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see https://ppair-my.uspto.gov/pair/PrivatePair. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/CARLOS A AZPURU/
Primary Examiner, Art Unit 1617

caz

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	
	)	
David CZEKAI	)	Group Art Unit: 1617
	)	
Application No.: 17/186,569	)	Examiner: Carlos A., Azpuru
	)	
Filed: February 26, 2021	)	Confirmation No.: 4113
	)	
For: GANAXOLONE FOR USE IN TREATMENT OF STATUS EPILEPTICUS	)	

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

Commissioner:

REPLY TO NON-FINAL OFFICE ACTION

The paper is filed in response to the Non-Final Office Action mailed April 20, 2021. Please amend the above-identified application as directed herein.

Reconsideration and further examination are respectfully requested.

Amendments to the Claims begin on page 2.

Remarks/Arguments follow the amendments section of this paper.

AMENDMENT TO THE CLAIMS

This listing of claims will replace all prior versions and listings of claims in the application:

1-54. (Cancelled)

55. (Currently Amended) A method of treating status epilepticus (SE), comprising administering to a subject in need thereof an effective amount of ganaxolone to suppress SE ~~for a period of at least 8 hours~~, wherein the effective amount of ganaxolone is administered as an intravenous bolus plus continuous infusion to produce and maintain a ganaxolone plasma concentration of ~~at least~~ about 500 ng/ml to about 1000 ng/ml for ~~at least~~ about 8 hours to about 12 hours.

56. (Previously Presented) The method of claim 55, wherein the intravenous bolus comprises about 5 mg to about 40 mg of ganaxolone.

57. (Previously Presented) The method of claim 56, wherein the intravenous bolus comprises about 30 mg of ganaxolone.

58. (Previously Presented) The method of claim 55, wherein the continuous intravenous infusion comprises infusion of about 20 mg of ganaxolone per hour to about 80 mg of ganaxolone per hour.

59. (Previously Presented) The method of claim 58, wherein about 80 mg of ganaxolone per hour are infused into the subject at the initiation of the continuous intravenous infusion and for at least about 2 hours thereafter.

60. (Previously Presented) The method of claim 59, wherein the amount of ganaxolone infused into the subject by the continuous intravenous infusion is decreased from about 80 mg per hour to about 40 mg per hour after about 2 hours.

61. (Currently Amended) The method of claim 60, wherein the 40 mg per hour continuous intravenous infusion is administered for about 6 hours to about 10 hours.

62. (Currently Amended) The method of claim 61, further comprising continuing to administer ganaxolone by the continuous intravenous infusion, wherein the amount of ganaxolone infused ~~into the subject by the continuous intravenous infusion~~ is ~~then~~ decreased ~~from about 40 mg per hour~~ to about 20 mg per hour.

63. (Previously Presented) The method of claim 62, wherein the 20 mg per hour continuous intravenous infusion is administered for about 12 hours to about 24 hours.

64. (Currently Amended) The method of claim [[55]]56, wherein a continuous intravenous infusion of ganaxolone is initiated periprocedurally with the intravenous bolus and the continuous intravenous infusion comprises: a) an infusion of about 80 mg ganaxolone per hour for about 2 hours, then b) an infusion of about 40 mg ganaxolone

per hour for about 6 hours to about 10 hours, then c) an infusion of about 20 mg ganaxolone per hour for about 12 hours to about 24 hours~~, and optionally wherein the 20 mg per hour infusion is increased to up to 45 mg per hour starting at about 24 hours after initiating the continuous intravenous infusion for up to about 12 hours~~.

65. (Currently Amended) The method of claim 55, wherein the intravenous bolus produces a ganaxolone plasma concentration in the subject of ~~at least~~ about 500 ng/ml to about 1000 ng/ml.

66. (Cancelled)

67. (Currently Amended) The method of claim [[55]]64, wherein the intravenous bolus is administered to the subject for about 1 minute to about 5 minutes.

68. (Cancelled)

69. (Cancelled)

70. (Currently Amended) The method of claim 64, further comprising a taper period ~~for~~ of about 12 hours~~, wherein the taper period starts at about 36 hours from the initiation of the continuous intravenous infusion~~.

71. (Cancelled)

72. (Currently Amended) The method of claim 55, wherein the subject has refractory status epilepticus.

73. (Cancelled)

74. (Cancelled)

75. (New) The method of claim 55, wherein the amount of ganaxolone infused into the subject by the continuous infusion is decreased at least once while the ganaxolone plasma concentration of about 500 ng/ml to about 1000 ng/ml is maintained.

76. (New) The method of claim 55, wherein the total daily dose of ganaxolone administered is from about 500 mg to about 900 mg.

77. (New) The method of claim 75, further comprising continuing to administer ganaxolone by continuous intravenous infusion after the ganaxolone plasma concentration of about 500 ng/ml to about 1000 ng/ml has been maintained for about 8 hours to about 12 hours, and wherein the amount of ganaxolone that is infused is reduced.

78. (New) The method of claim 64, wherein the subject has refractory status epilepticus.

79. (New) The method of claim 77, wherein the subject has refractory status epilepticus.

80. (New) The method of claim 57, wherein a continuous intravenous infusion of ganaxolone is initiated periprocedurally with the intravenous bolus and the continuous intravenous infusion comprises: a) an infusion of about 80 mg ganaxolone per hour for about 2 hours, then b) an infusion of about 40 mg ganaxolone per hour for about 6 hours to about 10 hours, then c) an infusion of about 20 mg ganaxolone per hour for about 12 hours to about 24 hours.

81. (New) The method of claim 80, wherein the subject has refractory status epilepticus.

REMARKS

I. CLAIM STATUS

With entry of this paper claims 55-65, 67, 70, 72, and 75-81 are pending and under examination. Claims 1-54 were previously cancelled, and claims 66, 68, 69, 71, 73, and 74 are cancelled herein, all without prejudice or disclaimer. Claim 55 is amended to recite that a ganaxolone plasma concentration of about 500 ng/ml to about 1000 ng/ml is maintained for about 8 to about12 hours, as was discussed during the examiner interview on June 24, 2021. Other claims are amended to provide greater clarity and new claims 75 to 81 are added. Exemplary support for the amended claims and new claims can be found in the as-filed specification at paragraphs [0009], [0012], [0013], [0015], [0020], [0062], [0076], [0077], and [0107].

II. EXAMINER INTERVIEW

Applicant thanks Examiner Azpuru for the telephone interview on June 24, 2021. The Applicant-Initiated Summary dated June 29, 2021, accurately summarizes the substance of the interview.

III. REJECTION UNDER 35 U.S.C. § 112(a) (ENABLEMENT)

Claims 55-64 and 67-74 are rejected under 35 U.S.C. § 112(a), as allegedly not being enabled because the upper limit of the ganaxolone plasma concentration is not recited. Without acquiescing to the rejection and solely to advance prosecution, Application has amended claim 55 to recite a ganaxolone plasma concentration of about 500 ng/ml to about 1000 ng/ml. Applicant respectfully requests reconsideration and withdrawal of the rejection.

IV. REJECTION UNDER 35 U.S.C. § 112(b) (INDEFINETNESS)

Claim 72 is rejected under 35 U.S.C. § 112(b), as allegedly being indefinite because the claim contains a typographical error. Claim 72 has been amended to recite "has" in place of "as." Applicant respectfully requests reconsideration and withdrawal of the rejection.

V. REJECTION UNDER 35 U.S.C. § 103 (OBVIOUSNESS)

The Office has rejected claims 55-74 as allegedly obvious over US Publication No.: 2016/0228454 (the "Prior Art"). Office Action at page 3. According to the Office, the Prior Art allegedly teaches a method for treating status epilepticus ("SE") by administering an injectable ganaxolone formulation. *Id.* at page 4. The Office alleges that the Prior Art discloses a method that comprises administering a bolus, which can provide a C_{max} of 100 ng/ml to 1000 ng/ml followed by an infusion that eliminates or suppresses seizure activity. *Id.* The Office acknowledges that the Prior Art does not recite the same periods of time for the bolus or infusion as are claimed. *Id.*

Applicant thanks the examiner for conducting the interview on June 24, 2021. During the interview the claims and Prior Art were discussed and Dr. Joseph Hulihan explained that the claimed method unexpectedly "breaks"[1] SE with exposure to ganaxolone for a period of time that was much lower expected. Dr. Hulihan also explained that this beneficially results in reduced drug exposure and improved safety. A Declaration under 37 C.F.R. § 1.132 by Dr. Hulihan that confirms the information he shared during the interview is filed concurrently herewith. The "Hulihan Declaration."

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[1] Dr. Hulihan explains that the term "breaking" SE refers to a treatment effect that cause seizure to stop and not rapidly reoccur when the plasma concentration of ganaxolone falls below about 500ng/ml or administration of ganaxolone is terminated. Hulihan Declaration at ¶ 7-8

The Prior Art discloses intravenous ganaxolone formulations comprising sulfobutyl ether-β-cyclodextrin and water. *See*, ¶ [0030] *et seq.* The prior art discloses that the formulations can be used to treat a wide variety of including a variety of seizure disorders, such as SE, PCDH19 female pediatric epilepsy and Lennox-Gastaut syndrome among others, stroke, traumatic brain injury, neurodegenerative disorders, and seizures that are complications of inflammatory disorders and lysosomal storage disorders. ¶ [0070] - [0074]. The prior art discloses a variety of ways to administer the formulations including a single bolus injection (¶ [0075], [0082]-[0085]), multiple boli over 1 to 10 days at intervals of 1 to 24 hours (¶ [0076], [0086]), single or multiple injections (¶ [0075]), intravenous infusion with or without a prior bolus (¶ [0077], [0087]), and bolus plus intravenous infusion (¶ [0077], [0088]-[0090]). Nothing in the Prior Art describes which method to select to treat SE nor specific parameters for the method, let alone maintaining a ganaxolone plasma concentration of about 500 ng/ml to 1000 ng/ml for about 8 to about 12 hours.

Assuming, for the sake of argument alone, that a person of ordinary skill in the art were to focus on the disclosure relating to administering the formulation as a bolus plus continuous infusion, they would have followed the guidance provided in the Prior Art, which discloses that the infusion should be administered for "1 to 10 consecutive days." ¶ [0088] - [0089].

The claimed method differs from the disclosure of the Prior Art by requiring the ganaxolone plasma concentration be maintained at about 500 ng/ml to about 1000 ng/ml for a short period of time of about 8 hours to about 12 hours. As explained by Dr. Hulihan, the *combination* of ganaxolone plasma concentration and time period are

important to for the therapeutic effect of "breaking" SE. Hulihan Declaration at ¶ 8 – 10. Dr. Hulihan explained that it was surprising and unexpected that SE could be broken using ganaxolone at that serum concentration for such a short period of time. Hulihan Declaration at ¶ 10.

Importantly, and as explained by Dr. Hulihan, the claimed method provides significant clinical advantages for patients. As shown by the examples in the application and further explained by Dr. Hulihan, the claimed method can effectively break SE. See, FIGs. 3, 5, 7, 9 and 15, and Hulihan Declaration at ¶ 11. Further, the method provides improved safety for patients by limiting exposure to high drug levels to a short period of about 8 to 12 hours, which reduces risk of unwanted adverse events. ¶ 11.

The Prior Art provides no information whatsoever that could reasonably be seen by a person of ordinary skill as suggesting that the claimed method should be investigated, and certainly does not provide the requisite reasonable expectation of success.

For at least these reason, the pending claims would not have been obvious over the Prior Art. Applicant, therefore, respectfully requests reconsideration and withdrawal of this rejection under 35 U.S.C. § 103(a).

VI. CONCLUSION

In view of the foregoing amendments and remarks, Applicant respectfully requests reconsideration of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account No. 50-1349.

Respectfully submitted,

HOGAN LOVELLS US LLP

/Robert H. Underwood, Reg. No. 45,170/

Robert H. Underwood
Registration No. 45,170

Date: July 8, 2021

Please recognize our Customer No. 24633 as our correspondence address

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	
	)	
David CZEKAI	)	Group Art Unit: 1617
	)	
Application No.: 17/186,569	)	Examiner: Carlos A., Azpuru
	)	
Filed: February 26, 2021	)	Confirmation No.: 4113
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For: GANAXOLONE FOR USE IN TREATMENT OF STATUS EPILEPTICUS	)	

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.

4. I submit this Declaration to provide a record of the information that I discussed during the examiner interview held for this patent application on June 24, 2021. Marinus Pharmaceuticals, Inc. will not provide me with any special or additional compensation in exchange for this Declaration, and I have no direct financial interest in the outcome of this patent application.

5. SE is a medical emergency requiring urgent care to avoid permanent brain damage, medical complications or death. SE is a rare condition for which there are a paucity of evidence-based treatments. SE can result from a number of causes such as infection, stroke, trauma and biochemical imbalances. The clinical objective in treating SE is to administer therapy to stop the seizures as quickly and safely as possible. A key objective is that the medication be administered for a limited duration to stop the seizures and that the effect lasts beyond discontinuation of the medication; that is, a treatment that can "break" the status and restore the brain to its normal state of activity without recurrence of seizures when the medication is discontinued.

6. Current therapy for SE typically involves administering benzodiazepines, such as lorazepam or midazolam, as first-line therapy. If needed, anti-epileptic medications, such as levetiracetam and valproate, are then administered as second line-therapy. In over half of the cases of convulsive SE, this type of treatment is not effective to stop seizures. SE patients that do not respond to second-line agents, may need to be placed in a medically induced coma using intravenous anesthetic drugs to stop the seizures. The comatose state is typically maintained for 24-48 hours, after which the anesthetic drug is tapered to determine if SE has been terminated. However, seizures frequently return when the drugs are withdrawn. This results in extended periods of treatment with powerful drugs, that can lead to permanent brain damage, medical complications and death.

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.

8. In our clinical investigations, we unexpectedly discovered that SE could be rapidly and persistently suppressed using less ganaxolone and for a much shorter period of time than was anticipated. We determined that administering ganaxolone as an intravenous bolus and continuous intravenous infusion to achieve and maintain a ganaxolone plasma concentration of about 500 ng/ml to about 1000 ng/ml for about 8 to about 12 hours resulted in rapid and persistent suppression of SE, without recurrence of SE when the rate of ganaxolone infusion was reduced and treatment was terminated (See, FIG. 15 of the patent application[1]).

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.

All statements made herein of my own knowledge are true, all statements made herein on information and belief are believed to be true, and these statements were made with the

[1] The high dose produced a ganaxolone plasma concentration of about 500 ng/ml to about 1000 ng/ml for about 8 hours, while the low dose and medium dose did not achieve this plasma concentration for the 8 hour period. See also, Table 5.

knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001, and may jeopardize the validity of the application or any patent issuing thereon.

Joseph Hulihan, M.D.

7-Jul-2021
Date

Curriculum Vitae
Joe Hulihan, MD, MS-HP

CONTACT INFORMATION

Position:	Chief Medical Officer Marinus Pharmaceuticals, Inc.
E-mail	jhulihan@marinuspharma.com
LinkedIn	www.linkedin.com/in/jhulihan
Mobile	1.267.798.9987
Mailing address	100 Matsonford Road, #5 Suite 500 Radnor, PA 19087

Summary of Professional Experience, Education/Training and Certifications

PROFESSIONAL EXPERIENCE – PHARMACEUTICAL INDUSTRY

Marinus Pharmaceuticals, Inc., Chief Medical Officer **2019-**

Responsible for clinical development of the neuroactive steroid, ganaxolone, for treatment of rare pediatric epilepsies, status epilepticus and other neuropsychiatric disorders

Paradigm Neuroscience: Principal **2015-**

Provide consulting services for pharmaceutical and device development in neurology and psychiatry, including clinical and strategic support for neurotherapeutics in all phases of development. Clients have included a range of organizations, including large and mid-size pharma, early stage pharmaceutical and device companies, startup ventures and medical communications companies.

Current/recent consulting engagements with role and therapeutic area:

Neuronasal, LLC, Wexford PA – Clinical Advisor: Concussion	2017-
Ophidion, Inc., Bethlehem PA – Clinical Advisor: siRNA technologies CNS disease	2017-
Zynerba Pharmaceuticals, Inc., Devon PA – Study physician: Epilepsy and Fragile X syndrome	2018-2020
Finn Partners, New York NY – Clinical Advisor: Schizophrenia, Rare Diseases	2018-2019
Cavion, Inc., Cambridge MA – Independent Safety Monitor: Essential Tremor	2017-2019

Johnson & Johnson **1999-2014**

Global Medical Affairs Leader, Neuroscience (Mood disorders), Janssen Global Services, LLC (2013-14)

Developed a global, comprehensive life cycle investigational plan for the lead antidepressant in development, esketamine, prioritizing clinical initiatives globally and by region; led Global Medical Affairs team for mood disorders and represented worldwide clinical groups on compound development teams, ensuring that development programs met global data needs; served on the Disease Area Leadership Team for Mood Disorders, participating in program decisions including stage-gate decisions for compounds transitioning to proof-of-concept and to Phase 3 development in depression, anxiety disorders, bipolar disorder and PTSD; worked with the global health outcomes/economics lead to develop market access strategies; collaborated with global commercial leader to prioritize areas for compound development; served on clinical development teams for three compounds in depression/anxiety indicatio ns; led advisory boards on clinical programs in US, Europe and Asia; made numerous presentations to internal and external audiences.

Vice President, Medical Affairs:
Neuroscience, Janssen Scientific Affairs (2007-13)
Neurology, Ortho-McNeil Neurologics/Ortho-McNeil Janssen Scientific Affairs (2004-07)

Led US medical affairs team, initially for neurology and subsequently for the overall neuroscience franchise; duties encompassed life cycle strategies, program development and achievement of financial targets, with operational budgets between $54 million and $125 million; developed medical affairs business plans for management review and approval; led teams up of to 125 associates including physicians and scientists, medical science liaisons, medical information, health outcomes/health economics, biostatistics, publications, clinical operations, epidemiology and department administration; recruited and developed high-potential scientists and managers; drove collaboration with clinical and commercial partners; supervised teams for study development and execution, and communication plans in psychiatry, neurology and pain medicine; ensured compliance with relevant legal and regulatory guidance; served on the company management board with shared accountability for overall company performance; participated in global development and commercial teams and in the assessment of licensing opportunities; presented numerous topics at internal management reviews, scientific meetings, advisory boards and symposia.

Director, CNS Research, Clinical Affairs, Ortho-McNeil Pharmaceutical:

Group Director (2003-04)
Senior Director (2002-03)
Director (1999-2002)

Had direct or supervisory responsibility for development of clinical protocols and review of proposals for investigator-initiated studies. Therapeutic areas encompassed adult and pediatric neurology, psychiatry and pain medicine including epilepsy, headache disorders, chronic pain, movement disorders, amyotrophic lateral sclerosis (ALS), impulse control disorders, PTSD and substance abuse/dependence; served as key medical affairs contact for franchise commercial, legal, regulatory, communications and other functions; in collaboration with marketing, led market development and launch activities for Topamax in epilepsy indications and in migraine prevention, and developed phase 3B/4 plans; developed and supervised publication and communication plans for clinical programs; served on topiramate global development team; presented at numerous internal and external meetings.

PROFESSIONAL EXPERIENCE – ACADEMIC MEDICINE

Graduate Medical Education

Temple University School of Medicine, Philadelphia, PA — 1992-99
Assistant / Associate professor of neurology

Hahnemann University School of Medicine, Philadelphia, PA — 1991-92
Clinical Instructor, Neurology

Clinical

Woodhaven Center (a residential facility for adults with developmental disabilities) — 1995-2002
Consulting Neurologist

Department of Neurology, Temple University Hospital — 1992-99

Co-Director/Director, EEG Laboratory and Intraoperative Monitoring

Committees
Ethics Committee
Pharmacy and Therapeutics Committee
Brain Death Protocol Review Committee

Department of Neurology, Hahnemann University Hospital — 1991-92

Director, EEG Laboratory

Mayo Clinic 1991
Associate Consultant

EDUCATION AND TRAINING

Graduate Education

Jefferson School of Population Health 2009-15
Certificate in Health Policy, June 2011
MS-Health Policy, May 2015

Drexel University School of Medicine (formerly Hahnemann University) 1982-86
MD, Honors in Neurology, 1986

Graduate Medical Training

Internship, Internal Medicine 1986-87
Crozer-Chester Medical Center / Hahnemann University Hospital

Residency in Neurology 1987-90
Hahnemann University Hospital

Fellowship, Clinical Neurophysiology 1990-91
Mayo Clinic, Rochester, MN

Undergraduate Education

Dickinson College, Carlisle, PA BS, 1977, Magna cum laude

MEDICAL LICENSURE

Pennsylvania License MD042454E 1987-Present

BOARD CERTIFICATION

American Board of Psychiatry and Neurology (Neurology) Certificate 35975, 1992
American Board of Clinical Neurophysiology 1994

Professional Organizations and Advocacy

PROFESSIONAL SOCIETIES

American Academy of Neurology 1992-2014, 2018-

American Public Health Association, Member 2015-

AcademyHealth, Member 2015-

International Society for CNS Clinical Trials and Methodology (Founding member) 2006-

Strategic Working Group on Innovation (2013-2014)
Suicidal Ideation and Behavior Working Group (2015-2020)

ADVISORY COMMITTEES / BOARDS

Board of Directors, American Society for Neurotherapeutics 2008-2014

Steering Committee, North American AED Pregnancy Registry 2002 -2011

AAN Residency Examination Subcommittee-Clinical Neurophysiology Chair (2000-2003) 1997-2003

Examiner, American Board of Psychiatry and Neurology 1995-2000

ADVOCACY / COMMUNITY SERVICE

Board of Trustees, Mercer Street Friends, Trenton, NJ (Social services agency focused on education, hunger and poverty) Board Chair, 2016-present	2012-
Member, Board of Directors, Pennswood Village (A continuing care residential community)	2015-2018
Chair, Dickinson College Philadelphia Regional Council	2015-2017
Epilepsy Foundation of Eastern Pennsylvania Chair, Professional Advisory Board (1996-2000) Professional Advisory Board (1994-2004) Board of Directors (1998-2004)	1994-2004

OTHER PROJECTS

Producer, *Two Trentons: An American City Speaks* (2019) – Feature-length documentary film

Publications

PEER-REVIEWED ARTICLES

1. Guterman EL, Betjemann JP, Aimetti A, Li JW, Wang Z, Yin D, Hulihan J, Lyons T, Miyasato G, Strzelczyk A. Association between treatment progression, disease refractoriness, and burden of illness among hospitalized patients with status epilepticus. *JAMA Neurology* 2021;78(5):588-95.
2. Alphs L, Mao L, Rodriguez SC, Hulihan J, Starr HL. Design and rationale of the paliperidone palmitate research in demonstrating effectiveness (PRIDE) study: a novel comparative trial of once-monthly paliperidone palmitate versus daily oral antipsychotic treatment for delaying time to treatment failure in persons with schizophrenia. *J Clin Psychiatry* 2014;75:1388-93.
3. Alphs L, Bossie C, Kern-Sliwa J, Fu D-J, Ma Y-W, Hulihan J. Paliperidone palmitate and risperidone long-acting injectable in subjects with schizophrenia recently treated with oral risperidone or other antipsychotics. *Neuropsychiatric Disease and Treatment* 2013;9:341-50.
4. Alphs L, Olson WH, Turkoz I, Fastenau J, Hulihan J. Cost and Cost-Effectiveness in a Randomized Trial of Long-Acting Risperidone for Schizophrenia (letter to the editor). *J Clin Psych* 2012;73:1368.
5. Loring DW, Williamson DJ, Meador KJ, Wiegand F, Hulihan J. Topiramate dose effects on cognition: a randomized double-blind study. *Neurology* 2011;76:131-7.
6. Lipton RB, Silberstein S, Dodick D, Cady R, Freitag F, Mathew N, Biondi DM, Ascher S, Olson WH, Hulihan J. Topiramate intervention to prevent transformation of episodic migraine: The topiramate INTREPID study. *Cephalalgia* 2011;31:18-30.
7. Piña-Garza JE, Schwarzman L, Wiegand F, Hulihan J. A pilot study of topiramate in childhood absence epilepsy. *Acta Neurol Scand* 2011;12:354-9.
8. Ramsay E, Faught E, Krumholz A, Naritoku D, Privitera M, Schwarzman L, Mao L, Wiegand F, Hulihan J; CAPSS-272 Study Group. Efficacy, tolerability, and safety of rapid initiation of topiramate versus phenytoin in patients with new-onset epilepsy: a randomized double-blind clinical trial. *Epilepsia* 2010;51:1970-7.
9. Elble RJ, Biondi DM, Ascher S, Wiegand F, Hulihan J. Carisbamate in essential tremor: brief report of a proof of concept study. *Movement Disorders* 2010; 25:634-8.

10. Bigal ME, Lipton RB, Biondi DM, Xiang J, Hulihan J. Weight change and clinical markers of cardiovascular disease risk during preventive treatment of migraine. *Cephalalgia* 2009;29:1188-96.

11. Diener HC, Dodick DW, Goadsby PJ, et al. Utility of topiramate for the treatment of patients with chronic migraine in the presence or absence of acute medication overuse. *Cephalalgia* 2009;29:1021-7.

12. Silberstein S, Lipton R, Dodick D, et al. Topiramate treatment of chronic migraine: a randomized, placebo - controlled trial of quality of life and other efficacy measures. *Headache* 2009;49:1153-62.

13. Sankar R, Ramsay RE, McKay A, Hulihan J, Wiegand F on behalf of the CAPSS -311 Study Group. A multicenter, outpatient, open-label study to evaluate the dosing, effectiveness, and safety of topiramate as monotherapy in the treatment of epilepsy in clinical practice. *Epilepsy Research* 2009;15:506–12.

14. Cady R, Freitag F, Mathew N, Elkind A, Mao L, Fisher A, Biondi D, Finlayson G, Greenberg S, Hulihan J. Allodynia-Associated Symptoms, Pain Intensity and Time to Treatment: Predicting Treatment Response in Acute Migraine Intervention. *Headache* 2009;49:350-63.

15. Dodick D, Freitag F, Banks J, Saper J, Xiang J, Rupnow M, Biondi D, Greenberg S, Hulihan J. Topiramate Versus Amitriptyline in Migraine Prevention: A 26-Week, Multicenter, Randomized, Double-Blind, Double-Dummy, Parallel-Group Noninferiority Trial in Adult Migrainers. *ClinicalTherapeutics* 2009;31:542-59.

16. Silberstein S, Diener HC, Lipton R, Goadsby P, Dodick D, Bussone G, Freitag F, Schwalen S, Ascher S, Morein J, Greenberg S, Biondi D, Hulihan J. Epidemiology, risk factors, and treatment of chronic migraine: a focus on topiramate. *Headache* 2008;48:1087-95.

17. Adelman J, Freitag FG, Lainez M, Shi Y, Ascher S, Mao L, Greenberg S, Hulihan J. Analysis of safety and tolerability data obtained from over 1,500 patients receiving topiramate for migraine prevention in controlled trials. *Pain Medicine* 2008;9:175-85.

18. Dodick DW, Silberstein S, Saper J, Freitag FG, Cady RK, Rapoport AM, Mathew NT, Hulihan J, Crivera C, Rupnow MF, Mao L, Finlayson G, Greenberg SJ. The impact of topiramate on health -related quality of life indicators in chronic migraine. *Headache* 2007;47:1398-408.

19. Freitag FG, Forde G, Neto W, Wang DZ, Schmitt J, Wu SC, Hulihan J. Analysis of pooled data from two pivotal controlled trials on the efficacy of topiramate in the prevention of migraine. *Journal of the American Osteopathic Association* 2007;107:251-8.

20. Freitag F, Finlayson G, Rapoport A, Elkind A, Diamond M, Unger J, Fisher A, Armstrong R, Hulihan J, Greenberg S: Effect of Pain Intensity and Time to Administration on Responsiveness of Almotriptan: Results from Axert 12.5 mg Time Versus Intensity Migraine Study (AIMS). *Headache* 2007;47:519-30.

21. Silberstein S, Lipton R, Dodick D, Freitag F, Ramadan N, Matthew N, Brandes J, Bigal M, Saper J, Ascher S, Jordan D, Greenberg S, Hulihan J: Efficacy and Safety of Topiramate for the Treatment of Chronic Migraine: A Randomized, Double-Blind, Placebo-Controlled Trial. *Headache* 2007;47:170-80.

22. Stacy M, Elble R, Ondo W, Wu S-C, Hulihan J, TRS Study Group: Assessment of interrater and intrarater reliability of the Fahn-Tolosa-Marin Tremor Rating Scale in essential tremor. *Movement Disorders* 2007;22:833-8.

23. Ondo WG, Jankovic J. Connor GS, Pahwa R, Elble R, Stacy MA, Koller WC, Schwarzman L, Wu S -C, Hulihan, J: Topiramate in Essential Tremor: A Double-Blind, Placebo-Controlled Trial. *Neurology* 2006;66:672-7.

24. Silberstein SD, Hulihan J, Karim MR, Wu SC, Jordan D, Karvois D, Kamin M. Efficacy and tolerability of topiramate 200 mg/d in the prevention of migraine with/without aura in adults: A randomized, placebo - controlled, double-blind, 12-week pilot study. Clinical Therapeutics 2006;28:1002-11.

25. Hulihan JF, Spivey JM: Once-Daily Formulation of Galantamine (letter to the editor). Journal of the American Medical Directors Association 7:338, 2006.

26. Roy Chengappa KN, Schwarzman LK, Hulihan JF, Xiang J, Rosenthal NR. Adjunctive topiramate therapy in patients receiving a mood stabilizer for bipolar I disorder: a randomized, placebo -controlled trial. *Journal of Clinical Psychiatry* 2006;67:1698-706.
27. Winner P, Pearlman EM, Linder SL, Jordan DM, Fisher AC, Hulihan JF for the Topiramate Pediatric Migraine Study Investigators. Topiramate for migraine prevention in children: A randomized, double - blind, placebo- controlled trial. *Headache* 2005;45:1304-12.
28. Naritoku DK, Hulihan JF, Schwarzman LK, Kamin M, Olson WH. Effect of co-therapy reduction on tolerability of epilepsy add-on therapy: a randomized controlled trial. *Annals of Pharmacotherapy* 2005; 39:418-23.
29. Cudkowicz ME, Shefner JM, Schoenfeld DA, Brown RH Jr, Johnson H, Qureshi M, Jacobs M, Rothstein JD, Appel SH, Pascuzzi RM, Heiman-Patterson TD, Donofrio PD, David WS, Russell JA, Tandan R, Pioro EP, Felice KJ, Rosenfeld J, Mandler RN, Sachs GM, Bradley WG, Raynor EM, Baquis GD, Belsh JM, Novella S, Goldstein J, Hulihan J. A randomized, placebo-controlled trial of topiramate in amyotrophic lateral sclerosis. *Neurology* 2003;61:456-64.
30. Edwards KR, Hulihan J, Kraut L, Kamin M. Efficacy of the anticonvulsant topiramate in the prophylactic treatment of episodic migraine: A combined analysis from pilot, double-blind, placebo-controlled trials. *CNS Spectr* 2003;8:428-32.
31. Meador KJ, Loring DW, Hulihan JF, Kamin M, Karim R for the CAPSS-027 Study Group. Differential cognitive and behavioral effects of topiramate and valproate. *Neurology* 2003;60:1483-8.
32. Mathew NT, Hulihan JF, Rothrock JF. Anticonvulsants in migraine prophylaxis. *Neurology* 2003;60 (Suppl 7):S45- S49.
33. Hulihan JF. Epilepsy in special populations: Children, the elderly, and patients with concurrent medical illness. *Postgraduate Medicine* 1997;102:165-78.
34. Hulihan JF. Ice cream headache (editorial). *British Medical Journal* 1997;314:1364.
35. Harada RN, Comerota AJ, Good GM, Hashemi HA, Hulihan JF. Stump pressure, electroencephalographic changes, and the contralateral carotid artery: Another look at selective shunting. *Am J Surg* 1995;170:148-53.
36. Hulihan JF, Syna DR. Electroencephalographic Sleep Features in Post-Anoxic Stupor and Coma. *Neurology* 1994;44:758-60.
37. Cascino GD, Hulihan JF, Sharbrough FW, Kelly PJ. Parietal Lobe Lesional Epilepsy: Electroclinical C orrelation and Operative Outcome. *Epilepsia* 1993;34:522-7.
38. Hulihan JF, Bebin EM, Westmoreland BF. Bilateral PLEDs in Mycoplasma Encephalitis. *Pediatric Neurology Journal* 1992;8:292-4.
39. Cascino GD, Kelly PJ, Sharbrough FW, Hulihan JF, Hirschorn KA, Trenerry MR. Long-Term Follow-Up of Stereotactic Lesionectomy in Partial Epilepsy: Predictive Factors and Electroencephalographic Results. *Epilepsia* 1992;33:639-44.
40. Tahmoush AJ, Gillespie JA, Hulihan JF, Siegal DR, Parry GJ, Kushner H, Heiman -Patterson TD: Clinical and Electrophysiologic Assessments in ALS Patients. *Electromyography and Clinical Neurophysiology* 1991;31:491-6.

POSTERS/PRESENTATIONS/ABSTRACTS

1. Specchio N, Amin S, Aimetti A, Hulihan J. Extended duration safety and efficacy of ganaxolone for the treatment of CDKL5 deficiency disorder: preliminary open-label extension analysis (Marigold study). *Seizure* 2020. Poster: Annual Meeting of the American Epilepsy Society (virtual), December 4-8, 2020.
2. Pestana-Knight EM, Aimetti A, Hulihan J. Effect of ganaxolone on seizure frequency across subpopulations of patients with CDKL5 deficiency disorder: subgroup analyses of the Marigold study. *Seizure* 2020. Poster: Annual Meeting of the American Epilepsy Society (virtual), December 4-8, 2020.

3. Sadleir L, Hulihan J, Messenheimer J, Ali S, Gutterman D, Sebree T, Scheffer I. Quality of Life and Qualitative Caregiver Assessments in Children and Adolescents with Developmental and Epileptic Encephalopathies Treated with Cannabidiol Transdermal Gel: An Open-label Clinical Trial. *Neurology* Apr 2020, 94 (15 Supplement) 1664.
   Poster, American Academy of Neurology Annual Meeting (Virtual), May 2020.
4. Scheffer I, Hulihan J, Messenheimer, J, Ali S, Davis S, Gutterman D, Sebree T, Sadleir L. Cannabidiol Transdermal Gel in Children and Adolescents with Developmental and Epileptic Encephalopathies: An Open-label Clinical Trial. Neurology Apr 2020, 94 (15 Supplement) 1631.
   Poster, American Academy of Neurology Annual Meeting (Virtual), May 2020.
5. Hulihan J, Adler L, Ratcliffe S, Alphs L. Population risks for suicide in US counties.
   Poster: International Society for CNS Trials and Methodology Autumn Conference, Los Angeles, October 25-27, 2018.
6. Hulihan J, Adler L, Ratcliffe S, Alphs L. Population correlates of suicide and homicide due to firearms in U.S. counties.
   Poster: American Public Health Association Annual Meeting, Atlanta, November 5-8, 2017.
7. Hulihan J, Adler L, Ratcliffe S, Alphs L. Population factors and suicide mortality in U.S. counties.
   Poster: International Society for CNS Trials and Methodology Autumn Conference, Philadelphia, September 26 - 27, 2016.
8. Hulihan J, Crawford AJ, Plumb J. Incarceration and infant mortality in US counties: policy implications.
   Poster: Reimagining Health in Cities: New Directions in Urban Public Health. Drexel University School of Public Health, Philadelphia, September 10-11, 2015.
9. Hulihan J. Esketamine Development Program.
   Invited presentation: International Forum on Mood and Anxiety Disorders. Vienna, December 11, 2014.
10. Singh J, Fedgchin M, Daly E, Xi L, Hulihan J, Melman C, De Bruecker G, Tadic A, Sienaert P, Wiegand F, Manji H, Drevets W, Van Nueten L. Efficacy and safety of intravenous esketamine in patients with treatment - resistant depression: a double-blind, double-randomization, placebo-controlled phase 2a study.
    Poster: International Forum on Mood and Anxiety Disorders. Vienna, December 11, 2014.
11. Hulihan JF, Bossie C, Alphs L. Schizophrenia trials comparing long-acting injectable vs. daily oral antipsychotic treatments: do pragmatic vs. explanatory study designs matter?
    Poster: International Congress on Schizophrenia Research. Orlando FL, April 21 -25, 2013.
12. Ferziger R, Mao L, Hulihan J, Bossie CA, Alphs L. A tale of two trial designs: evaluation of efficacy vs. effectiveness in schizophrenia.
    Poster, 34th Annual Meeting of the Society for Medical Decision-Making. Phoenix AZ, October 17-20, 2012.
13. Hulihan J, Bossie C, Fu D-J, Kern-Sliwa J, Verbanac J, Ma Y-W, Alphs L. Remission with continued paliperidone palmitate treatment in stable subjects with schizophrenia: Is there a relationship to functioning?
    Poster, Annual Meeting of the American Psychiatric Association, Philadelphia PA, May 5-9, 2012.
14. Hulihan J, Bossie C, Fu D-J, Kern-Sliwa J, Verbanac J, Ma Y-W, Alphs L. Remission with continued paliperidone palmitate treatment in stable subjects with schizophrenia: Is there a relationship to functioning?
    Poster, 3rd Biennial Schizophrenia International Research Society Conference, Florence, Italy, April 14 -18, 2012.
15. Bossie CA, Hulihan JF, Alphs L. Effectiveness vs Efficacy Rankings by a Modified PRECIS Tool for SchizophreniaTrials of Long-Acting Injectable vs Daily Oral Antipsychotic Treatments
    Poster, 3rd Biennial Schizophrenia International Research Society Conference, Florence, Italy, Apr 14 -18, 2012.

16. Bossie CA, Hulihan JF, Alphs L. Feasibility of Assessing the Pragmatic vs. Explanatory Design of a Clinical Trial. Poster, Annual Meeting of the International Society for CNS Clinical Trials and Methodology. Washington DC, February 21-23, 2012.
17. Ferziger R, Mao L, Bossie CA, Alphs L. A Tale of Two Trial Designs: Efficacy vs. Effectiveness in Schizophrenia. Poster, Annual Meeting of the International Society for CNS Clinical Trials and Methodology. Washington DC, February 21-23, 2012.
18. Alphs L, Bossie CA, Fu DJ, Hulihan J, Ma Y-w, Kern-Sliwa J. Paliperidone palmitate versus risperidone long-acting therapy in patients with schizophrenia recently treated with oral antipsychotics.
Poster, Annual Meeting of the American Psychiatric Association, Honolulu HI, May 2011.
19. Ferziger R, Alphs L, Turner N, Mao L, Rodriguez S, Dixon L, Davis J, Hulihan J. Paliperidone palmitate vs. oral antipsychotics for people with schizophrenia recently released from jail: rationale and methodology.
Poster, ISCTM Autumn Conference. Baltimore MD, October 2010.
20. Ferziger R, Alphs L, Turner N, Mao L, Rodriguez S, Dixon L, Davis J, Hulihan J. A multicenter effectiveness study of paliperidone palmitate vs oral antipsychotics for people with schizophrenia recently released from jail: study rationale and methodology.
Poster, American College of Neuropsychopharmacology Annual Meeting. Miami Beach, Dec 2010.
21. Ramsay E, Faught E, Krumholz A, Naritoku D, Privitera M, Schwarzman L, Mao L, Wiegand F, Hulihan J. Efficacy, Tolerability and Safety of Initial Monotherapy Topiramate vs Phenytoin in Patients with new - onset Epilepsy. *Epilepsia* 49 (S7):115,2008.
Poster, American Epilepsy Society, Seattle, December 5-9, 2008.
22. Sankar R, Ramsay E, McKay A, Zhu Y, Hulihan J, Wiegand F. A Multicenter, Outpatient, Open -label, Study to Evaluate the Dosing and Safety of Topiramate as Monotherapy in the Treatof Epilepsy in Clinical Practice. *Epilepsia* 48(Suppl 6):370,2007.
Poster, American Epilepsy Society, Philadelphia, November 30- December 4, 2007.
23. Loring D, Meador K, Williamson D, Wiegand F, Hulihan J. Topiramate Dose Effects on Neuropsychological Function: A Randomized Double-Blind Placebo-Controlled Study. *Epilepsia* 48(Suppl 6):216,2007.
Poster, American Epilepsy Society, Philadelphia, November 30- December 4,2007.
24. Silberstein S, Lipton R, Dodick D, Freitag F, Ramadan N, Mathew N, Brandes J, Bigal M, Saper J, Rozen T, Ascher S, Jordan D, Greenberg S, Hulihan J: Topiramate in Chronic Migraine: A Multicenter, Randomized, Placebo - Controlled Trial. *Neurology* 68:12 (S1)A196,2007.
Poster, American Academy of Neurology Annual Meeting, Boston, April 28 -May 5, 2007.
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Poster, American Academy of Neurology Annual Meeting, Boston, April 28 -May 5, 2007.
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Electronic Acknowledgement Receipt	
EFS ID:	43196588
Application Number:	17186569
International Application Number:	
Confirmation Number:	4113
Title of Invention:	GANAXOLONE FOR USE IN TREATMENT OF STATUS EPILEPTICUS
First Named Inventor/Applicant Name:	David CZEKAI
Customer Number:	24633
Filer:	Robert H. Underwood/Catherine Heath
Filer Authorized By:	Robert H. Underwood
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If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	
	)	
David CZEKAI	)	Group Art Unit: 1617
	)	
Application No.: 17/186,569	)	Examiner: Carlos A., Azpuru
	)	
Filed: February 26, 2021	)	Confirmation No.: 4113
	)	
For: GANAXOLONE FOR USE IN TREATMENT OF STATUS EPILEPTICUS	)	

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

SUPPLEMENTAL AMENDMENT

This paper is in response to the call from Examiner Azpuru on July 19, 2021, regarding the above-referenced application. The amendment supplements the response submitted on July 8, 2021, to the non-final Office Action mailed April 20, 2021. Reconsideration and further examination of the present application in light of the following:

Amendments to the Claims begin on page 2.

Remarks/Arguments follow the amendments section of this paper.

AMENDMENT TO THE CLAIMS

This listing of claims will replace all prior versions and listings of claims in the application:

1-54. (Cancelled)

55. (Previously Presented) A method of treating status epilepticus (SE), comprising administering to a subject in need thereof an effective amount of ganaxolone to suppress SE, wherein the effective amount of ganaxolone is administered as an intravenous bolus plus continuous infusion to produce and maintain a ganaxolone plasma concentration of about 500 ng/ml to about 1000 ng/ml for about 8 hours to about 12 hours.

56. (Previously Presented) The method of claim 55, wherein the intravenous bolus comprises about 5 mg to about 40 mg of ganaxolone.

57. (Previously Presented) The method of claim 56, wherein the intravenous bolus comprises about 30 mg of ganaxolone.

58. (Previously Presented) The method of claim 55, wherein the continuous intravenous infusion comprises infusion of about 20 mg of ganaxolone per hour to about 80 mg of ganaxolone per hour.

59. (Previously Presented) The method of claim 58, wherein about 80 mg of ganaxolone per hour are infused into the subject at the initiation of the continuous intravenous infusion and for at least about 2 hours thereafter.

60. (Previously Presented) The method of claim 59, wherein the amount of ganaxolone infused into the subject by the continuous intravenous infusion is decreased from about 80 mg per hour to about 40 mg per hour after about 2 hours.

61. (Previously Presented) The method of claim 60, wherein the 40 mg per hour continuous intravenous infusion is administered for about 6 hours to about 10 hours.

62. (Previously Presented) The method of claim 61, further comprising continuing to administer ganaxolone by the continuous intravenous infusion, wherein the amount of ganaxolone infused is decreased to about 20 mg per hour.

63. (Previously Presented) The method of claim 62, wherein the 20 mg per hour continuous intravenous infusion is administered for about 12 hours to about 24 hours.

64. (Previously Presented) The method of claim 56, wherein a continuous intravenous infusion of ganaxolone is initiated periprocedurally with the intravenous bolus and the continuous intravenous infusion comprises: a) an infusion of about 80 mg ganaxolone per hour for about 2 hours, then b) an infusion of about 40 mg ganaxolone

per hour for about 6 hours to about 10 hours, then c) an infusion of about 20 mg ganaxolone per hour for about 12 hours to about 24 hours.

65. (Previously Presented) The method of claim 55, wherein the intravenous bolus produces a ganaxolone plasma concentration in the subject of about 500 ng/ml to about 1000 ng/ml.

66. (Cancelled)

67. (Previously Presented) The method of claim 64, wherein the intravenous bolus is administered to the subject for about 1 minute to about 5 minutes.

68. (Cancelled)

69. (Cancelled)

70. (Previously Presented) The method of claim 64, further comprising a taper period of about 12 hours.

71. (Cancelled)

72. (Previously Presented) The method of claim 55, wherein the subject has refractory status epilepticus.

73. (Cancelled)

74. (Cancelled)

75. (Previously Presented) The method of claim 55, wherein the amount of ganaxolone infused into the subject by the continuous infusion is decreased at least once while the ganaxolone plasma concentration of about 500 ng/ml to about 1000 ng/ml is maintained.

76. (Previously Presented) The method of claim 55, wherein the total daily dose of ganaxolone administered is from about 500 mg to about 900 mg.

77. (Currently Amended) The method of claim 75, further comprising continuing ~~to administer ganaxolone by continuous~~ the intravenous infusion and reducing the amount of ganaxolone that is administered ~~after the ganaxolone plasma concentration of about 500 ng/m to about 1000 ng/ml has been maintained for about 8 hours to about 12 hours, and wherein the amount of ganaxolone that is infused is reduced~~.

78. (Previously Presented) The method of claim 64, wherein the subject has refractory status epilepticus.

79. (Previously Presented) The method of claim 77, wherein the subject has refractory status epilepticus.

80. (Previously Presented) The method of claim 57, wherein a continuous intravenous infusion of ganaxolone is initiated periprocedurally with the intravenous bolus and the continuous intravenous infusion comprises: a) an infusion of about 80 mg ganaxolone per hour for about 2 hours, then b) an infusion of about 40 mg ganaxolone per hour for about 6 hours to about 10 hours, then c) an infusion of about 20 mg ganaxolone per hour for about 12 hours to about 24 hours.

81. (Previously Presented) The method of claim 80, wherein the subject has refractory status epilepticus.

REMARKS

Examiner Azpuru telephoned the undersigned on July 19, 2021, regarding the response Applicant submitted on July 8, 2021 to the non-final Office Action mailed on April 20, 2021. The Examiner and undersigned discussed a proposed amendment to claim 77 to improve the clarity of the claim. Claim 77 is amended to improve clarity.

In view of the foregoing, Applicant respectfully requests reconsideration of this application and timely allowance of the pending claims. If it will facilitate prosecution of this application, the Examiner is invited to contact the undersigned at the telephone number below.

The Commissioner is authorize to any deficiency fees due from, or credit any overpayment in fees to, Deposit Account No. 50-1349, from which the undersigned is authorized to draw.

Respectfully submitted,
HOGAN LOVELLS US LLP

/Robert H. Underwood, Reg. No. 45,170/

Robert H. Underwood
Registration No. 45,170

Date: July 22, 2021

Please recognize our Customer No. 24633 as our correspondence address

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Electronic Acknowledgement Receipt	
EFS ID:	43315462
Application Number:	17186569
International Application Number:	
Confirmation Number:	4113
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If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

24633 7590 07/28/2021

HOGAN LOVELLS US LLP
IP GROUP, COLUMBIA SQUARE
555 THIRTEENTH STREET, N.W.
WASHINGTON, DC 20004

EXAMINER
AZPURU, CARLOS A

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 07/28/2021

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/186,569	02/26/2021	David CZEKAI	761996.110010	4113

TITLE OF INVENTION: GANAXOLONE FOR USE IN TREATMENT OF STATUS EPILEPTICUS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$600	$0.00	$0.00	$600	10/28/2021

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

PTOL-85 (Rev. 02/11)

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

24633 7590 07/28/2021
HOGAN LOVELLS US LLP
IP GROUP, COLUMBIA SQUARE
555 THIRTEENTH STREET, N.W.
WASHINGTON, DC 20004

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/186,569	02/26/2021	David CZEKAI	761996.110010	4113

TITLE OF INVENTION: GANAXOLONE FOR USE IN TREATMENT OF STATUS EPILEPTICUS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$600	$0.00	$0.00	$600	10/28/2021

EXAMINER	ART UNIT	CLASS-SUBCLASS
AZPURU, CARLOS A	1617	514-182000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-09 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1_____
2_____
3_____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. Fees submitted: ❑Issue Fee ❑Publication Fee (if required) ❑Advance Order - # of Copies _____

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

❑ Electronic Payment via EFS-Web ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

❑ Applicant asserting small entity status. See 37 CFR 1.27

❑ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

Ovid Exhibit 2008 - Page 53 of 60
Marinus v. Ovid - PGR2023-00020

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/186,569	02/26/2021	David CZEKAI	761996.110010	4113

24633 7590 07/28/2021

HOGAN LOVELLS US LLP
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555 THIRTEENTH STREET, N.W.
WASHINGTON, DC 20004

EXAMINER	
AZPURU, CARLOS A	
ART UNIT	**PAPER NUMBER**
1617	

DATE MAILED: 07/28/2021

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

Ovid Exhibit 2008 - Page 54 of 60
Marinus v. Ovid - PGR2023-00020

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. 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 1.14. This collection is estimated to take 30 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, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. 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.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 17/186,569	Applicant(s) CZEKAI et al.	
	Examiner CARLOS A AZPURU	Art Unit 1617	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to the amendment of 07/08/2021.
   ☑ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on 07/08/2021.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are 55-65,67,70,72 and 75-81 . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some *c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☑ Interview Summary (PTO-413), Paper No./Mail Date. 07202021.
5. ☐ Examiner's Amendment/Comment
6. ☑ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/CARLOS A AZPURU/
Primary Examiner, Art Unit 1617

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Withdrawn Rejections

The rejection under 35 USC 112, first paragraph, for scope of enablement, 35 USC 112, second paragraph, as well as 35 USC 103 over US 2016/0228454 are withdrawn in view of applicant's remarks and the declaration filed 07/08/2021.

Response to Amendment

The declaration under 37 CFR 1.132 filed 07/08/2021 is sufficient to overcome the rejection of claims 55-74 based upon US 2016/0228454 .

The declaration shows the cessation of SE using the parameters of the claims. This differentiates from the prior art in the duration of treatment needed to achieve cessation of SE.

Allowable Subject Matter

Claims 1-6 and 8-20 are allowed.

Reasons for Allowance

The following is an examiner's statement of reasons for allowance: The prior art neither teaches, nor fairly suggests the instantly claimed method of treating status epilepticus (SE). Specifically, the prior art treatment takes longer , and the instantly claimed method reaches cessation of SE activity by achieving the claimed treatment is achieved by the claimed Cmax within about 8 to about 12 hours at

the specified dosage by a bolus followed by continuous infusion. As such, the instantly claimed method is allowable over the prior art.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CARLOS A AZPURU whose telephone number is (571)272-0588. The examiner can normally be reached on 9 am- 3 pm, 4 pm-8pm.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann R Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see https://ppair-my.uspto.gov/pair/PrivatePair. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/CARLOS A AZPURU/
Primary Examiner, Art Unit 1617

caz

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/186,569	09/07/2021	11110100	761996.110010	4113

24633 7590 08/18/2021

HOGAN LOVELLS US LLP
IP GROUP, COLUMBIA SQUARE
555 THIRTEENTH STREET, N.W.
WASHINGTON, DC 20004

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

Marinus Pharmaceuticals, Inc., Radnor, PA;
David CZEKAI, Radnor, PA;
Maciej GASIOR, Radnor, PA;
Lorianne MASUOKA, Radnor, PA;
Julia TSAI, Radnor, PA;
Joseph HULIHAN, Radnor, PA;
Alex AIMETTI, Radnor, PA;

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The USA offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to encourage and facilitate business investment. To learn more about why the USA is the best country in the world to develop technology, manufacture products, and grow your business, visit SelectUSA.gov.