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# PROVISIONAL APPLICATION FOR PATENT COVER SHEET – Page 1 of 2

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

**Express Mail Label No.** _____

## INVENTOR(S)

| Given Name (first and middle [if any]) | Family Name or Surname | Residence (City and either State or Foreign Country) |
|---|---|---|
| David | Czekai | Radnor, PA |
| Maciej | Gasior | Radnor, PA |
| Lorianne | Masuoka | Radnor, PA |
| Julia | Tsai | Radnor, PA |
| | | |

Additional inventors are being named on the _____ separately numbered sheets attached hereto.

## TITLE OF THE INVENTION (500 characters max):

GANAXOLONE FOR USE IN TREATMENT OF STATUS EPILEPTICUS

Direct all correspondence to: **CORRESPONDENCE ADDRESS**

☑ The address corresponding to Customer Number: 23280

**OR**

☐ Firm or Individual Name

Address

| City | State | Zip |
|---|---|---|
| Country | Telephone | Email |

## ENCLOSED APPLICATION PARTS (*check all that apply*)

☑ Application Data Sheet. See 37 CFR 1.76.
☐ CD(s), Number of CDs _____
☑ Drawing(s) *Number of Sheets* 6
☐ Other (specify) _____
☑ Specification (e.g., description of the invention) *Number of Pages* 72

**Fees Due:** Filing Fee of $260 ($130 for small entity) ($65 for micro entity). If the specification and drawings exceed 100 sheets of paper, an application size fee is also due, which is $400 ($200 for small entity) ($100 for micro entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

## METHOD OF PAYMENT OF THE FILING FEE AND APPLICATION SIZE FEE FOR THIS PROVISIONAL APPLICATION FOR PATENT

☑ Applicant asserts small entity status. See 37 CFR 1.27.
☐ Applicant certifies micro entity status. See 37 CFR 1.29.
Applicant must attach form PTO/SB/15A or B or equivalent.
☐ A check or money order made payable to the *Director of the United States Patent and Trademark Office* is enclosed to cover the filing fee and application size fee (if applicable).

140
**TOTAL FEE AMOUNT ($)**

☑ Payment by credit card. Form PTO-2038 is attached.
☑ The Director is hereby authorized to charge the filing fee and application size fee (if applicable) or credit any overpayment to Deposit Account Number: 50-0552.

***USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT***

This collection of information is required by 37 CFR 1.51. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 10 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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

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# PROVISIONAL APPLICATION FOR PATENT COVER SHEET – Page 2 of 2

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☑ No.

☐ Yes, the invention was made by an agency of the U.S. Government. The U.S. Government agency name is: _____

☐ Yes, the invention was made under a contract with an agency of the U.S. Government. The name of the U.S. Government agency and Government contract number are: _____

## WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

SIGNATURE /Oleg Ioselevich/ DATE August 5, 2019

TYPED OR PRINTED NAME Oleg Ioselevich REGISTRATION NO. 56963 (*if appropriate*)

TELEPHONE 212-736-6048 DOCKET NUMBER 550.1013P

# 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.

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| Application Data Sheet 37 CFR 1.76 | Attorney Docket Number | 550.1013P |
|---|---|---|
| | Application Number | |
| Title of Invention | GANAXOLONE FOR USE IN TREATMENT OF STATUS EPILEPTICUS | |

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

## Secrecy Order 37 CFR 5.2:

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

## Inventor Information:

**Inventor 1** Remove

**Legal Name**

| Prefix | Given Name | Middle Name | Family Name | Suffix |
|---|---|---|---|---|
| | David | | Czekai | |

**Residence Information (Select One)** ● US Residency Non US Residency Active US Military Service

| City | Radnor | State/Province | PA | Country of Residence | US |
|---|---|---|---|---|---|

**Mailing Address of Inventor:**

| | |
|---|---|
| Address 1 | 5 Radnor Corporate Center |
| Address 2 | 100 Matsonford Rd |

| City | Radnor | State/Province | PA |
|---|---|---|---|
| Postal Code | 19087 | Country | US |

**Inventor 2** Remove

**Legal Name**

| Prefix | Given Name | Middle Name | Family Name | Suffix |
|---|---|---|---|---|
| | Maciej | | Gasior | |

**Residence Information (Select One)** ◉ US Residency Non US Residency Active US Military Service

| City | Radnor | State/Province | PA | Country of Residence | US |
|---|---|---|---|---|---|

**Mailing Address of Inventor:**

| | |
|---|---|
| Address 1 | 5 Radnor Corporate Center |
| Address 2 | 100 Matsonford Rd |

| City | Radnor | State/Province | PA |
|---|---|---|---|
| Postal Code | 19087 | Country | US |

**Inventor 3** Remove

**Legal Name**

| Prefix | Given Name | Middle Name | Family Name | Suffix |
|---|---|---|---|---|
| | Lorianne | | Masuoka | |

**Residence Information (Select One)** ◉ US Residency Non US Residency Active US Military Service

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| City | Radnor | State/Province | PA | Country of Residence | US |
|---|---|---|---|---|---|

**Mailing Address of Inventor:**

| | | | |
|---|---|---|---|
| Address 1 | 6 Radnor Corporate Center | | |
| Address 2 | 100 Matsonford Rd | | |
| City | Radnor | State/Province | PA |
| Postal Code | 19087 | Country | US |

Inventor 4 — Remove

**Legal Name**

| Prefix | Given Name | Middle Name | Family Name | Suffix |
|---|---|---|---|---|
| | Julia | | Tsai | |

**Residence Information (Select One)** ◉ US Residency ○ Non US Residency ○ Active US Military Service

| City | Radnor | State/Province | PA | Country of Residence | US |
|---|---|---|---|---|---|

**Mailing Address of Inventor:**

| | | | |
|---|---|---|---|
| Address 1 | 6 Radnor Corporate Center | | |
| Address 2 | 100 Matsonford Rd | | |
| City | Radnor | State/Province | PA |
| Postal Code | 19087 | Country | US |

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

## Correspondence Information:

**Enter either Customer Number or complete the Correspondence Information section below.**
**For further information see 37 CFR 1.33(a).**

☐ **An Address is being provided for the correspondence Information of this application.**

| Customer Number | 23280 | | |
|---|---|---|---|
| Email Address | ddk@ddkpatent.com | Add Email | Remove Email |

## Application Information:

| Title of the Invention | GANAXOLONE FOR USE IN TREATMENT OF STATUS EPILEPTICUS | | |
|---|---|---|---|
| Attorney Docket Number | 550.1013P | Small Entity Status Claimed | ☒ |
| Application Type | Provisional | | |
| Subject Matter | Utility | | |
| Total Number of Drawing Sheets (if any) | | Suggested Figure for Publication (if any) | |

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| **Application Data Sheet 37 CFR 1.76** | Attorney Docket Number | 550.1013P |
|---|---|---|
| | Application Number | |
| Title of Invention | GANAXOLONE FOR USE IN TREATMENT OF STATUS EPILEPTICUS | |

## Filing By Reference:

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

| Application number of the previously filed application | Filing date (YYYY-MM-DD) | Intellectual Property Authority or Country |
|---|---|---|
| | | |

## Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

## Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

| Please Select One: | ● Customer Number | US Patent Practitioner | ○ Limited Recognition (37 CFR 11.9) |
|---|---|---|---|
| Customer Number | 23280 | | |

## Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.
When referring to the current application, please leave the "Application Number" field blank.

| Prior Application Status | | | Remove |
|---|---|---|---|
| Application Number | Continuity Type | Prior Application Number | Filing or 371(c) Date (YYYY-MM-DD) |
| | | | |

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button. Add

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| Application Data Sheet 37 CFR 1.76 | Attorney Docket Number | 550.1013P |
|---|---|---|
| | Application Number | |
| Title of Invention | GANAXOLONE FOR USE IN TREATMENT OF STATUS EPILEPTICUS | |

## Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)[i] the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

Remove

| Application Number | Country[i] | Filing Date (YYYY-MM-DD) | Access Code[i] (if applicable) |
|---|---|---|---|
| | | | |

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button. Add

## Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

| Application Data Sheet 37 CFR 1.76 | Attorney Docket Number | 550.1013P |
|---|---|---|
| | Application Number | |
| Title of Invention | GANAXOLONE FOR USE IN TREATMENT OF STATUS EPILEPTICUS | |

# Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

**NOTE**: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

**1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)**

**A. Priority Document Exchange (PDX)** - Unless box A in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h)(1).

**B. Search Results from U.S. Application to EPO** - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

**2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)**

☐ A. Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

☐ B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

**NOTE:** Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

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| Application Data Sheet 37 CFR 1.76 | Attorney Docket Number | 550.1013P |
|---|---|---|
| | Application Number | |
| Title of Invention | GANAXOLONE FOR USE IN TREATMENT OF STATUS EPILEPTICUS | |

## Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

**Applicant** 1 — Remove

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

| ● Assignee | Legal Representative under 35 U.S.C. 117 | Joint Inventor |
|---|---|---|
| Person to whom the inventor is obligated to assign. | Person who shows sufficient proprietary interest | |

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor:

If the Applicant is an Organization check here. ☒

| Organization Name | Marinus Pharmaceuticals, Inc. | | |
|---|---|---|---|
| **Mailing Address Information For Applicant:** | | | |
| **Address 1** | 170 N. Radnor Chester Road | | |
| Address 2 | Suite 250 | | |
| **City** | Radnor | **State/Province** | PA |
| **Country** | US | Postal Code | 19087-5279 |
| Phone Number | | Fax Number | |
| Email Address | | | |

Additional Applicant Data may be generated within this form by selecting the Add button. Add

## Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

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| **Application Data Sheet 37 CFR 1.76** | Attorney Docket Number | 550.1013P |
|---|---|---|
| | Application Number | |
| Title of Invention | GANAXOLONE FOR USE IN TREATMENT OF STATUS EPILEPTICUS | |

**Assignee 1**

Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

Remove

If the Assignee or Non-Applicant Assignee is an Organization check here. ☒

| Organization Name | Marinus Pharmaceuticals, Inc. |
|---|---|

**Mailing Address Information For Assignee including Non-Applicant Assignee:**

| **Address 1** | 170 N. Radnor Chester Road | | |
|---|---|---|---|
| Address 2 | Suite 250 | | |
| **City** | Radnor | **State/Province** | PA |
| **Country** i | US | Postal Code | 19087-5279 |
| Phone Number | | Fax Number | |
| Email Address | | | |

Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button. Add

## Signature:

Remove

**NOTE:** This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). **However, if this Application Data Sheet is submitted with the INITIAL filing of the application and either box A or B is not checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).**

This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

| **Signature** | /Oleg Ioselevich/ | | | Date (YYYY-MM-DD) | 2019-08-05 |
|---|---|---|---|---|---|
| First Name | Oleg | Last Name | Ioselevich | Registration Number | 56963 |

Additional Signature may be generated within this form by selecting the Add button. Add

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This collection of information is required by 37 CFR 1.76. 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 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

# 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:

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| **Application Number:** | |
| **Filing Date:** | |
| **Title of Invention:** | GANAXOLONE FOR USE IN TREATMENT OF STATUS EPILEPTICUS |
| **First Named Inventor/Applicant Name:** | David Czekai |
| **Filer:** | Oleg Ioselevich |
| **Attorney Docket Number:** | 550.1013P |

Filed as Small Entity

**Filing Fees for Provisional**

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| **Pages:** | | | | |
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| **Miscellaneous-Filing:** | | | | |
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| **Application Number:** | 62882648 |
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| **Confirmation Number:** | 9952 |
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| **First Named Inventor/Applicant Name:** | David Czekai |
| **Customer Number:** | 23280 |
| **Filer:** | Oleg Ioselevich |
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| 1 | Provisional Cover Sheet (SB16) | ProvisionalCoverSheet_5Aug19.PDF | 304447<br>6849e2aaa93b84428cf1f589536d54d723c062e6 | no | 3 |
| **Warnings:** | | | | | |
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| 2 | Application Data Sheet | ADS_5Aug2019.PDF | 1256180<br>4e9b0e7f7ce272c6549c3bb6a5bd7853ad4047c7 | no | 9 |
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| **Information:** | | | | | |
| 3 | Specification | 550_1013P_ApplicationAsFiled_5Aug19.pdf | 614346<br>4260c1e509e0b518cca88420b03477decf8c4213 | no | 72 |
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| 4 | Drawings-only black and white line drawings | 550_1013P_Drawings_5Aug19.pdf | 5283783<br>743e0a821768b032b8bffabd5b5d0c76b178c8a7 | no | 6 |
| **Warnings:** | | | | | |
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| 5 | Fee Worksheet (SB06) | fee-info.pdf | 29544<br>ddc9474b75158124f2ecb6c7108a416d66b02714 | no | 2 |
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# GANAXOLONE FOR USE IN TREATMENT OF STATUS EPILEPTICUS

## BACKGROUND OF THE INVENTION

[0001] Status epilepticus ("SE") is a serious, life-threatening, and rare condition with a significant unmet medical need. With an annual incidence of 10 to 41 per 100,000 people (Falco-Walter et al., 2016), SE can occur in patients with epilepsy as well as in patients without a history of epilepsy. An estimated 50,000 to 150,000 people in the United States each year have SE (Glauser et al, 2016). Mortality due to SE can range from 3% to 40% depending on etiology, age, SE type, and SE duration (Knake et al, 2009; Treiman 2014).

[0002] In the clinical setting, SE can be recognized based on the presentation (i.e., convulsions) or through EEG activity indicating the presence of continuous ictal discharges (Brophy et al, 2012). Once diagnosed, SE is a neurological emergency that requires aggressive treatment to stop the seizures and prevent permanent neurological damage, including neuronal death (Treiman 2001; Bhattacharjee and Hirsch, 2015). A growing body of evidence from research and clinical observation supports the concept that SE becomes more difficult to control as its duration increases, and prolonged SE and refractoriness to treatment are associated with poor prognosis (Lowenstein and Alldredge, 1998). Early treatment is critical as the longer SE persists, the less likely it will resolve spontaneously and the higher the mortality is (Falco-Walter et al, 2016).

[0003] As SE is a medical emergency, the primary goal of treatment is to stop SE as rapidly as possible, maintain seizure control, and avoid medical complications. Treatment typically occurs in stages. In clinical settings, the first-line treatment for control of SE is intravenous (IV) administration of benzodiazepines (Glauser et al, 2016). However, between 25% and 36% of SE patients do not respond to first-line therapy of benzodiazepines (Rogawski et al, 2013).

[0004] In patients for whom benzodiazepine treatment fails, the guidelines call for sequential treatment with standard IV antiepileptic drugs (AEDs) (sometimes referred to as antiseizure medications (ASDs)) such as phenytoin, fosphenytoin, valproic acid, lacosamide, phenobarbital,

and/or levetiracetam as second-line therapies. However, none of these IV AEDs currently used to treat refractory status epilepticus (RSE) has been approved for this indication.

[0005] In SE animal models, traditional second-line therapies such as phenytoin (Bankstahl and Loscher, 2008), valproic acid (Bankstahl and Loscher, 2008), levetiracetam, and phenobarbital are inactive on non-convulsive EEG seizures and have varying degrees of effectiveness in blocking convulsive seizures (Saporito et al, 2019). Phenobarbital inhibits EEG seizures when administered close to the seizure onset; however, with delayed administration it is inactive (Jones et al, 2002). With delayed administration, levetiracetam blocks convulsions, but not EEG seizures (Zheng et al, 2010).

[0006] The third-line treatment for SE control consists of general IV anesthesia (e.g., propofol, midazolam, pentobarbital, etc.). However, because of the respiratory depressant effects of seizures and the general anesthetic treatment agents, full ventilator support is required to maintain adequate oxygenation saturation (Lawson et al, 2016). While the patient remains on high doses of sedative or general anesthetic, strategies to prevent ventilator-associated pneumonia have to be implemented. In addition, healthcare providers can encounter difficulties in weaning patients off the seizure-controlling anesthetic agent while inadvertently causing the patient to go back into SE or seizures (Lawson et al, 2016). Moreover, the major concerns of an anesthetic drug infusion are prolonged duration of mechanical ventilation, immobilization, hypotension, cardiac complications as well as propofol-infusion syndrome (Claasen et al, 2002; Phabphal et al, 2018).

[0007] Most AEDs are prone to many drug-drug interactions that may affect safety and limit treatment options. Also, some drugs (e.g., benzodiazepines, barbiturates) may be associated with diminishing efficacy over time (i.e., tolerance), and development of dependence or life-threatening central nervous system (CNS) depression especially when used with other CNS-depressant drugs (e.g., AEDs, anxiolytics, antidepressants, opiod analgesics, etc.) and substances (e.g., alcohol, heroin, etc.).

[0008] Many patients with SE become progressively refractory to treatment over time, such that up to 30% of patients with SE cannot be successfully treated and die within 30 days (Al-Mufti and Claassen, 2014; Trinka et al, 2015).

[0009] The prognosis worsens and the mortality increases for subjects whose SE develops into refractory status epilepticus (RSE) (Neligan et al, 2010).

[0010] Currently adopted definitions of different stages of SE include early status epilepticus (which is initially treated with benzodiazepine), established SE (when SE continues despite initial treatment with benzodiazepines) (ESE), refractory SE (RSE) (when SE continutes despite initial treatment with benzodiazepines and at least one 2nd line IV AED) and super refractory SE (SRSE) (when SE coninutes despite therapy with general anesthesia for at least 24 hours or when it recurses upon weaning off general anesthetics). (Sharvon and Ferlisi, 2011; Trinka, E. and R. Kalviainen (2017)).

[0011] RSE is a life-threatening condition and occurs in approximately 30% to 44% of patients with SE. It is associated with increased hospital length of stay and functional disability, with a mortality of approximately 17% (Mayer et al 2002; Gupta 2016).

[0012] RSE often has to be treated with general anesthetics such as pentobarbital or propofol that produce deep EEG suppression (burst suppression and a state of pharmacological coma). Their use, however, is associated with many serious side effects (e.g., severe hypotension, respiratory depression, and propofol infusion syndrome). Once initiated, pharmacological coma prolongs hospitalization for several days which puts patients at an additional risk of developing other serious medical complications (e.g., infections, paralytic ileus, and deep venous thrombosis) and long-term prognosis is poor. When pharmacological coma is initiated, the death rate is approximately 40% and even greater (63%) in elderly patients. Approximately 30% of the patients recover with some degree of neurological deficit, and only 30% of patients recover to baseline (Shorvon et al, 2012). Weaning patients off the seizure-controlling anesthetic agents can be a challenge when trying to meet the goal of having patients breathe on their own. Such weaning may inadvertently cause SE or seizure activity to resume.

[0013] For subjects with RSE who progress to super-refractory SE (SRSE), the prognosis is dire. Studies have shown that 10% to 15% of patients presenting to the hospital in SE develop SRSE (Novy and Rossetti, 2010; Shorvon 2012), and the SRSE mortality is approximately 40% (Strzelczyk et al, 2017). In general, approximately one-third of subjects with RSE and SRSE will die of their condition; one-third recover but with chronic neurologic or other deficits, and one-third have been generally described as returning to baseline (Hocker et al, 2013; Sutter et al, 2013). The longer subjects are kept in a long-term medically induced coma to stop the seizures, the worse the prognosis (Ferlisi and Shorvon, 2012).

[0014] In attempts to manage the symptoms, individuals with RSE are treated with a myriad of drugs that are not indicated for this condition and were not tested for this indication in well-powered, randomized, placebo-controlled studies.

[0015] In addition, there is no regulatory guidance for the clinical study design in the RSE population, and, as of 22 Mar 2019, there have been no completed randomized, placebo-controlled, clinical trials in the RSE population.

[0016] There is an unmet medical need for therapeutics effective against treatment-resistant forms of SE to prevent patients from needing to be treated as a last resort with third-line IV anesthetics, for which use is associated with many direct and indirect serious medical consequences including death in approximately 40% of patients (63% of patients $\geqslant$ 75 years of age) (Kantanen et al, 2015).

## OBJECTS AND SUMMARY OF THE INVENTION

[0017] It is an object of the invention to provide a treatment for status epilepticus.

[0018] It is an additional object of the invention to provide a treatment for Acute Repetitive Seizures (ARS).

[0019] It is another object of the invention to utilize ganaxolone's gamma-aminobutyric acid (GABA)-ergic mechanism of action to provide a therapeutic benefit in the treatment of status epilepticus and/or ARS.

[0020] In furtherance of the above objects and others, the present invention is directed in part to a method of treating a subject experiencing status epilepticus (e.g., a generalized convulsive status epilepticus, non-convulsive status epilepticus, early status epilepticus, established status epilepticus, refractory status epilepticus, or super-refractory status epilepticus) comprising administering a therapeutically effective amount of ganaxolone to reduce or eliminate seizure activity and/or reduce or eliminate convulsions and/or completely suppresses status epilepticus (i.e., suppress EEG seizure activity and convulsions) in the subject. In certain embodiments, the therapeutically effective amount of ganaxolone to reduce or eliminate seizure activity and/or completely suppresses status epilepticus in the subject is the amount that provides and maintains a plasma concentration of ganaxolone of about 50 ng/ml to about 3500 ng/ml in the subject over a time period sufficient to reduce or eliminate seizure activity and/or reduce or eliminate convulsions and/or completely suppresses status epilepticus in the subject. In certain embodiments, the plasma concentration of about 50 mg/ml to about 3500 ng/ml is provided by (i) administering a bolus (e.g., from about 5 mg to about 100 mg, from about 25 mg to about 60 mg, or from about 25 mg to about 30 mg) of ganaxolone over about 1 to about 5 minuntes intravenously; (ii) administering a continuous intravenous infusion of ganaxolone at a rate between about 5 mg/hour and about 130 mg/hour (e.g., from about 5 mg/hour to about 85 mg/hour) for about 8 hours to about 120 hours (e.g., for about 10 hours to about 96 hours), the continuous intravenous infusion starting at about the time of the bolus injection or a short time thereafter (e.g., within about 30 min); and (iii) lowering the rate of intravenous infusion rate over about 12 hours to about 24 hours (e.g., over 12 hours, about 10 hours, about 14 hours, about 16 hours, about 18 hours, or about 20 hours) before the continuous infusion is stopped. In certain embodiments, the plasma concentration of about 50 mg/ml to about 3500 ng/ml is provided by (i) administering a bolus (e.g., from about 5 mg to about 100 mg, from about 25 mg to about 60 mg, or from about 25 mg to about 30 mg) of ganaxolone over about 1 to about 5 minuntes intravenously; (ii) administering a continuous intravenous infusion of ganaxolone at a rate between about 5 mg/hour and about 130 mg/hour (e.g., from about 5 mg/hour to about 85

mg/hour) for about 24 hours to about 120 hours (e.g., for about 48 hours to about 96 hours), the continuous intravenous infusion starting at about the time of the bolus injection or a short time thereafter (e.g., within about 30 min); and (iii) lowering the rate of intravenous infusion rate over about 10 hours to about 24 hours (e.g., over 10 hours, about 12 hours, about 14 hours, about 16 hours, about 18 hours, or about 20 hours) before the continuous infusion is stopped. In some embodiments, a portion of the therapeutically effective amount (e.g., from about 5 mg to about 100 mg, from about 10 mg to about 90 mg, from about 15 mg to about 80 mg, from about 20 mg to about 70 mg, from about 25 mg to about 60 mg, etc.) is administered via a bolus intravenous injection, and the remaining portion of the therapeutically effective amount is administered via a continuous intravenous infusion. In some embodiments, for subjects weighing 40 kg or more, from about 5 mg to about 100 mg (e.g., from about 10 mg to about 90 mg, from about 15 mg to about 80 mg, from about 20 mg to about 70 mg, from about 25 mg to about 60 mg, etc.) of ganaxolone may be administered via the bolus intravenous injection, and the remainder of dose is administered via an intravenous infusion at a rate greater than about 10 mg/hour, 15 mg/hour, 20 mg/hour or 25 mg/hour for about 1 hour to about 120 hours. In some embodiments, the continuous intravenous infusion is at a rate from about 5 mg/hour to about 130 mg/hr, about 5 mg/hour to about 120 mg/hour, from about 5 mg/hour to about 110 mg/hr, from about 5 mg/hour to about 100 mg/hr, from about 5 mg/hour to about 90 mg/hr, or from about 5 mg/hour to about 85 mg/hr for about 1 hour to about 120 hours. In some embodiments, the continuous intravenous infusion is at a rate from about 50 mg/hr to about 130 mg/hr for at least 1 hour. In some embodiments, the therapeutically effective dose, or a portion thereof, is administered intravenously at a rate from about 40 mg/hour to about 140 mg/hour for about 1 hour to about 4 hours; thereafter, at a rate from about 20 mg/hour to about 70 mg/hour for about 1 hour to about 4 hours; thereafter, at a rate from about 10 mg/hour to about 35 mg/hour for about 1 hour to about 4 hours; thereafter, at a rate from about 10 ng/hour to about 30 mg/hour for about 1 hour to about 96 hours; and, thereafter at about 15 mg/hour to about 35 mg/hour for about 1 hour to about 96 hours. In some embodiments, after the administration at the rate from about 15 mg/hour to about 35 mg/hour for about 1 hour to about 96 hours, the rate is reduced by about 10% to about 50% every 1 hour to 12 hours (e.g., the rate may be reduced from about 15% to about 30% every 4 hours to 8 hours). In some of these embodiments, ganaxolone is administered at about 18 mg/hour, about 20 mg/hour, about 22 mg/hour; about 25 mg/hour, about 28 mg/hour,

about 30 mg/hour, about 35 mg/hour, about 40 mg/hour, about 45 mg/hour, about 50 mg/hour, about 60 mg/hour, about 65 mg/hour, or about 70 mg/hour, for at least about 1 hour of the administration. For subjects weighing less than 40 kg, in some embodiments, a bolus dose from about 0.07 mg/kg to about 1.43 mg/kg (e.g., from about 0.125 mg/kg to about 0.4 mg/kg) is administered (over 1 to 5 minutes); and, thereafter, via a continuous infusion from about 0.8 mg/kg/hour to about 2 mg/kg/hour for about 1 to 3 hours; followed by a continuous infusion at a rate from about 0.6 mg/kg/hour to about 1 mg/hr for about 4 to 8 hours; and, thereafter, followed by a continuous infusion at a rate from about 0.15 mg/kg/hour to about 0.4 mg/kg/hour for 13 to 19 hours. At the end of the 24 hours of continuous infusion, the infusion rate may be increased to, e.g., a rate from about 0.2 mg/kg/hour to about 0.6 hour for 24 to 48 hours or 24 to 96 hours. In all of these embodiments, one or more additional bolus dose(s) of ganaxolone from about 1 mg to about 100 mg, from about about 1 mg to about 90 mg, about 1 mg to about 80 mg, about 2 mg to about 75 mg, from about 3 mg to about 70 mg, from about 5 mg to about 60 mg, from about 5 mg to about 50 mg, from about 5 mg to about 45 mg, or from about 5 mg to about 35 mg may be administered intravenously over about 1 to about 5 minutes, e.g., in the event there is seizure(s) (i.e., abnormal EEG activity) and/or convulsion(s) relapse. In certain embodiments, the methods of the invention further comprise, after the intravenous infusion of ganaxolone, orally administering ganaxolone to the subject. The oral daily dose of ganaxolone may be, e.g., from about 200 mg to about 3000 mg, from about 400 mg to about 2000 mg, from about 600 mg to about 1900 mg, or from about 900 mg to about 1800 mg, and may be administered in an oral capsule, oral suspension or an oral tablet. In certain embodiments, the oral daily dose of ganaxolone may be, e.g., from about 200 mg to about 2000 mg, from about 400 mg to about 1500 mg, from about 400 mg to about 1250 mg, or from about 400 mg to about 1000 mg, and may be administered in an oral capsule, oral suspension or an oral tablet. The oral administration may continue, e.g., for about 7 days, 14 days, 21 days, 28 days or longer. In certain embodiments, an additional antiepileptic drug is administered before, during or after the continuous intravenous infusion of ganaxolone. Examples of additional antiepileptic drugs that may be administered are provided in the Additional Antiepileptic Drugs section below. In some embodiments, the additional antiepileptic drug may be selected from the group consisting benzodiazepines, phenytoin, fosphenytoin, valproic acid, phenobarbital, and/or levetiracetam. In some embodiments, the antiepileptic drug is a benzodiazepine (e.g., diazepam, lorazepam, etc.).

[0021] The invention is also directed to a method of treating status epilepticus (e.g., a generalized convulsive status epilepticus, non-convulsive status epilepticus, early status epilepticus, established status epilepticus, refractory status epilepticus, or super-refractory status epilepticus), comprising administering a therapeutic dose of ganaxolone to a subject experiencing status epilepticus in a manner which provides a plasma concentration of ganaxolone of about 50 ng/ml to about 3500 ng/ml over a time period of about 24 hours to about 120 hours, and from about 2 to 5 peaks in the plasma concentration of ganaxolone during said 24 hours to about 120 hours. In certain embodiments, a portion of the therapeutic dose is administered via an intravenous infusion at a rate from about 20 mg/hour to about 140 mg/hour for about 4 hours to about 120 hours, a ganaxolone plasma level from about 800 ng/ml to about 1600 ng/ml is maintained for about 1 hour to about 96 hours, and a portion of the dose is administered via a bolus injection. For subjects weighing 40 kg or more, the bolus injection may comprise, e.g., from about 5 mg to about 100 mg ganaxolone, and the amount of ganaxolone delivered via an intravenous infusion may be, e.g., from about 450 mg to about 3000 mg. In some embodiments, from about 450 mg to about 1000 mg of ganaxolone is administered over each 24 hours of said 24 hours to about 120 hours. For subjects weighing less than 40 kg, the bolus injection may comprise, e.g., from about 0.25 mg to about 16 mg, and from about 100 ng to about 600 mg of ganaxolone may be administered over each 24 hours of the intravenous infusion.

[0022] The invention is also directed to a method of treating status epilepticus (e.g., a generalized convulsive status epilepticus, non-convulsive status epilepticus, early status epilepticus, established status epilepticus, refractory status epilepticus, or super-refractory status epilepticus) comprising administering intravenously a therapeutically effective dose of ganaxolone, or a portion thereof, to reduce or eliminate seizure activity and/or reduce or eliminate convulsions and/or completely suppresses status epilepticus in the subject experiencing status epilepticus over a time period from about 1 hours to about 120 hours, from about 2 hours to about 100 hours, from about 3 hours to about 100 hours, from about 4 hours to about 100 hours, from about 4 hours to about 96 hours (e.g., via a continuous intravenous infusion), wherein the intravenous infusion is started after a bolus dose from about 5 mg to about 100 mg

(e.g., about 6 mg, 8 mg, 10 mg, 12 mg, 14 mg, 16 mg, 18 mg, 20 mg, 22 mg, 24 mg, 26 mg, 28 mg, 30 mg, 32 mg, 34 mg, 36 mg, 38 mg, 40 mg, 42 mg, 44 mg, 46 mg, 48 mg, 50 mg, 52 mg, 54 mg, 56 mg, 58 mg, 59 mg, 60 mg, 61 mg, 62 mg, 63 mg, 64 mg, 65 mg, 66 mg, 67 mg, 68 mg, 69 mg, 70 mg, 71 mg, 72 mg, 73 mg, 74 mg, 75 mg, 76 mg, 77 mg, 78 mg, 79 mg, 80 mg, 81 mg, 82 mg, 83 mg, 84 mg, 85 mg, 86 mg, 87 mg, 88 mg, 89 mg, 90 mg, 91 mg, 92 mg, 93 mg, 94 mg, 95 mg, 96 mg, 97 mg, 98 mg, or 99 mg) is intravenously administered to the subject (e.g., from about 1 second to about 1 hour, from about 1 second to about 45 minutes, from about 1 second to about 30 minutes, from about 1 second to about 15 minutes, from about 1 second to about 10 minutes, from about 1 second to about 5 minutes or from about 2 seconds to about 3 minutes after the bolus dose). In some of the these embodiments, the bolus dose is from about 5 mg to about 90 mg, from about 5 mg to about 80 mg, form about 5 mg to about 70 mg, from about 5 mg to about 60 mg, from about 5 mg to about 50 mg, from about 5 mg to about 40 mg, or form about 5 mg to about 30 mg.

[0023] The invention is further directed to a method of treating a subject experiencing status epilepticus (e.g., a generalized convulsive status epilepticus, non-convulsive status epilepticus, early status epilepticus, established status epilepticus, refractory status epilepticus, or super-refractory status epilepticus) comprising administering intravenously from about 450 mg to about 3000 mg ganaxolone over a time period from about 4 hours to about 120 hours at a rate sufficient to reduce or eliminate seizure activity and/or reduce or eliminate convulsions and/or completely suppresses status epilepticus in the subject. In certain embodiments, the rate is greater than about 10 mg/hour, 15 mg/hour, 20 mg/hour, 25 mg/hour, or 30 mg/hour. In some embodiments from about 5 mg to about 100 mg of ganaxolone is administered via a bolus intravenous injection, and the remainder of dose is administered via a continuous intravenous infusion at a rate greater than about 25 mg/hour for a time period from about 1 hour to about 120 hours.

[0024] The invention is also directed to a method of treating status epilepticus (e.g., a generalized convulsive status epilepticus, non-convulsive status epilepticus, early status epilepticus, established status epilepticus, refractory status epilepticus, or super-refractory status epilepticus) in a subject comprising administering administering from about 1 gram to

about 100 grams (e.g., from about 20 grams to about 70 grams, from about 25 grams to about about 65 grams, from about 30 grams to about 60 grams, from about 35 grams to about 55 grams, etc.) sulfobutylether-β-cyclodextrin to the subject per day in a formulation comprising ganaxolone.

[0025] The invention is further directed to a method of treating a subject experiencing status epilepticus (e.g., a generalized convulsive status epilepticus, non-convulsive status epilepticus, early status epilepticus, established status epilepticus, refractory status epilepticus, or super-refractory status epilepticus) comprising administering intravenously to the subject a formulation comprising ganaxolone and sulfobutylether-β-cyclodextrin in a weight ratio from about 1:50 to about 1:75, wherein from about 450 mg to about 1000 mg of ganaxolone and from about 1 gram to about 100 grams sulfobutylether-β-cyclodextrin is administered per day. In some embodiments, the weight ratio is about 1:60, about 1:65 or about 1:70.

[0026] The invention is further directed to a method of treating a subject experiencing status epilepticus (e.g., a generalized convulsive status epilepticus, non-convulsive status epilepticus, early status epilepticus, established status epilepticus, refractory status epilepticus, or super-refractory status epilepticus) comprising administering intravenously to the subject a formulation comprising ganaxolone and sulfobutylether-β-cyclodextrin in a weight ratio from about 1:50 to about 1:75 at a rate and for a duration sufficient to provide plasma concentration of ganaxolone of about 50 ng/ml to about 3500 ng/ml over a time period of about 24 hours to about 120 hours. In some of these embodiments, the weight ratio ganaxolone and sulfobutylether-β-cyclodextrin is about 1:51, about 1:52, about 1:53, about 1:54, about 1:55, about 1:56, about 1:57, about 1:58, about 1:59, about 1:60, about 1:61, about 1:62, about 1:63, about 1:64, about 1:65, about 1:66, about 1:67, about 1:68, about 1:69, about 1:70, about 1:71, or about 1:72.

[0027] In an additional aspect, the method of treating status epilepticus (e.g., a generalized convulsive status epilepticus, non-convulsive status epilepticus, early status epilepticus, established status epilepticus, refractory status epilepticus, or super-refractory status epilepticus) comprises administering ganaxolone via an intravenous infusion at a rate that is varied during administration from about 10 mg/hour to about 150 mg/hour, about 15 mg/hour to about 150

mg/hour or about 20 mg/hour to about 150 mg/hour. In some embodiments, the therapeutically effective dose, or a portion thereof, is administered parenterally at a rate from about 40 mg/hour to about 140 mg/hour for about 1 hour to about 4 hours; then, at a rate from about 20 mg/hour to about 70 mg/hour for about 1 hour to about 4 hours; then, at a rate from about 10 mg/hour to about 35 mg/hour for about 1 hour to about 4 hours; then, at a rate from about 10 ng/hour to about 30 mg/hour for about 1 hour to about 96 hours; and, then, at a rate from about 15 mg/hour to about 35 mg/hour for about 1 hour to about 96 hours. In some embodiments, after the administration at the rate from about 15 mg/hour to about 35 mg/hour for about 1 hour to about 96 hours, the rate is reduced by about 10% to about 50% every 1 hour to 12 hours (e.g., the rate may be reduced from about 15% to about 30% every 4 hours to 8 hours). In some of these embodiments, ganaxolone may be administered at a rate of at least about 18 mg/hour, about 20 mg/hour, about 22 mg/hour; about 25 mg/hour, about 28 mg/hour, about 30 mg/hour, about 35 mg/hour, about 40 mg/hour, about 45 mg/hour, about 50 mg/hour, about 60 mg/hour, about 65 mg/hour, or about 70 mg/hour, for at least about 1 hour of the administration. In certain embodiments, a bolus dose of ganaxolone is administered intravenously before the start of the intravenous infusion. The bolus dose of ganaxolone may comprise, e.g., from about 5 mg to about 100 mg ganaxolone. In certain embodiments, one or more additional bolus doses of ganaxolone are administered intravenously before, during or after the intravenous infusion. The additional bolus dose may comprise, e.g., from about 5 mg to about 100 mg ganaxolone. In certain embodiments, one or more oral doses of ganaxolone are administered before or after the intravenous infusion or bolus doses of ganaxolone. The oral daily dose of ganaxolone may be, e.g., from about 200 mg to about 3000 mg, from about 400 mg to about 2000 mg, from about 600 mg to about 1900 mg, or from about 900 mg to about 1800 mg, and may be administered in an oral capsule, oral suspension or an oral tablet. In certain embodiments, the oral daily dose of ganaxolone may be, e.g., from about 200 mg to about 2000 mg, from about 400 mg to about 1500 mg, from about 400 mg to about 1250 mg, or from about 400 mg to about 1000 mg, and may be administered in an oral capsule, oral suspension or an oral tablet. The oral administration may continue, e.g., for about 7 days, 14 days, 21 days, 28 days or longer. Thus, the methods of the present invention encompass, e.g., administration of one or more bolus dose(s) of ganaxolone, followed by administration of administering ganaxolone via an intravenous infusion; administration of one or more bolus dose(s) of ganaxolone, followed by administration

of administering ganaxolone via an intravenous infusion; and followed by administration of ganaxolone orally, e.g., in an oral capsule, an oral tablet, an oral suspension, or an oral solution; administration of ganaxolone orally, e.g., in an oral capsule, an oral tablet, an oral suspension or an oral solution, followed by administration of ganaxolone via an intravenous infusion; administration of ganaxolone orally, e.g., in an oral capsule, an oral tablet, an oral suspension or an oral solution, followed by administration of ganaxolone via an intravenous infusion, wherein one or more bolus dose(s) of ganaxolone is (are) administered during the intravenous infusion; administration of ganaxolone orally, e.g., in an oral capsule, an oral tablet, an oral suspension or an oral solution, followed by administration of ganaxolone via one or more intravenous bolus injection(s), and followed by administration of ganaxolone via an intravenous infusion; administration of ganaxolone orally, e.g., in an oral capsule, an oral tablet, an oral suspension or an oral solution, followed by administration of ganaxolone via one or more intravenous bolus injection(s), followed by administration of ganaxolone via an intravenous infusion, and followed by administration of ganaxolone orally, e.g., in an oral capsule, an oral tablet, an oral suspension or an oral solution, etc.

[0028] The invention is also directed in part to a method of treating status epilepticus (e.g., a generalized convulsive status epilepticus, non-convulsive status epilepticus, early status epilepticus, established status epilepticus, refractory status epilepticus, or super-refractory status epilepticus) comprising administering ganaxolone over a time period from about 2 hours to about 120 hours, from about 2 hours to about 100 hours, from about 3 hours to about 100 hours, from about 4 hours to about 100 hours, from about 4 hours to about 96 hours, from about 5 hours to about 96 hours, from about 6 hours to about 96 hours, from about 6 hours to about 90 hours, from about 6 hours to about 88 hours, or from about 10 hours to about 72 hours to a subject experiencing status epilepticus in an amount and at a rate sufficient to provide a plasma concentration of ganaxolone from about 50 ng/ml to about 3500 ng/ml, from about 75 ng/ml to about 3250 ng/ml, from about 100 ng/ml to about 3000 ng/ml, from about 125 ng/ml to about 2750 ng/ml, from about 150 ng/ml to about 2500 ng/ml, from about 175 ng/ml to about 2250 ng/ml, from about 200 ng/ml to about 2200 ng/nl, about 250 ng/ml to about 2150 ng/ml, from about 300 ng/ml to about 2100 ng/ml, from about 350 ng/ml to about 2100 ng/ml, from about 400 ng/ml to about 2100 ng/ml, or from about 450 ng/ml to about 2100 ng/ml, from about 500

ng/ml to about 2000 ng/ml, from about 500 ng/ml to about 1800 ng/ml, from about 500 ng/ml to about 1600 ng/ml, from about 500 ng/ml to about 1500 ng/ml, from about 600 ng/ml to about 1400 ng/ml, from about 600 ng/ml to about 1300 ng/ml, from about 650 ng/ml to about 1200 ng/ml, from about 700 ng/ml to about 1200 ng/ml, from about 750 ng/ml to about 1100 ng/ml, from about 800 ng/ml to about 1100 ng/ml for a time period from about 30 min to about 120 hours (e.g., for about 1 hour, 3 hours, 5 hours, 7 hours, 9 hours, 11 hours, 13 hours, 15 hours, 17 hours, 19 hours, 21 hours, 23 hours, 25 hours, 27 hours, 29 hours, 31 hours, 33 hours, 35 hours, 37 hours, 39 hours, 41 hours, 43 hours, 45 hours, 47 hours, 49 hours, 51 hours, 53 hours, 55 hours, 57 hours, 59 hours, 61 hours, 63 hours, 65 hours, 67 hours, 69 hours, 71 hours, 73 hours, 75 hours, 77 hours, 79 hours, 81 hours, 83 hours, 85 hours, 87 hours, 89 hours, 91 hours, 93 hours, or 95 hours).

[0029] The present invention is also directed in part to a method of treating status epilepticus (e.g., a generalized convulsive status epilepticus, non-convulsive status epilepticus, early status epilepticus, established status epilepticus, refractory status epilepticus, or super-refractory status epilepticus) comprising administering a bolus dose of ganaxolone intravenously in an amount sufficient to achieve a maximum plasma ganaxolone concentration (Cmax) from about about 50 ng/ml to about 3500 ng/ml, from about 75 ng/ml to about 3250 ng/ml, from about 100 ng/ml to about 3000 ng/ml, from about 125 ng/ml to about 2750 ng/ml, from about 150 ng/ml to about 2500 ng/ml, from about 175 ng/ml to about 2250 ng/ml, from about 200 ng/ml to about 2200 ng/nl, from about 250 ng/ml to about 2150 ng/ml, from about 300 ng/ml to about 2100 ng/ml, from about 350 ng/ml to about 2100 ng/ml, from about 400 ng/ml to about 2100 ng/ml, from about 450 ng/ml to about 2100 ng/ml, or from about 500 ng/ml to about to about 2000 ng/ml within 5 minutes of administration, and, after the bolus dose is administered (i.e., from about 1 second to about 1 hour, from about 1 second to about 45 minutes, from about 1 second to about 30 minutes, from about 1 second to about 15 minutes, from about 1 second to about 10 minutes, from about 1 second to about 5 minutes or from about 2 seconds to about 3 minutes after the bolus dose), administering ganaxolone via a continuous intravenous infusion over a time period from about 2 hours to about 120 hours, from about 2 hours to about 100 hours, from about 3 hours to about 100 hours, from about 4 hours to about 100 hours, or from about 4 hours to about 96 hours (e.g., over about 6 hours, 8 hours, 10 hours, 12 hours, 14 hours, 16 hours, 18 hours, 20

hours, 22 hours, 24 hours, 26 hours, 28 hours, 30 hours, 32 hours, 34 hours, 36 hours, 38 hours, 40 hours, 42 hours, 44 hours, 46 hours, 48 hours, 50 hours, 52 hours, 54 hours, 56 hours, 58 hours, 60 hours, 62 hours, 64 hours, 66 hours, 68 hours, 70 hours, 72 hours, 74 hours, 76 hours, 78 hours, 80 hours, 82 hours, 84 hours, 86 hours, 88 hours, 90 hours, 92 hours, or 94 hours) in an amount and at a rate sufficient to maintain a plasma concentration of ganaxolone from about 50 ng/ml to about 3500 ng/ml, from about 75 ng/ml to about 3250 ng/ml, from about 100 ng/ml to about 3000 ng/ml, from about 125 ng/ml to about 2750 ng/ml, from about 150 ng/ml to about 2500 ng/ml, from about 175 ng/ml to about 2250 ng/ml, from about 200 ng/ml to about 2200 ng/nl, from about 250 ng/ml to about 2150 ng/ml, from about 300 ng/ml to about 2100 ng/ml, from about 350 ng/ml to about 2100 ng/ml, from about 400 ng/ml to about 2100 ng/ml, from about 450 ng/ml to about 2100 ng/ml, from about 500 ng/ml to about 1800 ng/ml, from about 600 ng/ml to about 1700 ng/ml, from about 650 ng/ml to about 1600 ng/ml, from about 700 ng/ml to about 1500 ng/ml, from about 750 ng/ml to about 1400 ng/ml, from about 800 ng/ml to about 1300 ng/ml for from about 1 hour to about 96 hours. For subjects weighing 40 kg, or more, the total daily dose of ganaxolone may be, e.g., from about 450 mg to about 2000 mg, from about 500 mg to about 1900 mg, from about 500 mg to about 1800 mg, from about 550 mg to about 1600 mg, from about 550 mg to about 1400 mg, from about 550 mg to about 1200 mg, or from about 600 mg to about 1100 mg, and the bolus dose may comprise, e.g., from about 5 mg to about 100 mg.

[0030] The present invention is further directed in part to a method of treating status epilepticus (e.g., a generalized convulsive status epilepticus, non-convulsive status epilepticus, early status epilepticus, established status epilepticus, refractory status epilepticus, or super-refractory status epilepticus) comprising administering, a bolus dose of ganaxolone intravenously in an amount sufficient to achieve a maximum plasma ganaxolone concentration (Cmax) from about 50 ng/ml to about 3500 ng/ml, from about 75 ng/ml to about 3250 ng/ml, from about 100 ng/ml to about 3000 ng/ml, from about 125 ng/ml to about 2750 ng/ml, from about 150 ng/ml to about 2500 ng/ml, from about 175 ng/ml to about 2250 ng/ml, from about 200 ng/ml to about 2200 ng/nl, from about 250 ng/ml to about 2150 ng/ml, from about 300 ng/ml to about 2100 ng/ml, from about 350 ng/ml to about 2100 ng/ml, from about 400 ng/ml to about 2100 ng/ml, from about 450 ng/ml to about 2100 ng/ml, or from about 500 ng/ml to about 1500 ng/ml within about 5

minutes of administration; and, after the bolus dose (e.g., from about 1 second to about 1 hour, from about 1 second to about 45 minutes, from about 1 second to about 30 minutes, from about 1 second to about 15 minutes, from about 1 second to about 10 minutes, from about 1 second to about 5 minutes or from about 2 seconds to about 3 minutes after the bolus dose), administering ganaxolone intravenously over a time period from about 2 hours to about 120 hours, from about 2 hours to about 100 hours, from about 3 hours to about 100 hours, from about 4 hours to about 100 hours, from about 4 hours to about 96 hours, from about 5 hours to about 96 hours, from about 6 hours to about 96 hours, from about 6 hours to about 90 hours, or from about 6 hours to about 88 hours, or or from about 10 hours to 72 hours via an intravenous infusion in an amount and at a rate to maintain a plasma concentration of ganaxolone from about 600 ng/ml to about 1500 ng/ml for more than 1 hour (e.g., for about 2 hours, 4 hours, 6 hours, 8 hours, 10 hours, 12 hours, 14 hours, 16 hours, 18 hours, 20 hours, 22 hours, 24 hours, 26 hours, 28 hours, 30 hours, 32 hours, 34 hours, 36 hours, 38 hours, 40 hours, 42 hours, 44 hours, 46 hours, 48 hours, 50 hours, 52 hours, 54 hours, 56 hours, 58 hours, 60 hours, 62 hours, 64 hours, 66 hours, 68 hours, 70 hours, 72 hours, 74 hours, 76 hours, 78 hours, 80 hours, 82 hours, 84 hours, 86 hours, 88 hours, 90 hours, 92 hours, 94 hours, 96 hours, etc.).

[0031] The present invention is also directed in part to a method of treating status epilepticus (e.g., a generalized convulsive status epilepticus, non-convulsive status epilepticus, early status epilepticus, established status epilepticus, refractory status epilepticus, or super-refractory status epilepticus) in a subject comprising administering parenterally (e.g., via an intravenous (IV) infusion) from about 400 mg to about 1500 mg ganaxolone for at least one day to a subject experiencing status epilepticus. In certain embodiments, a portion of the daily dose is administered via a bolus injection, and the remaining portion of the dose is administered via a continuous infusion.

[0032] In addition, the invention is directed to a method of treating status epilepticus (e.g., a generalized convulsive status epilepticus, non-convulsive status epilepticus, early status epilepticus, established status epilepticus, refractory status epilepticus, or super-refractory status epilepticus) in a subject comprising administering from about 700 mg to about 1200 mg of ganaxolone intravenously, wherein the administration provides a plasma level of ganaxolone

from about 50 ng/ml to about 3500 ng/ml, from about 75 ng/ml to about 3250 ng/ml, from about 100 ng/ml to about 3000 ng/ml, from about 125 ng/ml to about 2750 ng/ml, from about 150 ng/ml to about 2500 ng/ml, from about 175 ng/ml to about 2250 ng/ml, from about 200 ng/ml to about 2200 ng/nl, from about 250 ng/ml to about 2150 ng/ml, from about 300 ng/ml to about 2100 ng/ml, from about 350 ng/ml to about 2100 ng/ml, from about 400 ng/ml to about 2100 ng/ml, from about 450 ng/ml to about 2100 ng/ml, from about 500 ng/ml to about 1400 ng/ml, from about 500 ng/ml to about 1300 ng/ml, from about 500 ng/ml to about 1200 ng/ml, from about 600 ng ml to about 1200 ng/ml, from about 600 ng/ml to about 1100 ng/ml, from about 650 ng/ml to about 1100 ng/ml, from about 700 ng/ml to about 1100 ng/ml, from about 750 ng/ml to about 1100 ng/ml, from about 800 ng/ml to about 1100 ng/ml for at least 1 hour (e.g., 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 24 hours, etc.), wherein a portion of the dose is administered via a bolus intravenous injection, and the remaining dose is administered via a continuous intravenous infusion.

[0033] The invention is also directed to a method of treating status epilepticus (e.g., a generalized convulsive status epilepticus, non-convulsive status epilepticus, early status epilepticus, established status epilepticus, refractory status epilepticus, or super-refractory status epilepticus) in a subject comprising administering from about 500 mg to about 1200 mg of ganaxolone parenterally (e.g., intravenously) for a time period from about 1 hour to 8 hours (e.g., 2, 4, 5 or 6 hours) at a variable rate from about 10 mg/hr to about 150 mg/hr, from about 15 mg/hr to about 140 mg/hr, or from about 15 mg/hr to about 120 mg/hr, wherein the administration stops EEG seizure activity (e.g., continuous ictal discharges) in the subject. In some embodiments, ganaxolone is administered at a rate from about 50 mg/hr to about 130 mg/hr.

[0034] The invention is further directed in part to a method of treating a subject experiencing non-convulsive EEG seizures, the method comprising administering a therapeutically effective amount of ganaxolone to stop or reduce frequency of the non-convulsive EEG seizures in the subject. In certain embodiments, the therapeutically effective amount of ganaxolone is the amount that provides and maintains a plasma concentration of ganaxolone from about 50 ng/ml

to about 3500 ng/ml, from about 75 ng/ml to about 3250 ng/ml, from about 100 ng/ml to about 3000 ng/ml, from about 125 ng/ml to about 2750 ng/ml, from about 150 ng/ml to about 2500 ng/ml, from about 175 ng/ml to about 2250 ng/ml, from about 200 ng/ml to about 2200 ng/nl, from about 250 ng/ml to about 2150 ng/ml, from about 300 ng/ml to about 2100 ng/ml, from about 350 ng/ml to about 2100 ng/ml, from about 400 ng/ml to about 2100 ng/ml, from about 450 ng/ml to about 2100 ng/ml, or from about 500 ng/ml to about 1900 ng/ml in the subject. In some embodiments, a portion of the therapeutically effective amount is administered via a bolus intravenous injection, and the remaining portion of the therapeutically effective amount is administered via a continuous intravenous infusion. For example, when the subject weighs 40 kg, or more, in some embodiments, from about 5 mg to about 100 mg of ganaxolone is administered via the bolus intravenous injection, and the remainder of dose is administered via an intravenous infusion at a rate greater than 10 mg/hour, 15 mg/hour, 20 mg/hour, 25 mg/hour, 30 mg/hour, 35 mg/hour, 40 mg/hour, 45 mg/hour, 50 mg/hour, 55 mg/hour, 60 mg/hour, 65 mg/hour, 70 mg/hour, 75 mg/hour, 80 mg/hour, or 85 mg/hour for a time period from about 1 hour to about 120 hours (e.g., 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, etc.).

[0035] The invention is also directed to a method of treating non-convulsive EEG seizures comprising administering intravenously a therapeutically effective dose of ganaxolone, or a portion thereof, to stop or reduce frequency of the non-convulsive EEG seizures in the subject over a time period from about 2 hours to about 120 hours, from about 2 hours to about 100 hours, from about 3 hours to about 100 hours, from about 4 hours to about 100 hours, from about 4 hours to about 96 hours, from about 5 hours to about 96 hours, from about 6 hours to about 96 hours, from about 6 hours to about 90 hours, from about 6 hours to about 88 hours, or from about 10 hours to 72 hours via a continuous intravenous infusion, wherein the intravenous infusion is started after (e.g.., from about 1 second to about 1 hour, from about 1 second to about 45 minutes, from about 1 second to about 30 minutes, from about 1 second to about 15 minutes, from about 1 second to about 10 minutes, from about 1 second to about 5 minutes or from about 2 seconds to about 3 minutes after the bolus dose) a bolus dose from about 5 mg to about 100 mg is intravenously administered to the subject.

[0036] The invention is further directed to a method of treating a subject experiencing non-convulsive EEG seizures comprising administering intravenously from about 450 mg to about 3000 mg ganaxolone over a time period from about 4 hours to about 120 hours at a rate greater than about 10 mg/hour, 15 mg/hour, 20 mg/hour, 25 mg/hour, or 30 mg/hour. In some embodiments from about 2 mg to about 100 mg of ganaxolone is administered via the bolus intravenous injection, and the remainder of dose is administered via a continuous intravenous infusion at a rate greater than 10 mg/hr, 15 mg/hour, 20 mg/hr, 25 mg/hr, or 30 mg/hr for a time period from about 1 hour to about 120 hours.

[0037] The invention is also directed to a method of treating status epilepticus (e.g., a generalized convulsive status epilepticus, non-convulsive status epilepticus, early status epilepticus, established status epilepticus, refractory status epilepticus, or super-refractory status epilepticus), comprising administering from about 450 mg to about 1000 mg of ganaxolone intravenously to a subject in need thereof for about 24 hours to about 120 hours, and administering a dose of an additional antiepileptic drug during said 24 hours to about 120 hours. The additional antiepileptic drug may be selected from the group consisting benzodiazepines, phenytoin, fosphenytoin, valproic acid, phenobarbital, and/or levetiracetam. In certain embodiments, the antiepileptic drug is a benzodiazepine (e.g., diazepam, lorazepam, etc.). In some of these embodiments, administration of ganaxolone and the additional antiepileptic drug provides a synergistic effect.

[0038] The invention is also directed to a method of treating Acute Repetitive Seizures (ARS) comprising administering a therapeutically effective amount of ganaxolone intravenously to a subject in need thereof. The therapeutically effective amount may comprise, e.g., from about 1 mg to about 1000 mg of ganaxolone and may be administered as one or more bolus doses, each bolus dose comprising from about 1 mg to about 50 mg, from about 1 mg to about 45 mg, from about 1 mg to about 40 mg, from about 2 mg to about 35 mg, from about 3 mg to about 30 mg, or from about 5 mg to about 30 mg and administered over about 1 to about 5 minutes. In some embodiments, the method further comprises administering, after the one or more bolus doses of ganaxolone, a continuous intravenous infusion of ganaxolone at a rate between about 5 mg/hour and about 130

mg/hour (e.g., from about 5 mg/hour to about 85 mg/hour) for about 24 hours to about 120 hours (e.g., for about 48 hours to about 96 hours), the continuous intravenous infusion started at about the time of the bolus injection or a short time thereafter (e.g., within about 30 min); and lowering the rate of intravenous infusion rate over about 10 hours to about 24 hours (e.g., over 10 hours, about 12 hours, about 14 hours, about 16 hours, about 18 hours, or about 20 hours) before the continuous infusion is stopped.

[0039] In certain embodiments, the methods of the invention further comprise administering one or more rescue bolus dose(s) of ganaxolone from about 1 mg to about 50 mg, from about 1 mg to about 45 mg, from about 1 mg to about 40 mg, from about 2 mg to about 35 mg, from about 3 mg to about 30 mg, or from about 5 mg to about 30 mg may be administered intravenously over about 1 to about 5 minutes during the intravenous infusion. The one or more rescue dose(s) may be administered, e.g., in the event there is seizure(s) (i.e., abnormal EEG activity) and/or convulsion(s) relapse. In some embodiments, one, two, three, four or five rescue doses are administered during the intravenous infusion.

[0040] In certain embodiments, the methods of the invention further comprise, after the intravenous infusion of ganaxolone, orally administering ganaxolone to the subject. The oral daily dose of ganaxolone may be, e.g., from about 200 mg to about 3000 mg, from about 400 mg to about 2000 mg, from about 600 mg to about 1900 mg, or from about 900 mg to about 1800 mg, and may be administered in an oral capsule, oral suspension, an oral solution, or an oral tablet. In certain embodiments, the oral daily dose of ganaxolone may be, e.g., from about 200 mg to about 2000 mg, from about 400 mg to about 1500 mg, from about 400 mg to about 1250 mg, or from about 400 mg to about 1000 mg. The oral administration may continue, e.g., for about 7 days, 14 days, 21 days, 28 days or longer).

[0041] In certain embodiments, the methods of the invention comprise administering some or all of the doses of ganaxolone in the form of nanoparticles.

## DEFINITIONS

[0042] Recitation of ranges of values are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated

herein, and each separate value is incorporated into the specification as if it were individually recited herein. The endpoints of all ranges are included within the range and independently combinable. All methods described herein can be performed in a suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such as"), is intended merely for illustration and does not pose a limitation on the scope of the invention unless otherwise claimed. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the invention.

[0043] The terms "a" and "an" do not denote a limitation of quantity, but rather denote the presence of at least one of the referenced item.

[0044] The term "about" is used synonymously with the term "approximately." The use of the term "about" with respect to doses and amounts of ganaxolone indicates that values slightly outside the cited values, i.e., plus or minus 0.1% to 20%. The use of the term "about" with respect to time periods of administration means for the purposes of the present invention to comprise 2 hours before and 2 hours after that time period. For example, a time period of "about 6 hours" encompasses a time period of 4 hours and a time period of 8 hours. The term "about" with respect to a recited pharmacokinetic parameter value (e.g., a plasma concentration) or a range of pharmacokinetic parameters values (e.g., a range of plasma concentrations values) encompass pharmacokinetic parameters and ranges within 80% to 120 % of the recited value or range.

[0045] An "active agent" is any compound, element, or mixture that when administered to a patient alone or in combination with another agent confers, directly or indirectly, a physiological effect on the patient. When the active agent is a compound, salts, solvates (including hydrates) of the free compound or salt, crystalline and non-crystalline forms, as well as various polymorphs of the compound are included. Compounds may contain one or more asymmetric elements such as stereogenic centers, stereogenic axes and the like, e.g. asymmetric carbon atoms, so that the compounds can exist in different stereoisomeric forms. These compounds can be, for example, racemates or optically active forms. For compounds with two or more

asymmetric elements, these compounds can additionally be mixtures of diastereomers. For compounds having asymmetric centers, it should be understood that all of the optical isomers in pure form and mixtures thereof are encompassed. In addition, compounds with carbon-carbon double bonds may occur in Z- and E-forms, with all isomeric forms of the compounds being included in the present invention. In these situations, the single enantiomers, i.e. optically active forms, can be obtained by asymmetric synthesis, synthesis from optically pure precursors, or by resolution of the racemates. Resolution of the racemates can also be accomplished, for example, by conventional methods such as crystallization in the presence of a resolving agent, or chromatography, using, for example a chiral HPLC column.

[0046] The term "antiepileptic" is a synonym of the term "antiseizure" and means a medication that is used to control seizures and/or epilepsy. The term "antiepileptic" encompasses anticonvulsant medications (i.e., medications that that prevent, stop, or lessens convulsions) and medications that prevent epileptic seizures.

[0047] The term "Acute Repetitive Seizures" (ARS) is a condition manifested by multiple seizures occurring over a relatively brief period of time -generally 24 hours- in patients with epilepsy. ARS could be convulsive or non-convulsive. ARS could progress in SE, but typically there is a recovery period (break) between the seizures and/or convulsions.

[0048] The abbreviation "EEG" means electroencephalography.

[0049] The terms "serum" and "plasma" as disclosed herein may be used interchangeably.

[0050] The terms "comprising," "including," and "containing" are non-limiting. Other non-recited elements may be present in embodiments claimed by these transitional phrases. Where "comprising," "containing," or "including" are used as transitional phrases other elements may be included and still form an embodiment within the scope of the claim. The open-ended transitional phrase "comprising" encompasses the intermediate transitional phrase "consisting essentially of" and the close-ended phrase "consisting of."

[0051] A "bolus dose" is a relatively large dose of medication administered in a short period, for example within 1 to 60 minutes (e.g., 3 or 5 minutes). For subjects weighing 40 kg or more, a bolus dose may comprise from about 5 mg to about 100 mg (e.g., from about 5 mg to about 60 mg, from about 5 mg to about 55 mg, from about 10 mg to about 50 mg, from about 15 mg to about 45 mg, etc.) of ganaxolone (e.g., 6 mg, 7 mg, 8 mg, 9 mg, 10 mg, 11 mg, 12 mg, 13 mg, 14 mg, 15 mg, 16 mg, 17 mg, 18 mg, 19 mg, 20 mg, 21 mg, 22 mg, 23 mg, 24 mg, 25 mg, 26 mg, 27 mg, 28 mg, 29 mg, 30 mg, 31 mg, 32 mg, 33 mg, 34 mg, 35 mg, 36 mg, 37 mg. 38 mg, 39 mg, 40 mg, 41 mg, 42 mg, 43 mg, 44 mg, 45 mg, 46 mg, 47 mg, 48 mg, 49 mg, 50 mg, 51 mg, 52 mg, 53 mg, 54 mg, 55 mg, 56 mg, 57 mg, 58 mg, 59 mg, 60 mg, 61 mg, 62 mg, 63 mg, 64 mg, 65 mg, 66 mg, 67 mg, 68 mg, 69 mg, 70 mg, 71 mg, 72 mg, 73 mg, 74 mg, 75 mg, 76 mg, 77 mg, 78 mg, 79 mg, 80 mg, 81 mg, 82 mg, 83 mg, 84 mg, 85 mg, 86 mg, 87 mg, 88 mg, 89 mg, 90 mg, 91 mg, 92 mg, 93 mg, 94 mg, 95 mg, 96 mg, 97 mg, 98 mg, 99 mg). For subjects weighing less than 40 kg, the bolus dose may comprise from about 0.07 mg to about 1.43 mg/kg (e.g., from about 0.125 mg/kg to about 0.4 mg/kg).

[0052] "$C_{max}$" is the concentration of ganaxolone in the plasma at the point of maximum concentration.

[0053] The abbreviation "eIND" means emergency treatment Investigational New Drug Application.

[0054] The abbreviation "GNX" means ganaxolone.

[0055] "Ganaxolone" means 3α-hydroxy-3β-methyl-5α-pregnan-20-one.

[0056] "Infusion" administration is a non-oral administration, typically intravenous, though other non-oral routes such as epidural administration are included in some embodiments. Infusion administration occurs over a longer period than a bolus administration, for example for a time period greater than 1 hour (e.g., from about 1 hour to about 120 hours).

[0057] A "subject" is a human in need of medical treatment for status epilepticus.

[0058] "Pharmaceutical compositions" are compositions comprising at least one active agent, such as a compound or salt, solvate, or hydrate of ganaxolone, and at least one other substance, such as a carrier. Pharmaceutical compositions optionally contain one or more additional active agents. When specified, pharmaceutical compositions meet the U.S. FDA's GMP (good manufacturing practice) standards for human or non-human drugs. "Pharmaceutical combinations" are combinations of at least two active agents which may be combined in a single dosage form or provided together in separate dosage forms with instructions that the active agents are to be used together to treat a disorder, such as status epilepticus.

[0059] "Povidone" also known as polyvidone and polyvinylpyrrolidone (PVP) is a water soluble polymer made from the monomer, N-vinylpyrrolidone. Plasdone C-12 and C-17 are pharmaceutical grade homopolymers of N-vinylpyrrolidone. Plasdone C-12 has a K value of 10-2-13.8 and nominal molecular weight of 4000 d. Plasdone C-17 has a K-value of 15.5-17.5 and nominal molecular weight of 10,000 d.

[0060] "Sterilize" means to inactivate substantially all biological contaminates in a sample, formulation, or product. A 1-million fold reduction in the bioburden is also considered "sterilized" for most pharmaceutical applications.

[0061] The term "status epilepticus" (SE) is defined as a prolonged self-sustaining seizure or recurrent seizures without recovery of consciousness between seizures (Lowenstein and Alldredge, 1998). The International League Against Epilepsy further defined SE as a condition resulting either from the failure of mechanisms responsible for seizure termination or from the initiation of mechanisms, which lead to abnormally, prolonged seizures (5 minutes for tonic-clonic SE and 10 minutes for focal SE with impaired consciousness) and which can have long-term consequences (after 30 minutes for tonic-clonic SE and after 60 minutes for focal SE with impaired consciousness), including neuronal death and/or injury, and alteration of neuronal networks, depending on the type and duration of seizures (Lowenstein and Alldredge, 1998; Brophy et al, 2012; Bhattacharjee and Hirsch, 2015; Glauser et al 2016). SE encompasses a generalized convulsive status epilepticus (GCSE), non-convulsive status epilepticus (NCSE), early status epilepticus, established status eplilepticus (ESE), refractory status epilepticus (RSE), and super-refractory status epilepticus (SRSE).

[0062] GCSE is defined as status epilepticus that is characterized by convulsions that are associated with tonic-clonic movements of the extremities and mental status impairment, and may result in focal neurologic deficits lasting hours to days following an episode (Brophy et al, 2012). GCSE is associated with many complications, including cardiac arrhythmias, rhabdomyolysis, pulmonary edema, electrolyte and glucose imbalance, and temperature disturbances.

[0063] NCSE is defined as status epilepticus in which seizure activity is seen on EEG without clinical symptoms; however, acutely ill subjects may present with impaired mental status following an NCSE episode (Brophy et al, 2012).

[0064] RSE is defined as status epilepticus that failed to abort after a first-line (i.e., a benzodiazepine) and a second-line anti-seizure medication have been given. Duration is not part of the definition for RSE, which is based solely on the medications given and persistence of seizures (Falco-Walter et al, 2016).

[0065] ESE is the stage right before RSE.

[0066] Early status epilepticus is the stage that precedes ESE and is generally treated with benzodiazepines.

[0067] SRSE is defined as SE that continues 24 hours or more after the onset of anesthesia, including those cases in which the SE recurs on the reduction or withdrawal of anesthesia' (Shorvon and Ferlisi, 2011).

[0068] The term "seizure" or "an epileptic seizure" means a transient occurrence of signs and/or symptoms related to abnormal, excessive or synchronous neuronal activity in the brain. Seizures are detected in the brain by measuring EEG activity. There can be seizures (in the brain) that will not be manifested as convulsions and can only be detected by EEG activity.

[0069] "Convulsions" are behavioral manifestations of seizures. This is what we "see" looking at a subject.

[0070] The term "seizure activity" encompasses convulsions and EEG seizures.

[0071] A "taper period" is a period during which the intravenous infusion rate of ganaxolone is gradually lowered prior to the discontinuation of the intravenous infusion.

[0072] A "therapeutically effective amount" or "effective amount" is that amount of ganaxolone to stop or reduce severity of status epilepticus or one or more of its symptom(s). The term "therapeutically effective amount" includes, for example, a prophylactically effective amount.

[0073] An "effective amount" of ganaxolone is an amount needed to achieve a desired pharmacologic effect or therapeutic improvement without undue adverse side effects. The effective amount of ganaxolone will be selected by those skilled in the art depending on the particular patient and the disease. It is understood that "an effective amount" or "a therapeutically effective amount" can vary from subject to subject, due to variation in metabolism of ganaxolone, age, weight, general condition of the subject, the condition being treated, the severity of the condition being treated, and the judgment of the prescribing physician.

[0074] "Treat" or "treatment" refers to any treatment of status epilepticus, such as reduce or eliminate seizure activity and/or reduce or eliminate convulsions and/or completely suppresses status epilepticus (i.e., suppress EEG seizure activity and convulsions).

[0075] "Titration" means a gradual decrease in dose at the end of the dosing interval. For the purposes of the present invention, "titration" does not encompass a bolus dose.

[0076] As used herein, "hr" means hour.

[0077] As used herein, "mg" means milligrams.

## BRIEF DESCRIPTION OF THE DRAWINGS

[0078] Figure 1 depicts EEG and BIS changes of the Phase 1 clinical study of Example 1. The changes are consistent with sedative/anesthetic effects of ganaxolone.

[0079] Figure 2 is a graph showing predicted ganaxolone plasma concentration against time.

[0080] Figure 3 is a graph showing predicted and actual ganaxolone plasma concentration against time for subject 004-101. The vertical line marks the time of seizure relapse.

[0081] Figure 4 is a snapshot of electroencephalography for subject 004-101.

[0082] Figure 5 is a graph showing predicted and actual ganaxolone plasma concentration against time for subject 004-102. The vertical line marks the beginning of the return of abnormal EEG activity that later required additional intervention.

[0083] Figure 6 is a snapshot electroencephalography for subject 004-102.

[0084] Figure 7 is a graph showing predicted and actual ganaxolone plasma concentration against time for subject 006-101. The vertical line marks the time of seizure relapse.

[0085] Figure 8 is a photograph of electroencephalography for subject 106-102. The vertical line marks the time of ganaxolone treatment initiation.

[0086] Figure 9 is a graph showing predicted and actual ganaxolone plasma concentration against time for subject 006-102. The vertical line marks the time of seizure relapse.

[0087] Figure 10 is a graph showing predicted and actual ganaxolone plasma concentration against time for subject 015-101.

[0088] Figure 11 is a snapshot of electroencephalography of Subject from eIND No. 131,642. Seizures appear as dark areas, as indicated by the comments on the upper margin.

## DETAILED DESCRIPTION

[0089] In SE, seizures can occur with or without behavior convulsions and non-convulsive EEG seizures can continue after the control of the convulsive SE (Saporito et al, 2019).

[0090] As seizures progress, gamma-aminobutyric acid type A ($GABA_A$) receptors that are specific to benzodiazepines become functionally inactive through down regulation which leads to the need for second- and third-line agents to control seizures by other mechanisms. Summary of available therapies for status epilepticus, including their adverse effects, are provided in Table 1.

**Table 1. Summary of Available Therapies in Status Epilepticus**

| Therapy | Adverse Effects and Other Clinical Considerations |
|---|---|
| First-line Therapy | |
| Benzodiazepines | Respiratory depression and hypotension |
| Second-line Therapy | |
| Fosphenytoin | Cardiovascular risk associated with rapid infusion and must be delivered slowly with cardiac monitoring for toxicity including severe hypotension and cardiac arrhythmias |
| Phenytoin | QT interval prolongation, arrhythmias, and purple glove syndrome; narrow therapeutic range |
| Valproic acid | Hepatotoxic effects, thrombocytopenia, pancreatitis, and hyperammonemia |
| Levetiracetam | Significantly less efficacious than valproic acid and phenytoin |
| Phenobarbital | Respiratory and circulatory depression |
| Lacosamide | Cardiac rhythm and conduction abnormalities |
| Third-line Therapy | |
| Propofol | Hypotension, respiratory depression, and propofol infusion syndrome; hemodynamic complications due to intubation |
| Midazolam | Respiratory depression and hypotension; hemodynamic complications due to intubation |
| Pentobarbital | Respiratory depression, hypotension, and bradycardia; hemodynamic complications due to intubation |

Source: Alvarez et al, 2011; Fernandez-Hernandez et al, 2016; Poblete and Sung, 2017

[0091] Seizures associated with SE are commonly refractory to these therapies.

[0092] δ-containing extrasynaptic $GABA_A$ receptors maintain their inhibitory activity during prolonged SE and are sensitive to neuroactive steroids (Joshi and Kapur 2012; Rogawski et al, 2013).

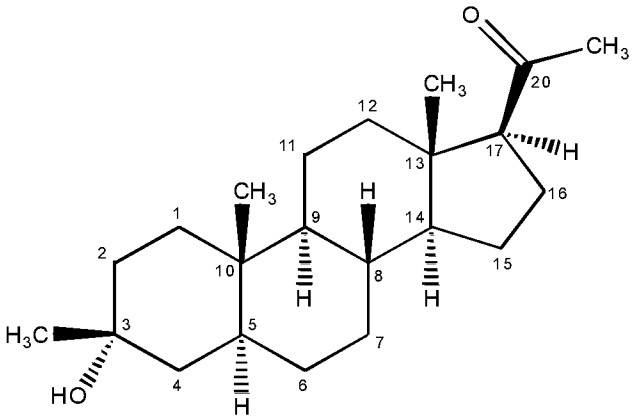
[0093] The preclinical and clinical data described herein supports efficacy of GNX in SE, including RSE. For example, in the ongoing study described in Example 2 (Study 1042-SE-2001), GNX therapy led to rapid cessation of RSE that was otherwise resistant to several second-line IV AEDs in all 5 subjects (100% positive response) enrolled. These data strongly support that GNX is efficacious for this population with RSE.

[0094] Furthermore, the available safety data indicate that treatment with GNX is not associated with producing cardio-pulmonary complications that would require urgent interventions.

## GANAXOLONE

[0095] Ganaxolone is the 3 β -methylated synthetic analogue of the neuroactive steroid allopregnanolone, but it is designed not to activate nuclear (classical) progesterone receptors. Ganaxolone interact with both synaptic and extra-synaptic GABAA receptors and at binding sites distinct from benzodiazepines. Whereas benzodiazepines might lose their inhibitory action, ganaxolone does not because it selectively binds to GABAA receptors containing the α and δ subunits. By enhancing GABAA receptor function, ganaxolone provides an alternative mechanism in the treatment of seizures and could serve as effective therapy in the management of SE, including generalized convulsive status epilepticus, non-convulsive status epilepticus, early status epilepticus, established status epilepticus, refractory status epilepticus, or super-refractory status epilepticus.

[0096] GNX (alternatively known as SPT3162, MD 9150000, CCD-1042, Mepalon, and 1042) is the subject of Investigational New Drug Application (IND) No. 129,433. The molecular formula of GNX is $C_{22}H_{36}O_2$, and the chemical structure is:




Ganaxolone

[0097] GNX (3α-hydroxy-3β-methyl-5α-pregnan-20-one) is a 3β-methyl analog of the endogenous neurosteroid allopregnanolone with similar biological activity (Carter et al 1997). In contrast to allopregnanolone, GNX is orally bioavailable.

[0098] GNX is a neuroactive steroid that acts as a positive allosteric modulator (PAM) of γ-aminobutyric acid type A ($GABA_A$) receptors in the CNS (Carter et al 1997). GNX affects $GABA_A$ receptors by interacting with a recognition site that is distinct from other allosteric $GABA_A$ receptor modulators such as benzodiazepines and barbiturates. GNX binds to synaptic- and extrasynaptic receptors, mediating both phasic and tonic modulation, respectively. The unique binding of GNX to these 2 distinct receptor types does not lead to the tolerance seen with benzodiazepines (Gasior et al., 1997, 2000; Mares and Stehlikova, 2010) and allows GNX to act as a broad-spectrum GABAergic compound with the potential to treat the myriad of symptoms related to pediatric genetic epilepsies, refractory seizures, cognitive and behavioral disorders, and sleep dysfunction.

[0099] GNX does not activate the progesterone receptor directly or indirectly, via metabolic conversion, confirming GNX's lack of hormonal activity.

[0100] GNX has the advantage of controlling both convulsive and non-convulsive seizures. In experimental animals, GNX produced immediate and prolonged cessation of benzodiazepine-

resistant SE as evidenced by a block of convulsions, reduction of EEG seizure activity, and increased survival (Saporito et al, 2019).

[0101] Ganaxolone is insoluble in water. Its solubilities in 95% alcohol, propylene glycol and polyethylene glycol are 13 mg/mL, 3.5 mg/mL and 3.1 mg/mL, respectively.

[0102] Ganaxolone has a relatively long half-life - approximately 20 hours in human plasma following oral administration (Nohria, V. and Giller, E., *Neurotherapeutics*, (2007) 4(1): 102-105). Furthermore, ganaxolone has a short $T_{max}$, which means that therapeutic blood levels are reached quickly.

**Ganaxolone safety information**

[0103] Ganaxolone is metabolized by CYP3A4/5, and *in vitro* data and human PK data from subjects taking strong CYP inducers (carbamazepine and phenytoin) has shown increased ganaxolone clearance with approximately a 45% lowering in overall ganaxolone levels and exposure.

[0104] In the ganaxolone development program overall, no clinically significant trends in electrocardiogram (ECG) intervals, vital signs, or physical or neurological examinations have been noted, and no mean changes from baseline in clinical laboratory results have been identified. In the completed placebo-controlled Phase 1, 2, and 3 studies, 0.32% of subjects who received ganaxolone and 0.46% of subjects who received placebo developed elevated LFTs during the study (>3x ULN AST and/or ALT). A subject participating in the ganaxolone pediatric epilepsy study developed liver failure, which was not considered to be related to ganaxolone. The subject was diagnosed with short bowel syndrome, liver steatosis and IgG-cholangitis, which were considered to be the causal factors for the subject's liver failure. There have been no other cases of Hy's Law or liver failure in the ganaxolone development program.

[0105] It is known that ganaxolone and its metabolites ar excreted to breast milk. After cessation of the dosing, plasma ganaxolone levels are expected to drop rapidly, but it is possible that low sub-therapeutic levels persist for several days as ganaxolone is slowly released from tissues.

[0106] Previous toxicology studies in animals focusing on prenatal and neonatal development have not demonstrated toxicities associated with ganaxolone. Ganaxolone has been administered to infants with severe forms of epilepsy as early as 4 months of age.

[0107] In clinical trials involving administration of ganaxolone over several weeks, the study drug has been tapered off over a 1 to 2-week period. There have been no reports of withdrawal symptoms emerging after cessation of ganaxolone.

## SUBJECT

[0108] A subject in the methods of the present invention is a human experiencing status epilepticus, including, e.g., a generalized convulsive status epilepticus, non-convulsive status epilepticus, early status epilepticus, established status epilepticus, refractory status epilepticus, or super-refractory status epilepticus. The human may be, e.g., from about 1 year to about 120 years old, from about 1 year to about 100 years old, from about 2 years to about 95 years old, from about 5 years to about 90 years old, from about 7 years to about 85 years old, from about 10 years old to about 85 years old, from about 12 years old to about 85 years old, from about 14 years old to about 85 years old, from about 16 years old to about 85 years old, from about 18 years old to about 85 years old, or from about 20 years old to about 85 years old.

[0109] In certain embodiments, the subject does not have a refractory genetic condition selected from the group consisting of PCDH19-related epilepsy, CDKL5 Deficiency Disorder (CDD), Dravet Syndrome, Lennox-Gastaut syndrome (LGS), Continuous Sleep Wave in Sleep (CSWS), Epileptic Status Epilepticus in Sleep (ESES), and other intractable and refractory genetic epilepsy conditions that clinically resemble PCDH19-related epilepsy, CDKL5 Deficiency Disorder, Dravet Syndrome, LGS, CSWS, and ESES. In certain embodiments, the subject does not have CDKL5 gene disorder. In certain embodiments, the subject does not have PCDH19-related epilepsy.

## DOSAGE

[0110] The amount of ganaxolone administered intravenously in the methods of the present invention may vary, e.g., from about 0.25 mg to about 3000 mg (e.g., about 1 mg, 2 mg, 3 mg, 4 mg, 5, mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 55 mg, 60 mg, 65 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 95 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 160 mg, 170 mg, 180 mg, 190 mg, 200 mg, 220 mg, 240 mg, 250 mg, 260 mg, 270 mg, 280 mg, 290 mg, 300 mg, 325 mg, 350 mg, 375 mg, 400 mg, 425 mg, 450 mg, 475 mg, 500 mg, 525 mg, 550 mg, 575 mg, 600 mg, 625 mg, 650 mg, 675 mg, 700 mg, 725 mg, 725 mg, 750 mg, 775 mg, 800 mg, 850 mg, 900 mg, 950 mg, 1000 mg, etc.).

[0111] The total daily dose of ganaxolone administered in the methods of the present invention may vary from about 450 mg to about 1000 mg. In certain embodiments, the total daily dose of ganaxolone is from about 500 mg to about 900 mg, from about 500 mg to about 875 mg, from about 525 mg to about 875 mg, from about 525 mg to about 850 mg, from about 525 mg to about 825 mg, from about 525 mg to about 800 mg, from about 525 mg to about 775 mg, from about 525 mg to about 750 mg, or from about 525 mg to about 725 mg.

[0112] In certain embodiments, the amount of ganaxolone administered is based on the subject's weight. A subject weighing less than 40 kg, may receive a bolus dose from about 0.07 mg/kg to about 1.43 mg/kg (e.g., from about 0.125 mg/kg to about 0.4 mg/kg) (over 1 to 5 minutes); and, thereafter, a continuous infusion at a rate from about 0.8 mg/kg/hour to about 2 mg/kg/hour for about 1 to 3 hours; and, thereafter, a continuous infusion at a rate from about 0.6 mg/kg/hour to about 1 mg/hr for about 4 to 8 hours; and, thereafter, at a rate from about 0.15 mg/kg/hour to about 0.4 mg/kg/hour for 13 to 19 hours. At the end of the 24 hours of continuous infusion, the infusion rate may be increased to, e.g., a rate from about 0.2 mg/kg/hour to about 0.6 hour for 24 to 48 hours or 24 to 96 hours. The dose may then be tampered by 10 to 25% every 6 hours and then discontinued. In some embodiments, the dose is reduced by about 25% every 6 hours (75%, 50%, and 25%) and then discontinued. In some embodiments, the taper is from 12 to 24 hours.

[0113] A subject weighing 40 kg or more, may receive a bolus dose from about 5 mg to about 100 mg (over about 1 to 5 minutes), and then a continuous infusion from about 60 mg/hour to about 160 mg/hour for 1 to 4 hours; followed by a continuous infusion rate from about 20 mg/hour to about 140 mg/hour for 4 to 8 hours; and, thereafter, at a rate from about 10 mg/hour to about 120 mg/hour for 12 to 19 hours. At the end of the first 24 hours of continuous infusion, the infusion rate may be increased for 24 to 48 hours or 24 to 96 hours. The dose may then be tampered by 10 to 25% every 6 hours and then discontinued. In some embodiments, the dose is reduced by about 25% every 6 hours (75%, 50%, and 25%) and then discontinued. In some embodiments, the taper is from 12 to 24 hours.

[0114] In certain embodiments, the methods of the invention comprise administering some or all of the doses of ganaxolone in the form of nanoparticles. Preparation and compositions of the exemplary nanoparticles are described in the Formulation section below.

[0115] In the embodiments, where the subject receives the drug for less than 2 hours or progresses to an IV anaesthetic drug (a 3$^{rd}$ line treatment) for seizure suppression, tapering of the dose is not required, and the methods of the invention do not comprise a tapering step.

[0116] In the methods of the invention, ganaxolone dose, or a portion thereof, is administered through a dedicated (peripheral or central) IV line.

## RATE OF ADMINISTRATION

[0117] The rate of infusion will generally vary between about 5 mg/hour to about 130 mg/hour, depending on clinical response and safety. In certain embodiments, the rate of administration is from about 5 mg/hour to about 90 mg/hour.

## TREATMENT DURATION

[0118] The duration of treatment may vary, e.g., from about 30 minutes to about 120 hours. In certain embodiments, the treatment duration is about 1 to about 5 days (e.g., about 24 hours, about 36 hours, about 48 hours, about 72 hours, about 96 hours, or about 120 hours). In certain

embodiments, the treatment includes a taper period of from about 10 hours to about 24 hours (e.g., an 18-hour taper).

[0119] In certain embodiments, treatment is continued until the subject achieves a seizure burden improvement of about 100.

[0120] Seizure burden is defined by the number of seizures in the entire duration of the EEG collection during the first 2 days of treatment. This will be compared to the seizure burden from the pre-dose EEG (up to 24 hours prior to study drug initiation through immediately prior to study drug administration). If a pre-dose EEG is not available the calculation should be done from the start of the EEG collection through the end of the first 2 days.

[0121] In certain embodiments, seizure burden assessed as duration of electrographic seizure activity per hour of EEG recording collected.

[0122] In certain embodiments, the seizure burden improvement is calculated about 12 to about 60 hours after the initiation of therapy.

[0123] If the seizure burden calculation indicates that the subject is unlikely to benefit from additional administration (e.g., if the partial seizure burden improvement is about 100%), the dosage may be tapered over 12 to 24 hours (e.g., 18 hours). Conversely, if the seizure burden calculation indicates that the subject may likely to benefit (e.g., if the partial seizure burden improvement is between 33-50%), administration of ganaxolone will continue for an additional time period (e.g., 24 to 48 hours). At the end of the additional time period, the subject may be reassessed and/or the dose of ganaxolone may be tapered over 12 to 24 hours (e.g., 18 hours).

[0124] For subjects who receive study drug for less than 2 hours and/or if at any time during study drug administration the subject progresses to an IV anesthetic (a 3rd line treatment) for seizure suppression no dose taper is required.

## FORMULATIONS

[0125] The formulations of the present invention comprise a therapeutically effective amount of ganaxolone to treat status epilepticus and one or more pharmaceutically acceptable excipient(s).

[0126] In certain embodiments, the formulation is an intravenous formulation. The intravenous formulation may be selected, e.g., from the group consisting of nanocrystal formulations; emulsions; lyocells; solvents or surfactants; liposomes; microemulsions; and liquids containing solid-lipid nanoparticles.

[0127] In certain embodiments, the intravenous formulation is an IV solution. An intravenous formulation is preferably a sterile liquid (e.g., aqueous liquid in the form of an emulsion, a suspension, a solution and the likes). In some of these embodiments, the IV solution comprises ganaxolone and a pharmaceutically acceptable solvent(s) and/or oil(s) that can solubilize ganaxolone.

[0128] In certain embodiments, the intravenous formulation is an oil-in-water emulsion.

[0129] In certain embodiments, the intravenous formulation is a liquid nanoparticulate formulation (e.g., a liquid comprising nanoparticles of ganaxolone). In some of the embodiments, the nanoparticulate formulation comprises ganaxolone and a polymeric and/or ionic stabilizer, and is free from complexing agents. In certain embodiments, the polymeric and ionic stabilizers are selected from the group consisting of surfactants. In certain embodiments, surfactants are selected from the group consisting of sorbitan esters, polyoxyethylene sorbitan fatty acid esters, poloxamers, cholesterol salts, and bile salts.

[0130] In certain embodiments, IV solution is a sterile 3 mg/ml ganaxolone in Captisol® (Sulfobutylether-β-Cyclodextrin), which may or may not be may be diluted with 0.9 % saline (i.e., sodium chloride) solution.

[0131] In certain embodiments, the formulation (e.g., an intravenous formulation) comprises ganaxolone and sulfobutylether-β-cyclodextrin (e.g., Captisol®) in a weight ratio from about 1:50 to about 1:75. In some of these embodiments, the weight ratio ganaxolone and Captisol® is

about 1:51, about 1:52, about 1:53, about 54:1, about 1:55, about 1:56, about 1:57, about 1:58, about 1:59, about 1:60, about 1:61, about 1:62, about 1:63, about 1:64, about 1:65, about 1:66, about 1:67, about 1:68, about 1:69, about 1:70, about 1:71, or about 1:72. In some of these embodiments, the weight ratio ganaxolone and Captisol® is about 1:60.

[0132] In certain embodiments, the formulation for the intravenous infusion may be a formulation as described and prepared in Applicant's prior U.S. Patent Publication No. 2017/0258812 (U.S. Serial No. 15/294,135, filed October 14, 2016), entitled "Injectable Neurosteroid Formulations Containing Nanoparticles," hereby incorporated by reference in its entirety, or a formulation as described and prepared in Applicant's prior U.S. Patent Publication No. 2016/0228454, entitled "Intravenous ganaxolone formulations and methods of use in treating status epilepticus and other seizure disorders," hereby incorporated by reference in its entirety. However, formulations for the intravenous infusion may be prepared in accordance with other methods known to those skilled in the art.

[0133] As described in U.S. Patent Publication No. 2016/0228454, an aqueous injectable ganaxolone formulation may comprise a) ganaxolone and sulfobutyl ether-β-cyclodextrin in an inclusion complex; and b) water. In some embodiments, the complex comprising ganaxolone and sulfobutyl ether-β-cyclodextrin comprises a 1:1 ganaxolone: sulfobutyl ether-β-cyclodextrin complex; and the w/w ratio of sulfobutyl ether-β-cyclodextrin to ganaxolone is about 52:1 or greater. In some embodiments, the formulatio may further comprise surfactant. In some embodiments, the surfactant is a sorbitan ester, a polyoxyethylene sorbitan fatty acid ester, a poloxamer, a cholesterol salt, or a bile salt. In some embodiments, the surfactant may comprise from about 1 to about 15 percent of the formjulation by weight. In some embodiments, the surfactant is polysorbate 80. In some embodiments, the formulation further comprises a buffer and has a pH of about 6.8 to about 7.6. In some embodiments, the buffer is a phosphate buffer. In some embodiments, the buffer is a combination of a monobasic phosphate buffer and a dibasic phosphate buffer, wherein the concentration of each phosphate buffer is 2 mM to 50 mM. In some embodiments, the buffer is a phosphate buffer. In some embodiments, the buffer is a combination of a monobasic phosphate buffer and a dibasic phosphate buffer, wherein the concentration of each phosphate buffer is 2 mM to 50 mM. In some embodiments, the

concentration of ganaxolone is 2 mg/ml to 8 mg/ml, the w/w ratio of sulfobutyl ether-β-cyclodextrin to ganaxolone is within the range from about 52:1 to about 90:1; the formulation contains a buffer and has a pH of 6.7 to 7.3; and the formulation contains from 1 to 15 weight percent surfactant. In some embodiments, the concentration of ganaxolone is 1 mg/ml to 5 mg/ml; the weight percent of sulfobutyl ether-β-cyclodextrin 25% to 35%; and the formulation contains from 5% to 15% (weight percent) of at least one of the following: a surfactant, ethanol, glycerin, or propylene glycol. In some embodiments, the formulation further comprises a preservative. In some embodiments, the preservative is benzyl alcohol, chlorbutanol, 2-ethoxyethanol, parabens (including methyl, ethyl, propyl, butyl, and combinations), benzoic acid, sorbic acid, chlorhexidene, phenol, 3-cresol, thimerosal, or a phenylmercurate salt.

[0134] As further described in U.S. Patent Publication No. 2016/0228454, the formulation may be a lyophilized ganaxolone formulation comprising ganaxolone and sulfobutyl ether-β-cyclodextrin, wherein the ganaxolone formulation is 1.0% to 1.5% ganaxolone. In some embodiments, the formulation may further comprise a bulking agent. In some embodiments, the bulking agent is mannitol, lactose, sucrose, trehalose, sorbitol, glucose, rafinose, glycine, histidine, polyethylene glycol (PEG), or polyvinyl pyrrolidone (PVP).

[0135] Ganaxolone formulations suitable for parenteral administration in the methods of the present invention may comprise physiologically acceptable sterile aqueous or non-aqueous solutions, dispersions, suspensions or emulsions, and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and non-aqueous carriers, diluents, solvents, or vehicles including water, ethanol, polyols (propylene glycol, polyethylene-glycol, glycerol, cremophor and the like), suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Additionally, ganaxolone can be dissolved at concentrations of >1 mg/ml using water soluble beta cyclodextrins (e.g. beta-sulfobutyl-cyclodextrin and 2-hydroxypropylbetacyclodextrin). A particularly suitable cyclodextrin is a substituted-β-cyclodextrin is Captisol®. Proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants. Ganaxolone formulations suitable for subcutaneous injection may also contain additives such as preserving, wetting, emulsifying, and

dispensing agents. Prevention of the growth of microorganisms can be ensured by various antibacterial and antifungal agents, such as parabens, benzoic acid, benzyl alcohol, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like. Prolonged drug absorption of the injectable pharmaceutical form can be brought about by the use of agents delaying absorption, such as aluminum monostearate and gelatin. Ganaxolone suspension formulations designed for extended release via subcutaneous or intramuscular injection can avoid first pass metabolism and lower dosages of ganaxolone will be necessary to maintain plasma levels of about 50 ng/ml. In such formulations, the particle size of the ganaxolone particles and the range of the particle sizes of the ganaxolone particles can be used to control the release of the drug by controlling the rate of dissolution in fat or muscle.

[0136] In certain embodiments, the intravenous formulation is a solution comprising a complexing agent(s). In some of these embodiments, a complexing agent is a molecule with a lipophilic core and hydrophilic outer shell capable of solubilizing ganaxolone

[0137] In certain embodiments, the formulation is an IV solution comprising ganaxolone and sulfobutylether cyclodextrin (Captisol®), wherein ganaxolone is solubilized in sulfobutylether cyclodextrin (Captisol®). In some embodiments, the solution comprises 3 mg of ganaxolone per 1 ml of the solution and is sterile. In certain embodiments, the solution is stable for at least 18 months, is stored refrigerated at a temperature from about 4°C to about 8°C.

[0138] In certain embodiments, the liquid formulation of the present invention may be a formulation as described and prepared in Applicant's prior U.S. Patent No. 8,022,054, entitled "Liquid Ganaxolone Formulations and Methods for the Making and Use Thereof", hereby incorporated by reference in its entirety. However, the oral liquid (e.g., suspension) formulation of ganaxolone may be prepared in accordance with other methods known to those skilled in the art.

[0139] As described in U.S. Patent No. 8,022,054, the liquid formulation may be an aqueous dispersion of stabilized particles comprising ganaxolone, a hydrophilic polymer, a wetting agent, and an effective amount of a complexing agent that stabilizes particle growth after an initial

particle growth and endpoint is reached, the complexing agent selected from the group of small organic molecules having a molecular weight less than 550 and containing a moiety selected from the group consisting of a phenol moiety, an aromatic ester moiety and an aromatic acid moiety, wherein the stabilized particles have a volume weighted median diameter (D50) of the particles from about 50 nm to about 500 nm, the complexing agent being present in an amount from about 0.05% to about 5%, w/w based on the weight of particles, the particles dispersed in an aqueous solution which further contains at least two preservatives in an amount sufficient to inhibit microbial growth. The hydrophilic polymer may be in an amount from about 3% to about 50%, w/w, based on the weight of the solid particles. The wetting agent may be an amount from about 0.01% to about 10%, w/w, based on the weight of the solid particles. Ganaxolone may be in an amount from about 10% to about 80% (and in certain embodiments form about 50% to about 80%) based on the weight of the stabilized particles. The stabilized particles may exhibit an increase in volume weighted median diameter (D50) of not more than about 150% when the particles are dispersed in simulated gastric fluid (SGF) or simulated intestinal fluid (SIF) at a concentration of 0.5 to 1 mg ganaxolone/mL and placed in a heated bath at 36° to 38° C for 1 hour as compared to the D50 of the stabilized particles when the particles are dispersed in distilled water under the same conditions, wherein the volume weighted median diameter (D50) of the stabilized particles dispersed in SGF or SIF is less than about 750 nm. The stabilized particles may exhibit an increase in volume weighted median diameter (D50) of not more than about 150% when the formulation is dispersed in 15 mL of SGF or SIF at a concentration of 0.5 to 1 mg ganaxolone/mL as compared to the D50 of the stabilized particles when the particles are dispersed in distilled water under the same conditions, wherein the volume weighted median diameter (D50) of the stabilized particles dispersed in SGF or SIF is less than about 750 nm.

[0140] The complexing agent can be any molecule with a lipophilic core and hydrophilic outer shell capable of solubilizing ganaxolone. In certain embodiments, complexing agent can be a substance containing a phenol moiety, an aromatic ester moiety or an aromatic acid moiety. In certain embodiments, complexing agents are selected from the group consisting of parabens, organic acids, carboxylic acids, aromatic acids, aromatic esters, acid salts of amino acids, methyl anthranilate, sodium metabisulphite, ascorbic acid and its derivatives, malic acid, isoascorbic acid, citric acid, tartaric acid, sodium sulphite, sodium bisulphate, tocopherol, water- and fat-

soluble derivatives of tocopherol, sulphites, bisulphites and hydrogen sulphites, para-aminobenzoic acid and esters, 2,6-di-t-butyl-alpha-dimethylamino-p-cresol, t-butylhydroquinone, di-t-amylhydroquinone, di-t-butylhydroquinone, butylhydroxytoluene (BHT), butylhydroxyanisole (BHA), pyrocatechol, pyrogallol, propyl/gallate, nordihydroguaiaretic acid, phosphoric acids, sorbic and benzoic acids, esters, ascorbyl palmitate, derivatives and isomeric compounds thereof, pharmaceutically acceptable salts thereof, and mixtures thereof. In certain embodiments, the complexing agent is selected from the group consisting of a paraben, benzoic acid, phenol, sodium benzoate, methyl anthranilate, and the like. The hydrophilic polymer may be a cellulosic polymer, a vinyl polymer and mixtures thereof. The cellulosic polymer may be a cellulose ether, e.g., hydroxypropymethylcellulose. The vinyl polymer may be polyvinyl alcohol, e.g., vinyl pyrrolidone/vinyl acetate copolymer (S630). The wetting agent may be sodium lauryl sulfate, a pharmaceutically acceptable salt of docusate, and mixtures thereof. The aqueous dispersion may further comprise a sweetener, e.g., sucralose. In certain embodiments, the preservative is selected from the group consisting of potassium sorbate, methylparaben, propylparaben, benzoic acid, butylparaben, ethyl alcohol, benzyl alcohol, phenol, benzalkonium chloride, and mixtures of any of the foregoing.

[0141] In some embodiments, liquid ganaxolone formulations are provided comprising the ganaxolone particles described herein and at least one dispersing agent or suspending agent for oral administration to a subject. The ganaxolone formulation may be a powder and/or granules for suspension, and upon admixture with water, a substantially uniform suspension is obtained. As described herein, the aqueous dispersion can comprise amorphous and non-amorphous ganaxolone particles of consisting of multiple effective particle sizes such that ganaxolone particles having a smaller effective particle size are absorbed more quickly and ganaxolone particles having a larger effective particle size are absorbed more slowly. In certain embodiments the aqueous dispersion or suspension is an immediate release formulation. In another embodiment, an aqueous dispersion comprising amorphous ganaxolone particles is formulated such that about 50% of the ganaxolone particles are absorbed within about 3 hours after administration and about 90% of the ganaxolone particles are absorbed within about 10 hours after administration. In other embodiments, addition of a complexing agent to the aqueous dispersion results in a larger span of ganaxolone containing particles to extend the drug

absorption phase such that 50-80% of the particles are absorbed in the first 3 hours and about 90% are absorbed by about 10 hours.

[0142] A suspension is "substantially uniform" when it is mostly homogenous, that is, when the suspension is composed of approximately the same concentration of ganaxolone at any point throughout the suspension. Preferred embodiments are those that provide concentrations essentially the same (within 15%) when measured at various points in a ganaxolone aqueous oral formulation after shaking. Especially preferred are aqueous suspensions and dispersions, which maintain homogeneity (up to 15% variation) when measured 2 hours after shaking. The homogeneity should be determined by a sampling method consistent with regard to determining homogeneity of the entire composition. In one embodiment, an aqueous suspension can be re-suspended into a homogenous suspension by physical agitation lasting less than 1 minute. In another embodiment, an aqueous suspension can be re-suspended into a homogenous suspension by physical agitation lasting less than 45 seconds. In yet another embodiment, an aqueous suspension can be re-suspended into a homogenous suspension by physical agitation lasting less than 30 seconds. In still another embodiment, no agitation is necessary to maintain a homogeneous aqueous dispersion.

[0143] In some embodiments, ganaxolone formulations are powders for aqueous dispersion and comprise stable ganaxolone particles having an effective particle size by weight of less than 500 nm formulated with ganaxolone particles having an effective particle size by weight of greater than 500 nm. In such embodiments, the formulations have a particle size distribution wherein about 10% to about 100% of the ganaxolone particles by weight are between about 75 nm and about 500 nm, about 0% to about 90% of the ganaxolone particles by weight are between about 150 nm and about 400 nm, and about 0% to about 30% of the ganaxolone particles by weight are greater than about 600 nm. The ganaxolone particles describe herein can be amorphous, semi-amorphous, crystalline, semi-crystalline, or mixture thereof.

[0144] In one embodiment, the aqueous suspensions or dispersions described herein comprise ganaxolone particles or ganaxolone complex at a concentration of about 20 mg/ml to about 150 mg/ml of suspension. In another embodiment, the aqueous oral dispersions described herein

comprise ganaxolone particles or ganaxolone complex particles at a concentration of about 25 mg/ml to about 75 mg/ml of solution. In yet another embodiment, the aqueous oral dispersions described herein comprise ganaxolone particles or ganaxolone complex at a concentration of about 50 mg/ml of suspension. The aqueous dispersions described herein are especially beneficial for the administration of ganaxolone to infants (less than 2 years old), children under 10 years of age and any patient group that is unable to swallow or ingest solid oral dosage forms.

[0145] Liquid ganaxolone formulation for oral administration can be aqueous suspensions selected from the group including, but not limited to, pharmaceutically acceptable aqueous oral dispersions, emulsions, solutions, and syrups. See, e.g., Singh et al., Encyclopedia of Pharmaceutical Technology, 2nd Ed., pp. 754-757 (2002). In addition to ganaxolone particles, the liquid dosage forms may comprise additives, such as: (a) disintegrating agents; (b) dispersing agents; (c) wetting agents; (d) at least one preservative, (e) viscosity enhancing agents, (f) at least one sweetening agent, (g) at least one flavoring agent, (h) a complexing agent, and (i) an ionic dispersion modulator. In some embodiments, the aqueous dispersions can further comprise a crystalline inhibitor.

[0146] Examples of disintegrating agents for use in the aqueous suspensions and dispersions include, but are not limited to, a starch, e.g., a natural starch such as corn starch or potato starch, a pregelatinized starch such as National 1551 or Amijele®, or sodium starch glycolate such as Promogel® or Explotab®; a cellulose such as a wood product, microcrystalline cellulose, e.g., Avicel®, Avicel® PH101, Avicel® PH102, Avicel® PH105, Elcema® P100, Emcocel®, Vivacel®, Ming Tia®, and Solka-Floc®, methylcellulose, croscarmellose, or a cross-linked cellulose, such as cross-linked sodium carboxymethylcellulose (Ac-Di-Sol®), cross-linked carboxymethylcellulose, or cross-linked croscarmellose; a cross-linked starch such as sodium starch glycolate; a cross-linked polymer such as crosspovidone; a cross-linked polyvinylpyrrolidone; alginate such as alginic acid or a salt of alginic acid such as sodium alginate; a clay such as Veegum® HV (magnesium aluminum silicate); a gum such as agar, guar, locust bean, Karaya, pectin, or tragacanth; sodium starch glycolate; bentonite; a natural sponge; a surfactant; a resin such as a cation-exchange resin; citrus pulp; sodium lauryl sulfate; sodium lauryl sulfate in combination starch; and the like.

[0147] In some embodiments, the dispersing agents suitable for the aqueous suspensions and dispersions described herein are known in the art and include, for example, hydrophilic polymers, electrolytes, Tween® 60 or 80, PEG, polyvinylpyrrolidone (PVP; commercially known as Plasdone®), and the carbohydrate-based dispersing agents such as, for example, hydroxypropylcellulose and hydroxypropylcellulose ethers (e.g., HPC, HPC-SL, and HPC-L), hydroxypropylmethylcellulose and hydroxypropylmethylcellulose ethers (e.g. HPMC K100, HPMC K4M, HPMC K15M, and HPMC K100M), carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose acetate stearate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol (PVA), polyvinylpyrrolidone/vinyl acetate copolymer (Plasdone®, e.g., S-630), 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde (also known as tyloxapol), poloxamers (e.g., Pluronics F68®, F88®, and F108®, which are block copolymers of ethylene oxide and propylene oxide); and poloxamines (e.g., Tetronic 9080, also known as Poloxamine 9080, which is a tetrafunctional block copolymer derived from sequential addition of propylene oxide and ethylene oxide to ethylenediamine (BASF Corporation, Parsippany, N.J.)). In other embodiments, the dispersing agent is selected from a group not comprising one of the following agents: hydrophilic polymers; electrolytes; Tween® 60 or 80; PEG; polyvinylpyrrolidone (PVP); hydroxypropylcellulose and hydroxypropyl cellulose ethers (e.g., HPC, HPC-SL, and HPC-L); hydroxypropyl methylcellulose and hydroxypropyl methylcellulose ethers (e.g. HPMC K100, HPMC K4M, HPMC K15M, HPMC K100M, and Pharmacoat® USP 2910 (Shin-Etsu)); carboxymethylcellulose sodium; methylcellulose; hydroxyethylcellulose; hydroxypropylmethyl-cellulose phthalate; hydroxypropylmethyl-cellulose acetate stearate; non-crystalline cellulose; magnesium aluminum silicate; triethanolamine; polyvinyl alcohol (PVA); 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde; poloxamers (e.g., Pluronics F68®, F88®, and F108®, which are block copolymers of ethylene oxide and propylene oxide); or poloxamines (e.g., Tetronic 908®, also known as Poloxamine 908%).

[0148] Wetting agents (including surfactants) suitable for the aqueous suspensions and dispersions described herein are known in the art and include, but are not limited to, acetyl

alcohol, glycerol monostearate, polyoxyethylene sorbitan fatty acid esters (e.g., the commercially available Tweens® such as e.g., Tween 20® and Tween 80® (ICI Specialty Chemicals)), and polyethylene glycols (e.g., Carbowaxs 3350® and 1450®, and Carpool 934® (Union Carbide)), oleic acid, glyceryl monostearate, sorbitan monooleate, sorbitan monolaurate, triethanolamine oleate, polyoxyethylene sorbitan monooleate, polyoxyethylene sorbitan monolaurate, sodium oleate, sodium lauryl sulfate, sodium docusate, triacetin, vitamin E TPGS, sodium taurocholate, simethicone, phosphotidylcholine and the like.

[0149] Suitable preservatives for the aqueous suspensions or dispersions described herein include, for example, potassium sorbate, parabens (e.g., methylparaben and propylparaben) and their salts, benzoic acid and its salts, other esters of parahydroxybenzoic acid such as butylparaben, alcohols such as ethyl alcohol or benzyl alcohol, phenolic compounds such as phenol, or quaternary compounds such as benzalkonium chloride. Preservatives, as used herein, are incorporated into the dosage form at a concentration sufficient to inhibit microbial growth. In one embodiment, the aqueous liquid dispersion can comprise methylparaben and propylparaben in a concentration ranging from about 0.01% to about 0.3% methylparaben by weight to the weight of the aqueous dispersion and 0.005% to 0.03% propylparaben by weight to the total aqueous dispersion weight. In yet another embodiment, the aqueous liquid dispersion can comprise methylparaben 0.05 to about 0.1 weight % and propylparaben from 0.01-0.02 weight % of the aqueous dispersion.

[0150] Suitable viscosity enhancing agents for the aqueous suspensions or dispersions described herein include, but are not limited to, methyl cellulose, xanthan gum, carboxymethylcellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, Plasdone.RTM. S-630, carbomer, polyvinyl alcohol, alginates, acacia, chitosans and combinations thereof. The concentration of the viscosity enhancing agent will depend upon the agent selected and the viscosity desired.

[0151] Examples of natural and artificial sweetening agents suitable for the aqueous suspensions or dispersions described herein include, for example, acacia syrup, acesulfame K, alitame, anise, apple, aspartame, banana, Bavarian cream, berry, black currant, butterscotch, calcium citrate, camphor, caramel, cherry, cherry cream, chocolate, cinnamon, bubble gum, citrus, citrus punch,

citrus cream, cotton candy, cocoa, cola, cool cherry, cool citrus, cyclamate, cylamate, dextrose, eucalyptus, eugenol, fructose, fruit punch, ginger, glycyrrhetinate, glycyrrhiza (licorice) syrup, grape, grapefruit, honey, isomalt, lemon, lime, lemon cream, monoammonium glyrrhizinate (MagnaSweet®), maltol, mannitol, maple, marshmallow, menthol, mint cream, mixed berry, neohesperidine DC, neotame, orange, pear, peach, peppermint, peppermint cream, Prosweet®. Powder, raspberry, root beer, rum, saccharin, safrole, sorbitol, spearmint, spearmint cream, strawberry, strawberry cream, stevia, sucralose, sucrose, sodium saccharin, saccharin, aspartame, acesulfame potassium, mannitol, talin, sucralose, sorbitol, Swiss cream, tagatose, tangerine, thaumatin, tutti fruitti, vanilla, walnut, watermelon, wild cherry, wintergreen, xylitol, or any combination of these flavoring ingredients, e.g., anise-menthol, cherry-anise, cinnamon-orange, cherry-cinnamon, chocolate-mint, honey-lemon, lemon-lime, lemon-mint, menthol-eucalyptus, orange-cream, vanilla-mint, and mixtures thereof. In one embodiment, the aqueous liquid dispersion can comprise a sweetening agent or flavoring agent in a concentration ranging from about 0.0001% to about 10.0% the weight of the aqueous dispersion. In another embodiment, the aqueous liquid dispersion can comprise a sweetening agent or flavoring agent in a concentration ranging from about 0.0005% to about 5.0% wt % of the aqueous dispersion. In yet another embodiment, the aqueous liquid dispersion can comprise a sweetening agent or flavoring agent in a concentration ranging from about 0.0001% to 0.1 wt %, from about 0.001% to about 0.01 weight %, or from 0.0005% to 0.004% of the aqueous dispersion.

[0152] In addition to the additives listed above, the liquid ganaxolone formulations can also comprise inert diluents commonly used in the art, such as water or other solvents, solubilizing agents, and emulsifiers.

[0153] In some embodiments, the ganaxolone formulations can be self-emulsifying drug delivery systems (SEDDS). Emulsions are dispersions of one immiscible phase in another, usually in the form of droplets. Generally, emulsions are created by vigorous mechanical dispersion. SEDDS, as opposed to emulsions or microemulsions, spontaneously form emulsions when added to an excess of water without any external mechanical dispersion or agitation. An advantage of SEDDS is that only gentle mixing is required to distribute the droplets throughout the solution. Additionally, water or the aqueous phase can be added just prior to administration,

which ensures stability of an unstable or hydrophobic active ingredient. Thus, the SEDDS provides an effective delivery system for oral and parenteral delivery of hydrophobic active ingredients. SEDDS may provide improvements in the bioavailability of hydrophobic active ingredients. Methods of producing self-emulsifying dosage forms are known in the art include, but are not limited to, for example, U.S. Pat. Nos. 5,858,401, 6,667,048, and 6,960,563, each of which is specifically incorporated by reference.

[0154] Exemplary emulsifiers are ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butyleneglycol, dimethylformamide, sodium lauryl sulfate, sodium docusate, cholesterol, cholesterol esters, taurocholic acid, phosphotidylcholine, oils, such as cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil, and sesame oil, glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols, fatty acid esters of sorbitan, or mixtures of these substances, and the like.

[0155] In certain preferred embodiments, the liquid pharmaceutical formulation comprising ganaxolone, hydroxypropyl methylcellulose, polyvinyl alcohol, sodium lauryl sulfate, simethicone, methyl paraben, propyl paraben, sodium benzoate, citric acid, and sodium citrate at pH 3.8 – 4.2. The suspension may comprise ganaxolone at a concentration of 50 mg/ml. The formulation may further comprise a pharmaceutically acceptable sweetener (e.g., sucralose) and/or a pharmaceutically acceptable flavorant (e.g., cherry). The formulation may be enclosed, e.g., in a 120 mL, 180 mL, 240 mL, or 480 mL bottle.

[0156] A formulation for oral administration may be an oral solid dosage form (e.g., an oral capsule or tablet) or a liquid (e.g., an oral suspension comprising ganaxolone). In certain embodiments, the oral suspension is administered to the patient via the use of an oral syringe.

[0157] In certain embodiments, the liquid formulation of the present invention may be a formulation as described and prepared in Applicant's prior U.S. Patent No. 8,022,054, entitled "Liquid Ganaxolone Formulations and Methods for the Making and Use Thereof", hereby incorporated by reference in its entirety. However, the oral liquid (e.g., suspension) formulation

of ganaxolone may be prepared in accordance with other methods known to those skilled in the art.

[0158] In certain preferred embodiments, the oral solid formulation of the present invention may be a formulation as described and prepared in Applicant's prior U.S. Patent No. 7,858,609, entitled "Solid Ganaxolone Formulations and Methods for the Making and Use Thereof", hereby incorporated by reference in its entirety. However, the oral solid dosage formulation of ganaxolone may be prepared in accordance with other methods known to those skilled in the art.

[0159] For example, as disclosed in U.S. Patent No. 7,858,609, the oral solid formulation may comprise stabilized particles comprising ganaxolone, a hydrophilic polymer, a wetting agent, and an effective amount of a complexing agent that stabilizes particle growth after an initial particle growth and endpoint is reached, the complexing agent being a small organic molecule having a molecular weight less than 550 and containing a moiety selected from the group consisting of a phenol moiety, an aromatic ester moiety and an aromatic acid moiety, wherein the stabilized particles have a volume weighted median diameter (D50) of the particles is from about 50 nm to about 500 nm, the complexing agent being present in an amount from about 0.05% to about 5% w/w, based on the weight particles of the solid. The hydrophilic polymer may be in an amount from about 3% to about 50%, w/w, based on the weight of the solid particles. The wetting agent may be an amount from about 0.01% to about 10%, w/w, based on the weight of the solid particles. Ganaxolone may be in an amount from about 10% to about 80% (and in certain embodiments form about 50% to about 80%) based on the weight of the stabilized particles. The stabilized particles may exhibit an increase in volume weighted median diameter (D50) of not more than about 150% when the particles are dispersed in simulated gastric fluid (SGF) or simulated intestinal fluid (SIF) at a concentration of 0.5 to 1 mg ganaxolone/mL and placed in a heated bath at 36° to 38° C for 1 hour as compared to the D50 of the stabilized particles when the particles are dispersed in distilled water under the same conditions, wherein the volume weighted median diameter (D50) of the stabilized particles dispersed in SGF or SIF is less than about 750 nm. The stabilized particles may exhibit an increase in volume weighted median diameter (D50) of not more than about 150% when the formulation is dispersed in 15 mL of SGF or SIF at a concentration of 0.5 to 1 mg ganaxolone/mL as compared to the D50 of the stabilized particles

when the particles are dispersed in distilled water under the same conditions, wherein the volume weighted median diameter (D50) of the stabilized particles dispersed in SGF or SIF is less than about 750 nm. The solid stabilized particles may be combined with optional excipients and prepared for administration in the form of a powder, or they may be incorporated into a dosage form selected from the group consisting of a tablet or capsule. The complexing agent may be a paraben, benzoic acid, phenol, sodium benzoate, methyl anthranilate, and the like. The hydrophilic polymer may be a cellulosic polymer, a vinyl polymer and mixtures thereof. The cellulosic polymer may be a cellulose ether, e.g., hydroxypropymethylcellulose. The vinyl polymer may be polyvinyl alcohol, e.g., vinyl pyrrolidone/vinyl acetate copolymer (S630). The wetting agent may be sodium lauryl sulfate, a pharmaceutically acceptable salt of docusate, and mixtures thereof. When the particles are incorporated into a solid dosage form, the solid dosage form may further comprise at least one pharmaceutically acceptable excipient, e.g., an ionic dispersion modulator, a water soluble spacer, a disintegrant, a binder, a surfactant, a plasticizer, a lubricant, a diluent and any combinations or mixtures thereof. The water soluble spacer may be a saccharide or an ammonium salt, e.g., fructose, sucrose, glucose, lactose, mannitol. The surfactant may be, e.g., polysorbate. The plasticizer may be, e.g., polyethylene glycol. The disintegrant may be cross-linked sodium carboxymethylcellulose, crospovidone, mixtures thereof, and the like.

[0160] A capsule may be prepared, e.g., by placing the bulk blend ganaxolone formulation, described herein, inside of a capsule. In some embodiments, the ganaxolone formulations (non-aqueous suspensions and solutions) are placed in a soft gelatin capsule. In other embodiments, the ganaxolone formulations are placed in standard gelatin capsules or non-gelatin capsules such as capsules comprising HPMC. In other embodiments, the ganaxolone formulations are placed in a sprinkle capsule, wherein the capsule may be swallowed whole or the capsule may be opened and the contents sprinkled on food prior to eating. In some embodiments of the present invention, the therapeutic dose is split into multiple (e.g., two, three, or four) capsules. In some embodiments, the entire dose of the ganaxolone formulation is delivered in a capsule form.

[0161] In certain embodiments, each capsule contains either 200 mg or 225 mg ganaxolone, and hydroxypropyl methylcellulose, sucrose, polyethylene glycol 3350, polyethylene glycol 400,

sodium lauryl sulfate, sodium benzoate, citric acid anhydrous, sodium methyl paraben, microcrystalline cellulose, 30% Simethicone Emulsion, gelatin capsules, polysorbate 80, and sodium chloride. In some of the embodiments, the size of the capsule is 00.

[0162] Alternatively, the oral dosage forms of the present invention may be in the form of a controlled release dosage form, as described in U.S. Patent No. 7,858,609, herein incorporated by reference.

[0163] In certain preferred embodiments, the oral solid formulation of the present invention may be a formulation as described and prepared in Applicant's prior U.S. Patent No. 8,367,651, entitled "Solid Ganaxolone Formulations and Methods for the Making and Use Thereof", hereby incorporated by reference in its entirety.

[0164] As described in U.S. Patent No. 8,367,651, solid stabilized particles may comprise ganaxolone, a hydrophilic polymer, a wetting agent, and an effective amount of a complexing agent that stabilizes particle growth after an initial particle growth and endpoint is reached, the complexing agent being a small organic molecule having a molecular weight less than 550 and containing a moiety selected from the group consisting of a phenol moiety, an aromatic ester moiety and an aromatic acid moiety, wherein the stabilized particles have a volume weighted median diameter (D50) of the particles is from about 50 nm to about 500 nm and the concentration of ganaxolone in the solid stabilized particles is at least 50% by weight. The hydrophilic polymer maybe in an amount from about 3% to about 50%, w/w, based on the weight of the solid particles. The wetting agent may be in an amount from about 0.01% to about 10%, w/w, based on the weight of the solid particles. In some of the embodments, the stabilized particles exhibit an increase in volume weighted median diameter (D50) of not more than about 150% when the particles are dispersed in simulated gastric fluid (SGF) or simulated intestinal fluid (SIF) at a concentration of 0.5 to 1 mg ganaxolone/mL and placed in a heated bath at 36° to 38° C. for 1 hour as compared to the D50 of the stabilized particles when the particles are dispersed in distilled water under the same conditions, wherein the volume weighted median diameter (D50) of the stabilized particles dispersed in SGF or SIF is less than about 750 nm. In some embodiments, the stabilized particles exhibit an increase in volume weighted median

diameter (D50) of not more than about 150% when the formulation is dispersed in 15 mL of SGF or SIF at a concentration of 0.5 to 1 mg ganaxolone/mL as compared to the D50 of the stabilized particles when the particles are dispersed in distilled water under the same conditions, wherein the volume weighted median diameter (D50) of the stabilized particles dispersed in SGF or SIF is less than about 750 nm. In some embodiments, ganaxolone may be present in an amount greater than 50% to about 80%, based on the weight of the particles. In some embodiments, the stabilized particles may exhibit an increase in volume weighted median diameter (D50) of not more than about 150% when the particles are dispersed in simulated gastric fluid (SGF) or simulated intestinal fluid (SIF) at a concentration of 0.5 to 1 mg ganaxolone/mL and placed in a heated bath at 36° to 38° C. for 1 hour, as compared to the D50 of the stabilized particles when the particles are dispersed in distilled water under the same conditions, wherein the volume weighted median diameter (D50) of the stabilized particles dispersed in SGF or SIF is less than about 750 nm. In some embodiments, the solid stabilized particles may be in the form of a powder. In some embodiments, the particles may be incorporated into a dosage form selected from the group consisting of a tablet or capsule. In some embodiments, the volume weighted median diameter (D50) of the stabilized particles dispersed in distilled water is from about 100 nm to about 350 nm. In some embodiments, the complexing agent is selected from the group consisting of parabens, benzoic acid, methyl anthranilate, and pharmaceutically acceptable salts thereof and mixtures thereof. In some embodiments, paraben is selected from the group consisting of methylparaben, ethylparaben, propylparaben, pharmaceutically acceptable salts thereof and mixtures thereof. In some embodiments, the hydrophilic polymer is selected from the group consisting of a cellulosic polymer, a vinyl polymer and mixtures thereof. In some embodiments, the cellulosic polymer is a cellulose ether. In sme embodiments, the cellulose ether is hydroxypropylmethylcellulose. In some embodiments, the vinyl polymer is polyvinyl alcohol. In some embodiments, the wetting agent is selected from the group consisting of sodium lauryl sulfate, a pharmaceutically acceptable salt of docusate, and mixtures thereof. Is some embodiments, the particles are incorporated into a solid dosage form, further comprising at least one pharmaceutically acceptable excipient selected from the group consisting of an ionic dispersion modulator, an water soluble spacer, a disintegrant, a binder, a surfactant, a plasticizer, a lubricant, and any combinations or mixtures thereof. In some embodiments, the pharmaceutically acceptable excipient comprises an ionic dispersion modulator. In some

embodiments, the ionic dispersion modulator is in an amount from about 1% to about 50%, w/w, based on the weight of the solid particles. In some embodiments, the ionic dispersion modulator is a salt. In some embodiments, the ionic dispersion modulator is an inorganic salt is selected from the group consisting of a magnesium salt, a calcium salt, a lithium salt, a potassium salt, a sodium salt and mixtures thereof. In some embodiments, the ionic dispersion modulator is an organic salt is selected from the group consisting of a citrate salt, a succinate salt, a fumarate salt, a malate salt, maleate salt, a tartrate salt, a glutarate salt, a lactate salt and mixtures thereof. In some embodiments, the pharmaceutically acceptable excipient comprises a water soluble spacer. In some embodiments, the water soluble spacer is in an amount from about 2% to about 60%, w/w, based on the weight of the solid particles. In some embodiments, the water soluble spacer is a saccharide or an ammonium salt. In some embodiments, the saccharide is selected from the group consisting of fructose, sucrose, glucose, lactose, mannitol and mixtures thereof. In some embodiments, the disintegrant is selected from the group consisting of cross-linked sodium carboxymethylcellulose, crospovidone and any combinations or mixtures thereof. In some embodiments, the surfactant is a polysorbate. In some embodiments, the plasticizer is polyethylene glycol. In some embodiments, the solid dosage form is an immediate release dosage form. In some embodiments, the solid dosage form is a controlled release dosage form. In some embodiments, the particles are incorporated into an oral solid dosage form comprising (i) a controlled release component comprising a first portion of the stabilized particles; and a controlled release material, and (ii) an immediate release component comprising a second portion of the stabilized particles, the first and second portion of stabilized particles having a volume weighted median diameter (D50) of from about 50 nm to about 500 nm. In some embodiments, the ratio of ganaxolone in controlled release to immediate release is from about 4:1 to about 1:4. In some embodiments, the dosage form provides a therapeutic effect for about 8 to about 24 hours after administration. In some embodiments, the complexing agent is in an amount from about 0.05% to about 5%, w/w, based on the weight of the solid particles. In some embodiments, the complexing agent comprises methylparaben or a salt thereof. In some embodiments, the complexing agent comprises benzoic acid or a salt thereof. In some embodiments, the complexing agent comprises methyl anthranilate. In some embodiments, the formulation includes from about 200 mg to about 800 mg ganaxolone.

[0165] As further described in U.S. Patent No. 8,367,651, solid stabilized particles paticles may also comprise ganaxolone, a hydrophilic polymer, a wetting agent, and an effective amount of a complexing agent selected from the group of small organic molecules having a molecular weight less than 550 and containing a moiety selected from the group consisting of a phenol moiety, an aromatic ester moiety and an aromatic acid moiety, the stabilized particles having a volume weighted median diameter (D50) of the particles from about 50 nm to about 500 nm, the concentration of ganaxolone in the solid stabilized particles being at least 50% by weight. In some embodiments, ganaxolone is present in an amount greater than 50% to about 80%, based on the weight of the particles. In some embodimens, the particles are incorporated into a dosage form selected from the group consisting of a tablet or capsule. In some embodimens, the complexing agent is selected from the group consisting of parabens, benzoic acid, methyl anthranilate, and pharmaceutically acceptable salts thereof and mixtures thereof.

[0166] In certain preferred embodiments, the formulation of the present invention may be a pharmaceutical composition described and prepared in Applicant's prior U.S. Patent No. 9,029,355, entitled "Solid Ganaxolone Formulations and Methods for the Making and Use Thereof", hereby incorporated by reference in its entirety.

[0167] In certain embodiments, the composition may comprise the ganaxolone nanoparticles as described above, further in formulations as described in U.S. Patent No. 9,029,355, hereby incorporated by reference. In some embodiments, the pharmaceutical composition is a compressed tablet. In some embodiments, the pharmaceutical composition is contained inside a capsule.

[0168] Oral dosage forms described in U.S. Serial Application No. 16/185,677, entitled "GANAXOLONE FOR USE IN TREATING GENETIC EPILEPTIC DISORDERS", filed on November 9, 2018, herein incorporated by reference, may also be used in the methods of present invention.

ADDITIONAL ANTIEPILEPTIC DRUGS

[0169] In certain embodiments, the additional antileptic drug administered along with ganaxolone is selected from the group consisting of chlordesmethyldiazepam, loreclezole,

methsuximide, dipropylacetamide, pheneturide, 2-fluoro-2-phenyl-1,3-propanediyl dicarbamate, ethylphenylhydantoin, 6-methoxytryptoline, N-desmethylclobazam, anthranilic acid, Org 2766, sulthiame, dimethadione, 2-(2,3-dicarboxycyclopropyl)glycine, NCS 382, pipequaline, bretazenil, denzimol, stiripentol, progabide acid, brivaracetam, U 54494A, epidiolex, bromides, mephenytoin, ethosuximide, trimethadione, mebeverine, 5-(2-cyclohexylidene-ethyl)-5-ethylbarbiturate, 2-propyl-2-pentenoic acid, neo-kyotorphin, 4-phenyl-perhydropyrrole(1,2-a)pyrazine-1,3-dione, alpha-hexachlorocyclohexane, abecarnil, tramiprosate, thioperamide, DN 1417, remacemide, bemethyl, taglutimide, N-(4,4-diphenyl-3-butenyl)nipecotic acid, gaboxadol, ZK 93423, PD 117302, ZK 93426, indeloxazine, milacemide, primidone, ZK 91296, ezogabine, kavain, vanillin, neurotropin, fosphenytoin, zaleplon, CGP 39551, 2-amino-7-phosphonoheptanoic, 2-amino-4-phosphonobutyric acid, 3-(2-carboxypiperazin-4-yl)propyl-1-phosphonic acid, 2-amino-4-methyl-5-phosphono-3-pentenoic acid, rimcazole, angelicin, tiagabine, levetiracetam, zonisamide, paraldehyde, 2,3-piperidinedicarboxylic acid, 6-(1H-imidazol-1-yl)-7-nitro-2,3(1H,4H)-quinoxalinedione, eslicarbazepine acetate, vigabatrin, 1-(4-chlorophenyl)-4-piperidin-1-yl-1,5-dihydroimidazol-2-one, glutamic acid diethyl ester, fludiazepam, gidazepam, ethotoin, mephobarbital, acetazolamide, NNC 711, indol-3-yl pyruvic acid, rufinamide, topiramate, clonazepam, tiletamine, riluzole, progabide, deramciclane, doramectin, chlormethiazole, L 701324, clorazepate dipotassium, lacosamide, thiopental, valproic acid, felbamate, 2,3-dioxo-6-nitro-7-sulfamoylbenzo(f)quinoxaline, 7-nitroindazole, GYKI 52466, phenazepam, 4-amino-3-phenylbutyric acid, eperisone, sidnocarb, ryodipine, nimetazepam, nitrazepam, meprobamate, clobazam, estazolam, lorazepam, benzobarbital, magnesium sulfate, tizanidine, lamotrigine, flunarizine, pregabalin, gabapentin, phenytoin, phenobarbital, oxcarbazepine, carbamazepine, medazepam, pharmaceutically acceptable salts thereof, and mixtures of any of the foregoing.

[0170] In certain embodiments, the additional antileptic drug administered along with ganaxolone is selected from the group consisting of benzodiazepines, phenytoin, fosphenytoin, valproic acid, phenobarbital, and/or levetiracetam.

[0171] In certain embodiments, the additional antiepileptic drug is a benzodiazepine (e.g., diazepam, lorazepam, etc.).

## DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

[0172] The following examples of formulations in accordance with the present invention are not to be construed as limiting the present invention in any manner and are only samples of the various formulations described herein.

### EXAMPLE 1

### PRELIMINARY CLINICAL EVIDENCE OF INTRAVENOUS GANAXOLONE PHARMACOKINETICS AND PHARMACODYNAMICS

[0173] One clinical trial evaluating the IV GNX solution formulation was completed. The clinical trial was a Phase 1 study that was designed to investigate the safety, pharmacokinetics, and pharmacodynamics of bolus and continuous infusion IV GNX in healthy subjects. IV bolus doses ranging from 10 to 30 mg over durations of 2 minutes to 1 hour or a bolus dose of 6 mg over 5 minutes followed with a continuous infusion of 20 mg/hr for 4 hours were evaluated.

[0174] Pharmacokinetic analysis showed all 30 healthy subjects treated with active GNX had quantifiable GNX levels in plasma and GNX concentrations in plasma were generally proportional to the administered dose. Plasma concentrations that were achieved in this study were in the range of those associated with a potential anti-convulsant effect, based on historic data from subjects given oral GNX. Analysis of pharmacodynamic data showed that the bispectral index (BIS) score correlated with estimated GNX plasma concentrations at the time of BIS measurement. As expected, higher plasma concentration was associated with lower BIS scores (Figure 1). There was little or no delay between the appearance of drug in plasma and a change in the BIS score.

[0175] Safety data from subjects administered IV GNX from the study are presented in Example 3.

## EXAMPLE 2

## PRELIMINARY CLINICAL EVIDENCE OF EFFICACY IN SUBJECTS WITH STATUS EPILEPTICUS

[0176] Example 2 is an ongoing, double-blind, randomized, placebo-controlled Phase 2 study designed to evaluate the safety, tolerability, and efficacy of adjunctive IV GNX in subjects with SE who have failed initial treatment with benzodiazepines and at least one AED. The study consists of a small open-label group to optimize the infusion parameters and provide a preliminary assessment of safety, efficacy, and tolerability of GNX administration, followed by a double-blind group who will be randomized to receive GNX or placebo in a 1:1 ratio. In both the open-label and double-blind groups, the study drug treatment is adjunctive therapy to standard of care, and subjects will receive a study drug bolus dose with a concurrent continuous infusion treatment with the goal of administering a therapeutic dose as quickly as possible to stop the seizures and prevent permanent neurological damage. Specifically, study drug will be added to the standard of care at the time that the first 2nd-line IV AED has failed and the second 2nd-line IV AED is medically indicated during the treatment of SE. Study drug must be administered with the second-line IV AED as close to the dose initiation of the second $2^{nd}$-line IV AED as possible, but before the initiation of the third-line IV anesthetic for burst suppression.

[0177] Ganaxolone for this study is a proprietary IV formulation solubilized by Captisol® (betadex sulfobutyl ether sodium). The maximum level of Captisol® will not exceed 50 g/per day. Ganaxolone for IV administration will be provided to the site as individual glass vials containing 3 mg/mL of ganaxolone for the open-label group and 5 mg/mL of ganaxolone for the double-blind group. Placebo for double-blind group IV administration will be provided to the site as blinded matching vials containing 0.9% sodium chloride solution.

[0178] The primary objective of the study is to establish that IV GNX given concomitantly with second-line IV AED therapy is safe and effective in stopping SE that has already failed at least one second-line IV AED therapy and prevents escalation of treatment requiring an IV anesthetic drug (a third-line treatment) for seizure suppression. Secondary objectives include assessment of

mortality, seizure cessation in subjects with SE, and evaluation of pharmacokinetics of IV GNX in subjects with SE.

[0179] Approximately 262 subjects will be enrolled across the open-label and the double-blind groups.

[0180] Total adjunctive GNX therapy infusion treatment is planned to be 3 or 5 days (including an 18-hour taper). All subjects will have a 3-minute bolus dose with a continuous infusion at the rate from about 10 mg/hour to about 85 mg/hour or from about 18 mg/hr to 80 mg/hr, and an 18-hour taper. Once study drug administration is started it will be delivered for a full 2 or 4 days (48 or 96 hours) prior to tapering. At the end of second day administration, the decision to administer the study drug for an additional 2 days (i.e., for a total of 4 days) will be made. If in the investigator's medical judgment the subject will continue benefitting from study drug administration, ganaxolone will be administered to the additional 2 days.

[0181] Ganaxolone dose will be tapered prior to the discontinuation. To taper ganaxolone after 2 or 4 days of treatment, the continuous infusion will be reduced by 25% every 6 hours; 75%, 50%, 25% over 18 hours and then discontinued. If the infusion rate becomes too low during these 18-hours to sustain the infusion line it can be discontinued at that point. It is contemplated that, if a subject takes study drug for less than 2 hours and/or requires an IV anesthetic drug (a 3rd line treatment) for seizure suppression, they should be discontinued from the study drug without the study drug taper.

[0182] The following dosing schedule is planned.

[0183] Subjects weighing at least 40 kg:

[0184] A 25-mg bolus dose (over ~3 minutes) will be administered with a continuous infusion of 80 mg/hour for 2 hours followed by a continuous infusion rate of 40 mg/hour for 6 hours, and then 18 mg/hour for the remaining 16 hours of Day 1. At the end of the first 24 hours of continuous infusion (Day 1), the infusion rate will be increased to 29 mg/hour for the remaining treatment, Day 2 (24-48hours) or Day 2 through 4 (24-96hours).

**Dosing for Subjects ≥ 40 kg (on an mg/hour basis)**

| Days | Start Time from Dose Initiation | Dose Level of Study Drug IV (infusion rate) | Duration |
|---|---|---|---|
| Day 1 | 0 hours: bolus dose via syringe or infusion pump | 25 mg | 3 minutes |
| Day 1 | 0 hours through 2 hours post-dose: continuous infusion, started with bolus | 80 mg/hour | 2 hours |
| Day 1 | 2 hours post-dose through 8 hours post-dose | 40 mg/hour | 6 hours |
| Day 1 | 8 hours post-dose through 24 hours post-dose | 18 mg/hour | 16 hours |
| Day 2 or Day 2 through Day 4 | 24 hours post-dose through 48 hours post dose (Day 2) or 24 hours post-dose though 96 hours post-dose (Day 2-4) | 29 mg/hour | 24-72 hours (Day 2 or Day 4) |
| | **Taper for subjects discontinuing study drug** | | |
| Day 3 or Day 5 | 48 or 96 hours post-dose: 18-hour taper | Reduce infusion rate by 25% | 6 hours |
| | | Reduce infusion rate by 25% | 6 hours |
| | | Reduce infusion rate by 25% | 6 hours |

[0185] Subjects weighing < 40 kg will be dosed on a per-kilogram basis:

[0186] A 0.375-mg/kg bolus dose (over ~3 minutes) will be administered with a continuous infusion of 1.2 mg/kg/hour for 2 hours followed by a continuous infusion rate of 0.6 mg/kg/hour for 6 hours, and 0.27 mg/kg/hour for the remaining 16 hours of Day 1. At the end of the first 24 hours of continuous infusion (Day 1), the infusion rate will be increased to 0.435 mg/kg/hour for the remaining treatment period, Day 2 (24-48hours) or Day 2 through 4 (24-96hours).

**Dosing for Subjects < 40 kg (on an mg/kg/hour basis)**

| Days | Start Time from Dose Initiation | Dose Level of Study Drug | Duration |
|---|---|---|---|
| Day 1 | 0 hours: bolus dose via syringe or infusion pump | 0.375 mg/kg | 3 minutes |

| | | | |
|---|---|---|---|
| Day 1 | 0 hours through 2 hours post-dose: continuous infusion, started with bolus | 1.2 mg/kg/hour | 2 hours |
| Day 1 | 2 hours post-dose through 8 hours post-dose | 0.6 mg/kg/hour | 6 hours |
| Day 1 | 8 hours post-dose through 24 hours post-dose | 0.27 mg/kg/hour | 16 hours |
| Day 2 or Day 2 through Day 4 | 24 hours post-dose through 48 hours post dose (Day 2) or 24 hours post-dose though 96 hours post-dose (Days 2-4) | 0.435 mg/kg/hour | 24-72 hours (Day 2 or Days 2-4) |
| | **Taper for subjects discontinuing study drug** | | |
| Day 3 or Day 5 | 48 or 96 hours post-dose: 18-hour taper | Reduce infusion rate by 25% | 6 hours |
| | | Reduce infusion rate by 25% | 6 hours |
| **Days** | **Start Time from Dose Initiation** | **Dose Level of Study Drug** | **Duration** |
| | | Reduce infusion rate by 25% | 6 hours |

[0187] These infusion dosing parameters are expected to result in daily doses of ganaxolone of about $\leqslant$ 714 mg/day and Captisol of about $\leqslant$50 grams/day. Based on PK modeling, it is predicted that maximum concentrations of ganaxolone should remain within 1,000 ng/mL during infusion, but some variability is expected due to, for example, differences in subjects' weight.

[0188] As of 22 Mar 2019, 5 subjects have been enrolled into the Study 1042-SE-2001 open-label group under the original protocol that limits daily Captisol exposure at 35 g/day. In all 5 cases, the initial 3-minute bolus dose of 30 mg GNX with concurrent continuous infusion at 85 mg/hr for 2 hours followed by 40 mg/hr for 2 hours of GNX infusion resulted in the immediate cessation of seizures as evidenced by EEG activity in subjects with SE that was otherwise resistant to several second line IV AEDs considered standard-of-care. The initial EEG pattern post-infusion initiation was described by study physicians as a "light" burst suppression that was maintained for several hours in all subjects. Although some subjects required intubation for airway protection, no subjects had to be intubated as a direct result of GNX therapy. In addition, no GNX-related cardiovascular events that required pharmacological intervention were

observed. It was observed that when GNX exposure was lowered (20 mg/hr for 2 hours and ending with 10 mg/hr for the remaining 18 hours on Day 1) in order not to exceed this limit, seizure control could not be maintained and seizure activity (but not SE) re-occurred as evidenced by EEG changes. Pharmacokinetic modeling data (Figure 2) from these 5 subjects suggested that exposure levels of GNX at approximately 1000 ng/mL were associated with rapid and complete SE suppression, and lower GNX exposures at < 500 ng/mL were associated with seizure relapse.

[0189] Seizure activity relapsed when plasma concentrations of GNX decreased < 500 ng/mL in 4 out of 5 subjects.

[0190] Case reports of the 5 subjects are presented below.

[0191] **Subject 004-101**

[0192] Subject 004-101 was a 75-year-old female who presented with a subdural hematoma due to a fall (Day 1). Levetiracetam was started. Upon physician exam, the subject was noted to be lying in the bed unresponsive to both verbal and noxious stimuli. Pupils were equal, round, and reactive to light, no corneal, no gag, and vestibulo-occular reflex was intact. Blood pressure and saturation were stable. Due to the mental status change, the decision was made to intubate the subject for airway protection. On Day 3, EEG showed partial seizures and additional infusions of levetiracetam were given, followed by multiple infusions of lacosamide. During the study enrollment discussion, the family reported that the subject was slow to come out of anesthesia in the past.

[0193] On Day 3, IV GNX was administered starting with a 30 mg bolus over 3 minutes and a continuous infusion of 85 mg/hr for 2 hours. Almost immediately the EEG showed seizure suppression, with the EEG pattern described as by the Principal Investigator as, "putting the subject in weak burst suppression." During the second hour of treatment the study drug administration was interrupted for 14 minutes while the subject was intubated for airway protection. The intubation was not considered related to the study drug; the decision to intubate was made before starting GNX infusion. The continuous infusion was restarted without incident.

Dosing continued per protocol with infusion rate reductions to 40 mg/hr at 2 hours post-dose, 20 mg/hr at 4 hours post-dose, and 10 mg/hr at 6 hours post dose. Seizure relapse occurred at approximately 5 hours post infusion start, at which time the subject was receiving GNX at a 20 mg/hr infusion rate. GNX was discontinued on Day 2. The subject's GNX plasma concentration was < 500 ng/mL at the time of seizure relapse (Figure 3). A snapshot of the subject's EEG patterns prior to and after initiation of GNX is provided in Figure 4.

[0194] **Subject 004-102**

[0195] Subject 004-102 was a 43-year-old female with a history of seizures who presented in NCSE (Day 1). Prior AED medications included lamotrigine. The subject was intubated and given a single dose of fosphenytoin followed by levetiracetam. On the same day, IV GNX 30 mg bolus was given over 3 minutes and the continuous infusion (85 mg/hr) was initiated. There was no seizure activity noted on EEG at 60 minutes and 2 hours post-dose initiation. As per the protocol, GNX was decreased to 40 mg/hr, 20 mg/hr, and 10 mg/hr sequentially. The 10 mg/hr was continued for the remaining 18 hours of Day 1. The subject continued to be seizure free; however, a concerning EEG pattern returned between 5 to 6 hours post-dose initiation, at which time the subject was receiving GNX at a 20 mg/hr infusion rate. The subject's GNX plasma concentration at the time of seizure relapse is shown in Figure 5. A return of an EEG pattern occurred around the same timeframe and it evolved over the next 48 hours and required additional intervention approximately 42.5 hours post-dose initiation while the subject was receiving GNX at a 20 mg/hr infusion rate. GNX was discontinued on Day 2. A snapshot of the subject's qualitative EEG patterns prior to and after initiation of GNX is provided in Figure 6.

[0196] **Subject 006-101**

[0197] Subject 006-101 was a 59-year-old female who presented in NCSE, etiology unknown (Day 1). Subject was unresponsive to verbal and physical stimuli. A single dose of lacosamide was given and subject was intubated for airway protection. EEG showed epileptiform discharges associated with obtundation and limb switches, and was subject was given lorazepam dose with

no improvement. On the same day, IV GNX 30 mg bolus was given and the continuous infusion (85 mg/hr) was initiated. Per site report, the SE aborted within 1 minute of the bolus administration. There was no seizure activity noted on EEG at 60 minutes and 2 hours post-dose initiation. Per the protocol, GNX was sequentially decreased to 40 mg/hr, 20 mg/hr, and 10 mg/hr. Seizure relapse occurred at approximately 6 hours post infusion start, at which time the subject was receiving GNX at a 20 mg/hr infusion rate. GNX taper was initiated on Day 4. The subject's GNX plasma concentration was < 500 ng/mL at the time of seizure relapse (Figure 7). A snapshot of the subject's EEG patterns prior to and after initiation of GNX is provided in Figure 8.

[0198] The SE relapse occurred while the subject's infusion rate was 10 mg/hr. The two adjacent PK sample results were within the low predicted values for the infusion rate. It was confirmed that PK samples were collected from the infusion site. It was confirmed that the correct analysis procedures where performed by the bioanalytical laboratory.

[0199] **Subject 006-102**

[0200] Subject 006-102 was an 88-year-old female with a history of seizures and dementia who was transferred from a nursing home after having been found by her daughter with altered mental status and inability to verbalize her complaints (Day 1). The family confirmed that the subject had fallen and possibly hit her head the previous week. Subdural hematoma (1.4 cm) was identified on computed tomography (CT) scan. Subject was intubated, placed on propofol, and transferred from the remote hospital to the study site where she was prepared for evacuation of the subdural hematoma. Propofol was stopped. During physical examination, the subject's eyes opened spontaneously, the pupils were equal round, and reactive to the light. She followed simple commands and moved all the extremities spontaneously. The subject was administered single doses of levetiracetam on Day 1 and Day 4 and twice daily dosing on Day 3. Three single doses of lorazepam were administered on Day 5 prior to GNX administration along with multiple doses of levetiracetam and a single dose of lacosamide. On Day 5, the subject had worsening neurological exam and CT of the head showed signs of stroke on the right cerebral hemisphere. On the same day, an EEG confirmed a diagnosis of NCSE at which time the subject was enrolled

in the clinical study and started on IV GNX 30 mg bolus dose plus continuous infusion (85 mg/hr). Per site report, the SE aborted upon administration of the bolus GNX administration. There was no seizure activity noted on EEG at 60 minutes, 2 hours, and 4 hours post-dose initiation. Per the protocol, GNX was sequentially decreased to 40 mg/hr, 20 mg/hr, and 10 mg/hr. Seizure relapse occurred at approximately 6 hours post infusion start, at which time the subject was receiving GNX at a 20 mg/hr infusion rate. GNX taper was initiated on the fourth day of GNX therapy. The subject's GNX plasma concentration was < 500 ng/mL at the time of seizure relapse (Figure 9).

[0201] **Subject 015-101**

[0202] Subject 015-101 was a 24-year-old female who presented with focal convulsive SE due to a tumor (Day 1). Recent medical history included convulsive seizures, SE, and Glioblastoma multiform of parietal lobe. Subject was administered levetiracetam for SE and lorazepam, diazepam, dexamethasone, and multiple doses of levetiracetam for seizure control prior to study enrollment. On Day 3, the subject was enrolled in the study and started on IV GNX 30 mg bolus dose plus continuous infusion (85 mg/hr). At the start of dose initiation the subject was alert. Shortly after the bolus started the subject developed significant somnolence. She was arousable to voice but required continuous stimulation to stay awake or follow commands. She maintained her airway and was able to endorse that the numbness had resolved and reported that she no longer felt twitches. She had a feeling of impending doom and death. The subject had significant direction-changing nystagmus and complained of blurry vision. At the same time she developed urinary retention with urgency. The bladder scanner demonstrated at least 750 mL of urine and Foley catheter was placed. During the next 2 hours the subject remained somnolent and was becoming increasingly restless. As per the protocol, GNX was decreased to 40 mg/hr at 2 hours post dose initiation. Approximately 10 to 15 minutes after the infusion rate was decreased to 40 mg/hr, the subject's arousal improved, she became conversational, and wanted to eat. She had no seizures at this time. Vital signs remained stable. During the GNX infusion, concomitant lacosamide was increased due to increased numbness. Seizures did not return during the treatment period and the investigator tapered the study drug per the protocol after

2 days. Once the GNX taper was completed the investigator reported there were no sequelae. The subject's GNX plasma concentration over time is provided in Figure 10.

[0203] In summary, all 5 subjects showed immediate cessation of SE with the initiation of the initial bolus plus continuous infusion dose. Based on these data, the United States Food and Drug Administration (FDA) allowed the daily limit of Captisol exposure to increase to 50 g/day (and the total daily dose of GNX to increase from 500 to 715 mg), thereby allowing for GNX exposure to be maintained at > 500 ng/ml for approximately 8 hours.

[0204] Under the protocol amended with the 50 g/day Captisol limit, 1 subject was enrolled in the open-label study as of 26 Mar 2019. The male subject presented with NCSE due to a tumor. The subject failed 3 second-line IV AEDs and qualified for the study based on the study's inclusion/exclusion criteria. Within 3 minutes after starting the IV GNX infusion, the RSE ceased and seizure protection was maintained for the remaining 48 hours of GNX treatment. The subject was successfully weaned off GNX (i.e., no seizure relapse). Based on the preliminary assessment, the only safety finding related to GNX was an increased sedation (likely due to a concomitant use of GNX with several AEDs with CNS-depressant properties as part of standard of care anti-seizure therapy). Pharmacokinetic data were unavailable at the time of this report.

[0205] In addition, GNX has been administered to 2 subjects with SRSE under separate emergency treatment INDs (eINDs).

[0206] Under eIND No. 131,642, IV GNX was administered to a subject with SRSE who was unable to maintain status cessation with ketamine and barbiturates. The Day 1 dosage regimen delivered 900 mg of GNX, equating to a 900 to 1200 ng/mL plasma concentration of GNX. As the subject could not be maintained in burst suppression, the clinical team was able to utilize EEG changes to gauge the response (Figure 11). The effect of GNX started at 60 mg/hr dose and resulted in complete seizure cessation at the 120 mg/hr dose. However, due to the dosing plan agreed upon with the FDA with a daily Captisol limit of 63 g/day, the initial 120 mg/hr dose on Day 1 could not be maintained for longer than 1 hour and then had to be decreased to the

30 mg/hr dose. The first seizures re-occurred within 15 to 20 minutes of the change in GNX dose from 120 mg/hr to 30 mg/hr.

[0207] Additionally, under eIND No. 137,883, IV GNX was administered to a pediatric subject with SRSE who had previously failed treatment with levetiracetam, topiramate, clobazam, phenobarbital, rufinamide, perampanel, pentobarbital, and ketamine. At the time of the eIND, no pediatric pharmacokinetic data was available for the IV formulation of GNX. The dose regimen (GNX initiated at 75 mg/hr and rate decreased to 40 mg/hr 1 hour later) was based on plasma drug concentration levels measured in adults and designed to achieve a plasma drug concentration of approximately 1000 ng/mL within 1 hour and hold that level for 23 additional hours. At the time of GNX initiation, the subject was intubated and receiving pentobarbital at a rate of 2.25 mg/kg/hr. At the time of the GNX bolus infusion, the EEG showed a continuous suppressed background. This activity lasted for approximately 2 hours at which point the pentobarbital was decreased to 1 mg/kg/h. On examination the subject had nonreactive pupils and GNX infusion was stopped.

[0208] With these encouraging data, Marinus received permission from the U.S. FDA to increase daily Captisol limits from 35 to 50 g/day. One subject under the increased Captisol daily limit experienced rapid RSE cessation following GNX treatment despite failing 3 second-line IV AEDs and was successfully weaned off GNX without seizure relapse.

[0209] This study is ongoing and once completed will be used to design the pivotal Phase 3 study in subjects with RSE.

[0210] All references, publications and patent documents cited herein, as well as text appearing in the figures and sequence listing, are hereby incorporated by reference in their entirety for all purposes to the same extent as if each were so individually denoted.

[0211] In the preceding specification, the invention has been described with reference to specific exemplary embodiments and examples thereof. It will, however, be evident that various modifications and changes may be made thereto without departing from the broader spirit and

scope of the invention as set forth in the claims that follow. The specification and drawings are accordingly to be regarded in an illustrative manner rather than a restrictive sense.

[0212] Citation of any document herein is not intended as an admission that such document is pertinent prior art, or considered material to the patentability of any claim of the present application. Any statement as to content or a date of any document is based on the information available to applicant at the time of filing and does not constitute an admission as to the correctness of such a statement.



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**WHAT CLAIMED IS:**

1. A method of treating status epilepticus, comprising administering a therapeutic dose of ganaxolone to a subject experiencing status epilepticus in a manner which achieves and maintains a plasma concentration of ganaxolone from about 50 ng/ml to about 3500 ng/ml over a time period from about 30 minutes to about 120 hours, and wherein the administration reduces or eliminates seizure activity and/or reduces or eliminates convulsions and/or completely suppresses status epilepticus.

2. The method of claim 1, wherein a portion of the therapeutic dose of ganaxolone is administered via an intravenous infusion over a time period from about 1 hour to about 120 hours.

3. The method of claim 1, wherein a portion of the therapeutic dose of ganaxolone is administered via a bolus dose and the remaining portion of the dose is administered via an intravenous infusion over a time period from about 2 hours to about 120 hours.

4. The method of claim 2 or 3, wherein the intravenous infusion is at a rate greater than about 10 mg/hour, about 15 mg/hour, about 20 mg/hour, about 25 mg/hour, or about 30 mg/hour.

5. The method of claim 4, wherein the rate various during the intravenous administration from about 10 mg/hour to about 150 mg/hour.

6. The method of claim 5, wherein ganaxolone is administered at a rate from about 40 mg/hour to about 140 mg/hour for about 1 hour to about 4 hours; thereafter, at a rate from about 20 mg/hour to about 70 mg/hour for about 1 hour to about 4 hours; thereafter, at a rate from about 10 mg/hour to about 35 mg/hour for about 1 hour to about 4 hours; thereafter, at a rate from about 10 mg/hour to about 30 mg/hour for about 1 hour to about 96 hours; and, thereafter, at a rate from about 15 mg/hour to about 35 mg/hour for about 1 hour to about 96 hours.

7. The method of claim 6, wherein, after the administration at the rate from about 15 mg/hour to about 35 mg/hour for about 1 hour to about 96 hours, the rate is reduced by about 10% to about 50% every 1 hour to 12 hours.

8. The method of claim 7, wherein the rate is reduced by about 15% to about 30% every 4 hours to 8 hours.

9. The method of claim 8, wherein, before the start of the intravenous administration from about 10 mg/hour to about 150 mg/hour, from about 5 mg to about 100 mg of ganaxolone is administered as an intravenous bolus dose.

10. The method of claim 9, wherein the intravenous bolus dose provides ganaxolone Cmax from about 500 ng/ml to about 2000 ng/ml.

11. The method of claim 9, wherein the total daily dose of ganaxolone is from about 450 mg to about 1200 mg.

12. The method of any one of claims 1 to 3, wherein the total daily dose of ganaxolone is from about 450 mg to about 1200 mg.

13. The method of claim 3, wherein the bolus dose comprising an amount of ganaxolone sufficient to provide ganaxolone Cmax from about 500 ng/ml to about 2000 ng/m within 5 minutes of the bolus administration.

14. The method of claim 5, further comprising orally administering to the subject from about 400 mg to about 2000 mg ganaxolone daily in one, two or three divided doses.

15. A method of treating status epilepticus, comprising administering a therapeutic dose of ganaxolone to a subject experiencing status epilepticus in a manner which provides a plasma concentration of ganaxolone from 50 ng/ml to about 3500 ng/ml over a time period from about 24 hours to about 120 hours, and from about 2 to 5 peaks in the plasma concentration of ganaxolone during said 24 hours to about 120 hours.

16. The method of claim 16, wherein a portion of the therapeutic dose is administered via an intravenous infusion at a rate from about 60 mg/hour to about 150 mg/hour for about 1 hour to about 24 hours of the intravenous infusion.

17. The method of any one of claims 15 or 16, wherein a ganaxolone plasma level of about 800 ng/ml to about 1200 ng/ml is maintained for about 1 to about 96 hours.

18. The method of claim 3, wherein the bolus dose comprises from about 5 mg to about 100 mg ganaxolone.

19. The method of any one of claims 1 to 18, further comprising administering one or more additional bolus dose(s) of ganaxolone from about 1 mg to about 50 mg, from about 1 mg to about 45 mg, from about 1 mg to about 40 mg, from about 2 mg to about 35 mg, from about 3 mg to about 30 mg, or from about 5 mg to about 30 mg intravenously over about 1 to about 5 minutes.

20. The method of any one of claims 1 to 18, where the status epilepticus is generalized convulsive status epilepticus, non-convulsive status epilepticus, early status epilepticus, established status epilepticus, refractory status epilepticus, or super-refractory status epilepticus.

21. The method of claim 20, wherein the status epilepticus is refractory status epilepticus.

22. The method of claim 20, wherein the status epilepticus is non-convulsive status epilepticus.

23. The method of claim 20, further comprising administering from about 1 gram to about 100 grams sulfobutylether-β-cyclodextrin to the subject per day.

24. The method of claim 23, wherein ganaxolone and sulfobutylether-β-cyclodextrin are administered in one formulation.

25. The method of claim 24, wherein a weight ratio of ganaxolone and sulfobutylether-β-cyclodextrin is from about 1:50 to about 1:75.

26. The method of claim 23, wherein from about 50 grams to about 63 grams of sulfobutylether-β-cyclodextrin is administered per day.

27. The method of claim 1, wherein the plasma concentration of ganaxolone is from about 75 ng/ml to about 3250 ng/ml, from about 100 ng/ml to about 3000 ng/ml, from about 125 ng/ml to about 2750 ng/ml, from about 150 ng/ml to about 2500 ng/ml, from about 175 ng/ml to about

2250 ng/ml, from about 200 ng/ml to about 2200 ng/nl, from about 250 ng/ml to about 2150 ng/ml, from about 300 ng/ml to about 2100 ng/ml, from about 350 ng/ml to about 2100 ng/ml, from about 400 ng/ml to about 2100 ng/ml, from about 450 ng/ml to about 2100 ng/ml, or from about 500 ng/ml to about 2000 ng/ml.

28. The method of claim 1, wherein the administration provides a Cmax that is from about 80% to 120 % of the Cmax provided by a formulation comprising the therapeutic dose of ganaxolone administered in claim 1.

29. The method of claim 1, wherein the administration provides a Tmax that is from about 80% to 120 % of the Tmax provided by a formulation comprising the therapeutic dose of ganaxolone administered in claim 1.

30. The method of claim 1, wherein the administration provides an AUC that is from about 80% to 120 % of the AUC provided by a formulation comprising the therapeutic dose of ganaxolone administered in claim 1.

31. A method of completely suppressing status epilepticus comprising administering a therapeutically affective amount of ganaxolone.

32. The method of claim 31, wherein the status epilepticus is generalized convulsive status epilepticus, non-convulsive status epilepticus, early status epilepticus, established status epilepticus, refractory status epilepticus, or super-refractory status epilepticus.

33. The method of claim 32, wherein the status epilepticus is refractory status epilepticus.

34. The method of claim 32, wherein the status epilepticus is non-convulsive status epilepticus.

35. The method of claim 31 or 32, further comprising administering from about 1 gram to about 100 grams sulfobutylether-β-cyclodextrin to the subject per day.

36. The method of claim 35, wherein ganaxolone and sulfobutylether-β-cyclodextrin are administered in one formulation.

37. The method of claim 36, wherein a weight ratio of ganaxolone and sulfobutylether-β-cyclodextrin is from about 1:50 to about 1:75.

38. The method of claim 37, wherein from about 50 grams to about 63 grams of sulfobutylether-β-cyclodextrin is administered per day.

39. A method of eliminating seizure activity comprising administering to a subject in need thereof a therapeutic dose of ganaxolone.

40. The method of claim 39, wherein said seizure activity is an acute repetitive seizure, generalized convulsive status epilepticus, non-convulsive status epilepticus, early status epilepticus, established status eplilepticus, refractory status epilepticus, or super-refractory status epilepticus.

41. A method of reducing and/or eliminating convulsions in a patient in need thereof comprising administering a therapeutically effective amount of ganaxolone.

42. The method claim 41, wherein the convulsions are selected from the group consisting of acute repetitive seizures, generalized convulsive status epilepticus, refractory status epilepticus, and super-refractory status epilepticus.

43. A method of treating acute repetitive seizures in a subject in need thereof comprising administering to the subject an amount of ganoxolone in a manner which achieves and maintains a plasma concentration of ganaxolone from about 50 ng/ml to about 3500 ng/ml over a time period from about 30 minutes to about 120 hours, and wherein the administration reduces or eliminates seizure activity and/or reduces or eliminates convulsions in the subject.

44. The method of claim 43, wherein at least a portion of said amount is administered intravenously.

45. The method of claim 44, wherein said portion is administered via one or more bolus injections.

46. The method of claim 45, wherein the one or more bolus injections are followed by an intravenous infusion of ganaxolone over a time period from about 1 hour to about 120 hours.

## ABSTRACT OF THE DISCLOSURE

Uses of ganaxolone in treatment of status epilepticus (e.g., a generalized convulsive status epilepticus, non-convulsive status epilepticus, early status epilepticus, established status epilepticus, refractory status epilepticus, or super-refractory status epilepticus) and acute repetitive seizures are described. A dose of ganaxolone is administered to a subject experiencing status epilepticus in an amount and at a rate sufficient to reduce or eliminate seizure activity and/or reduce or eliminate convulsions and/or completely suppresses status epilepticus (i.e., suppress EEG seizure activity and convulsions) in the subject.



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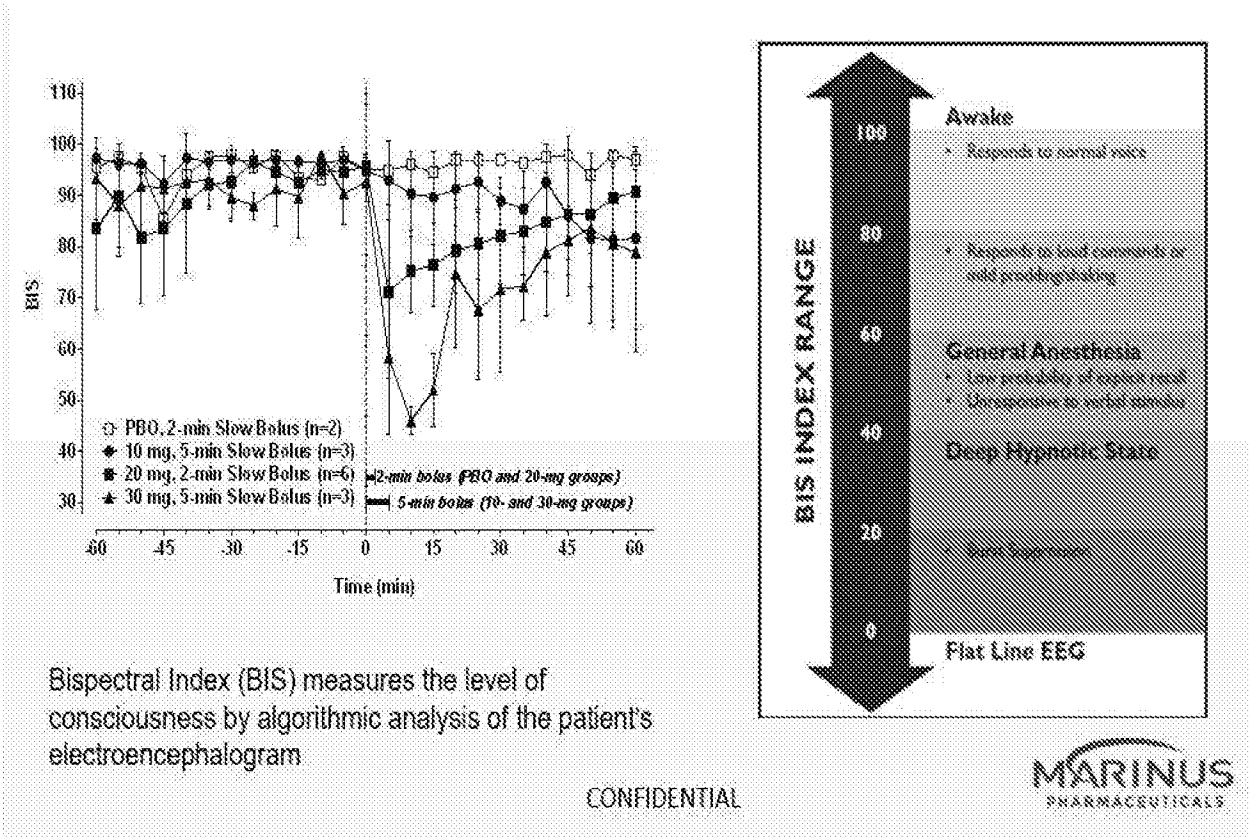



BIS = bispectral index, EEG = electroencephalography, PBO = placebo

Figure 1

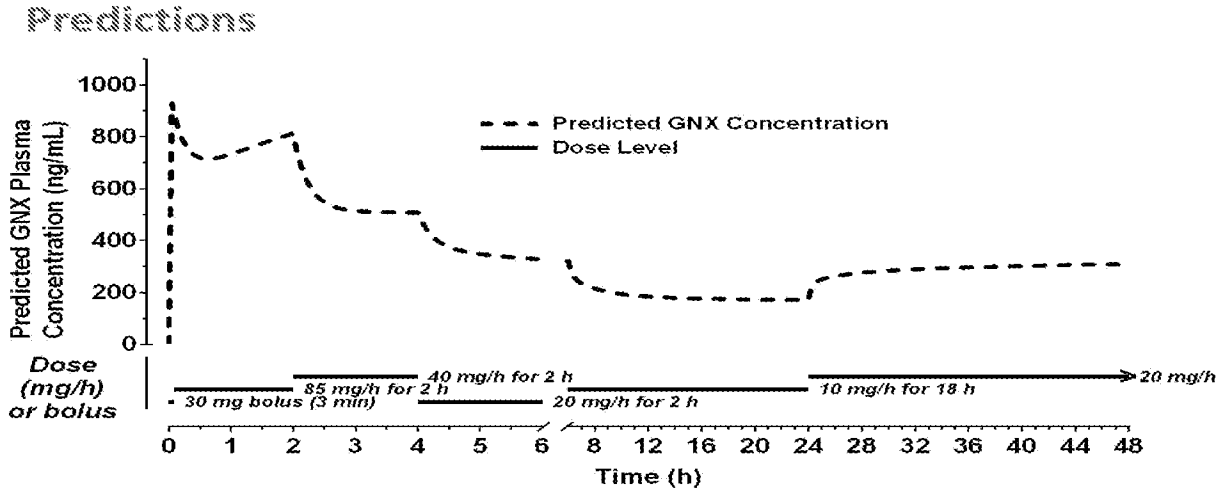



Figure 2

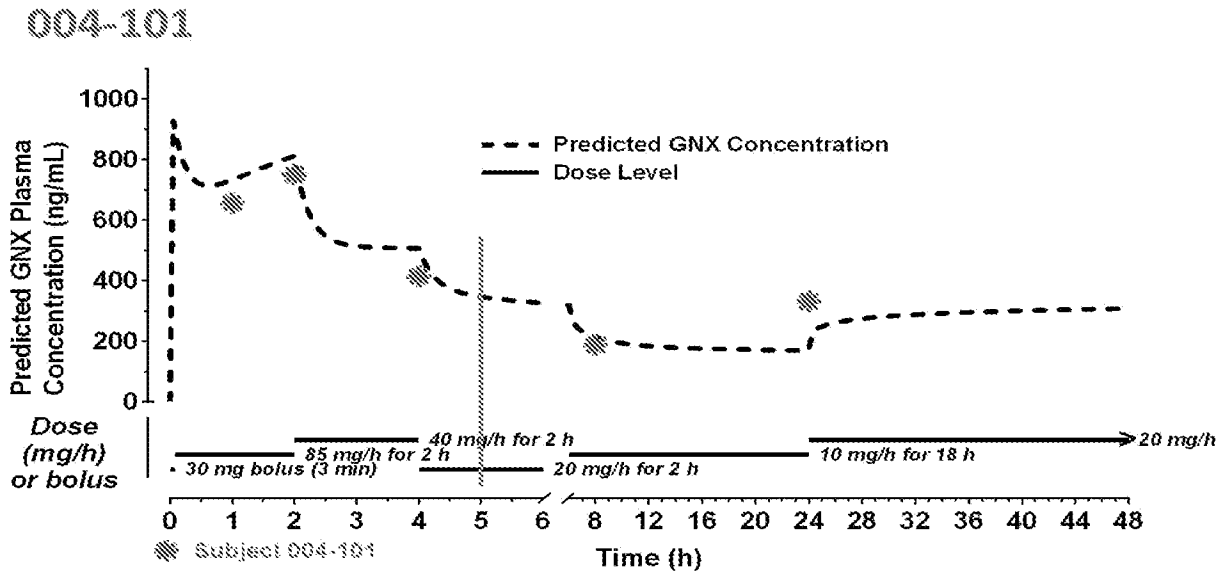



Figure 3

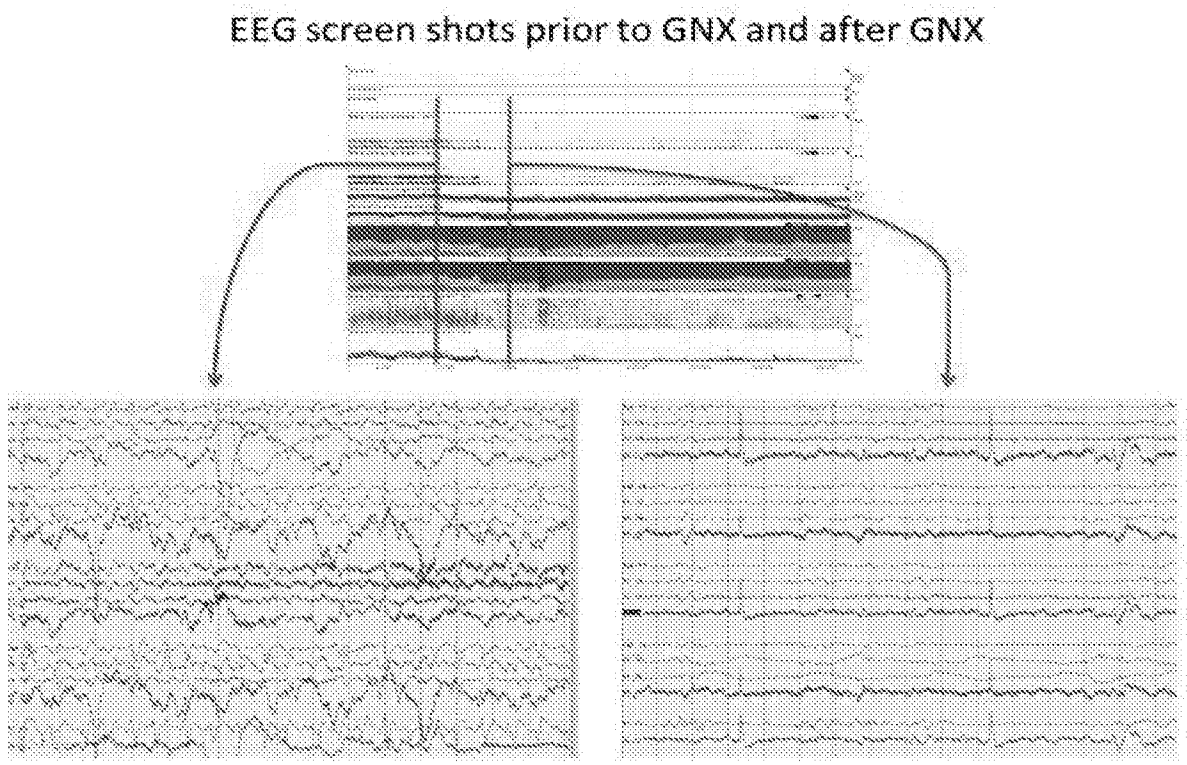



Figure 4

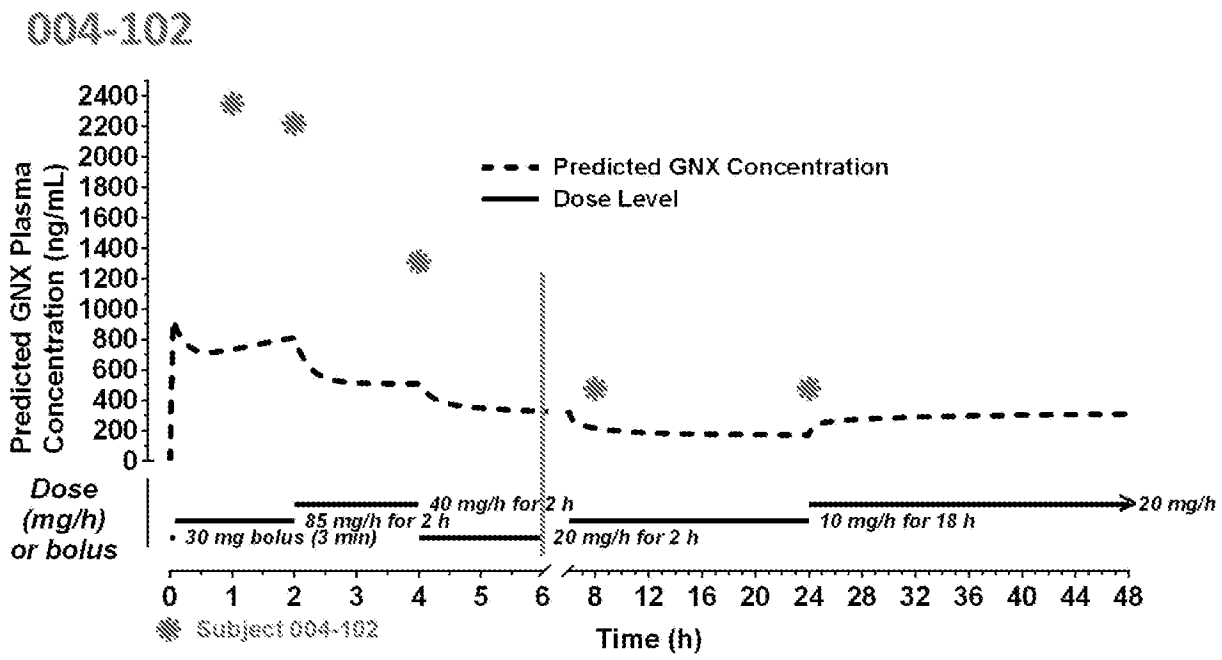



Figure 5

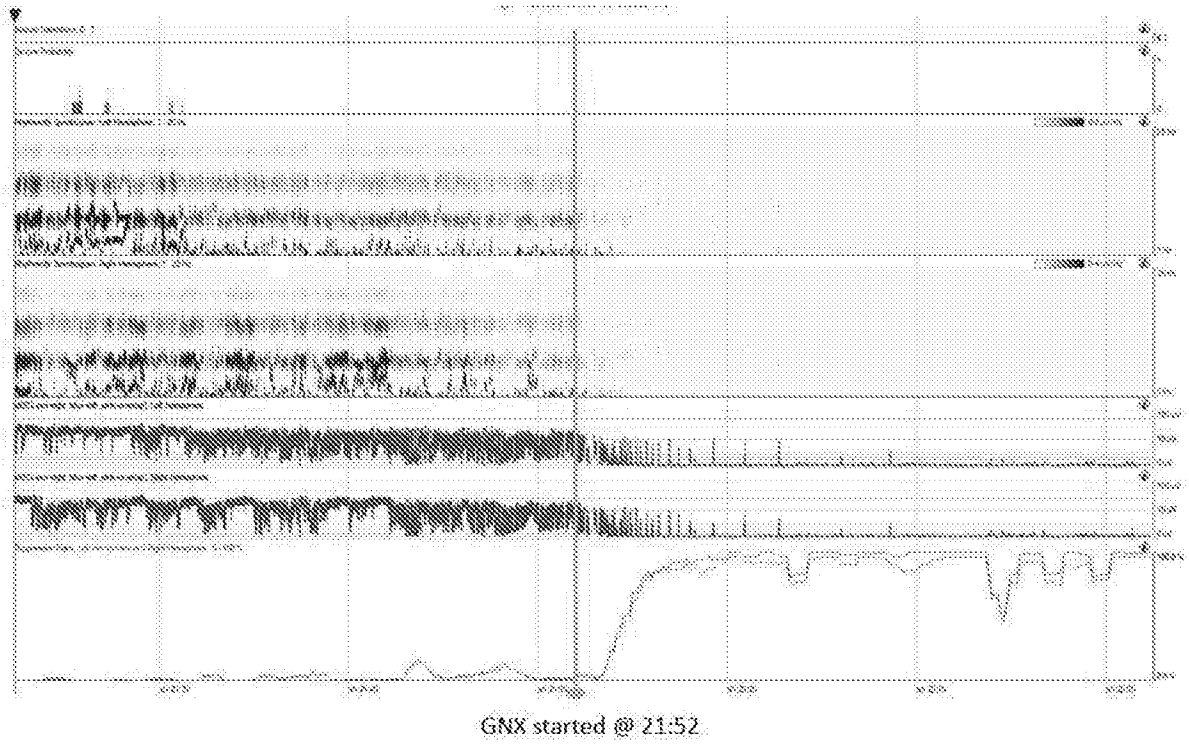



Figure 6

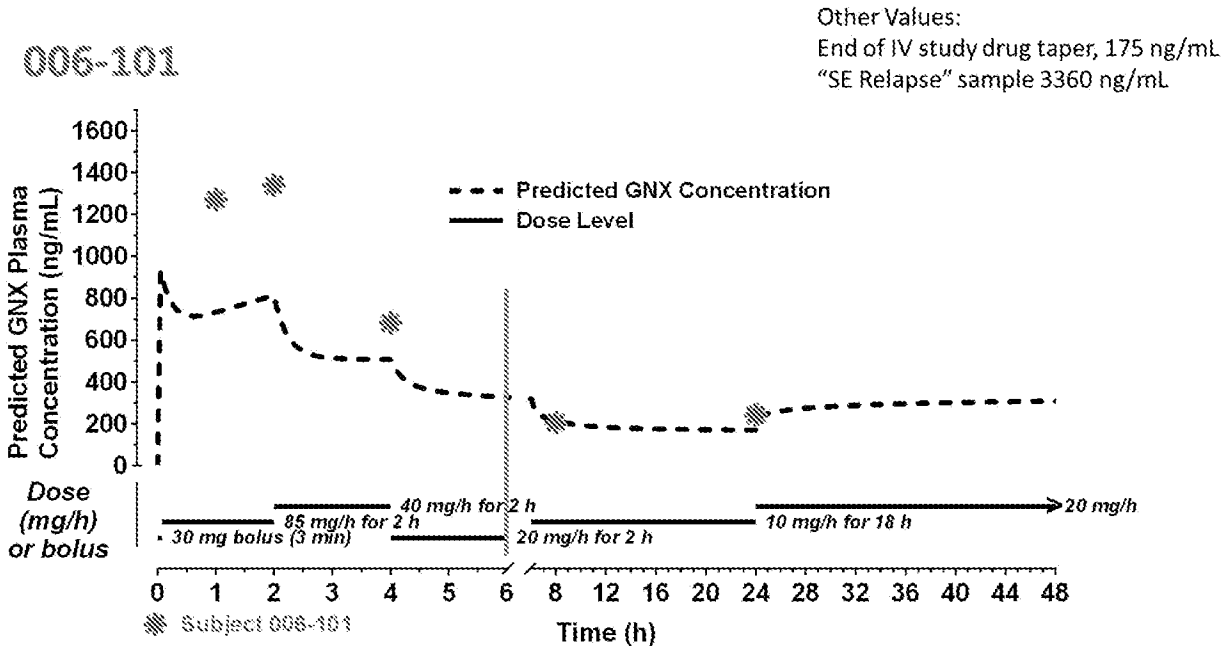
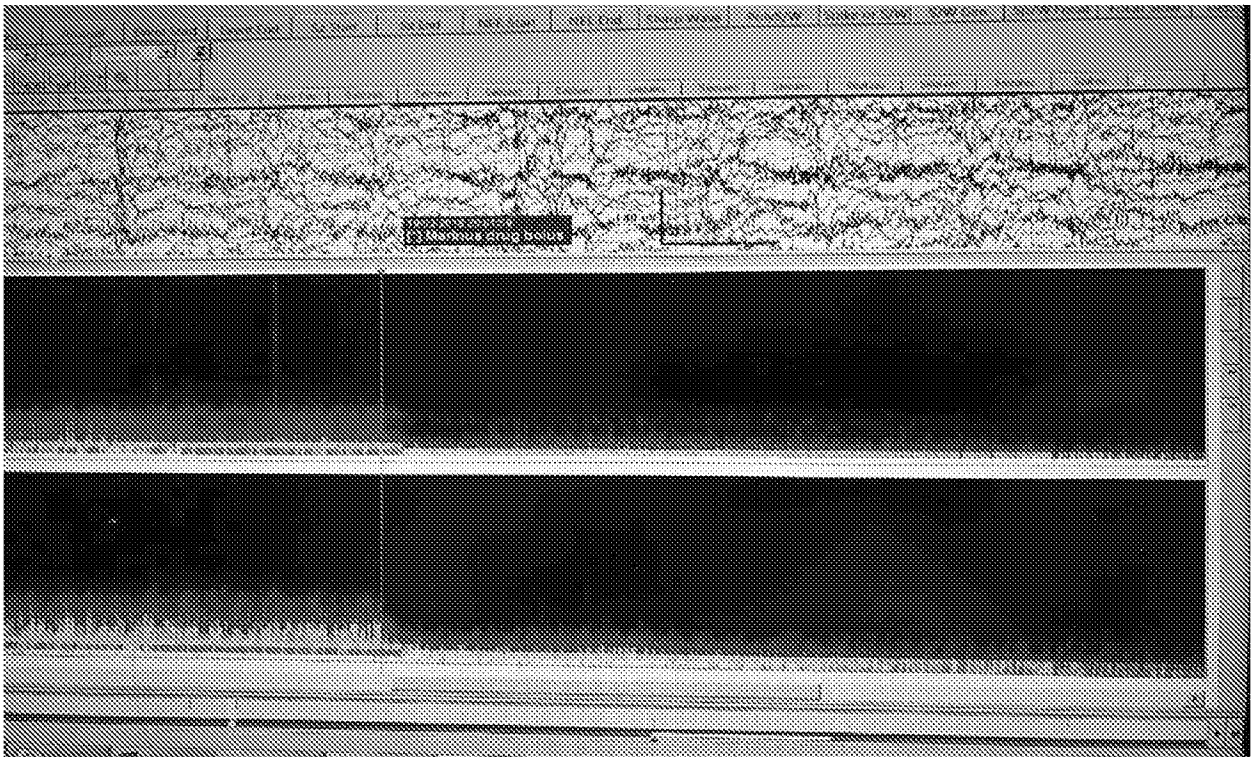



Figure 7



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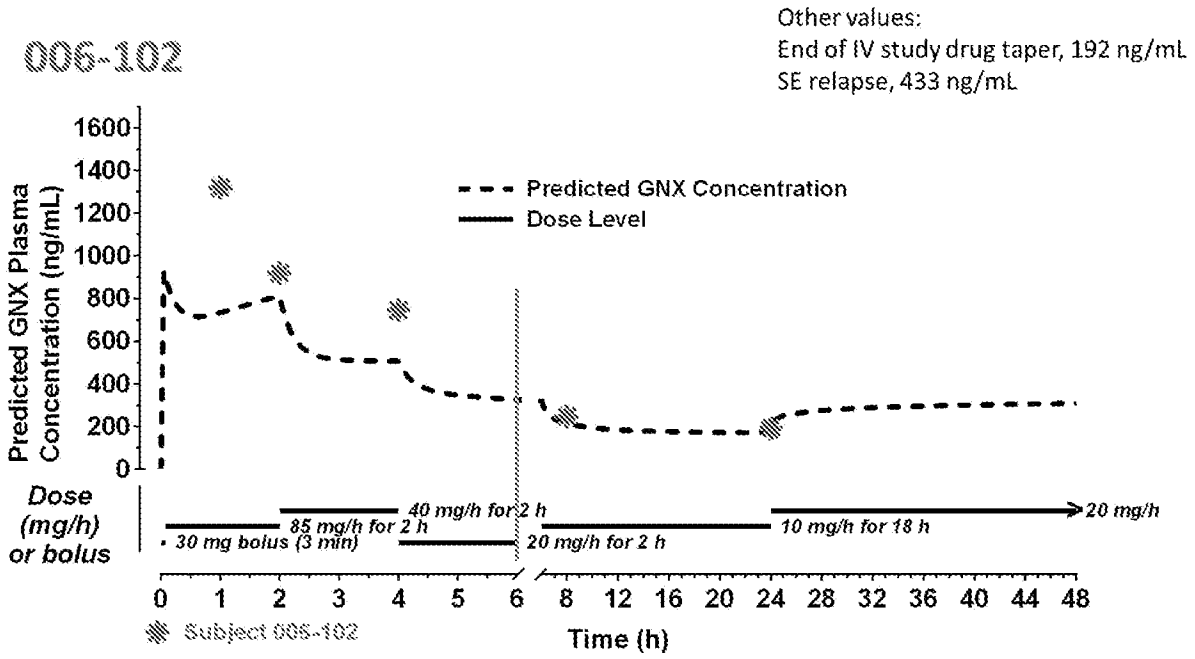


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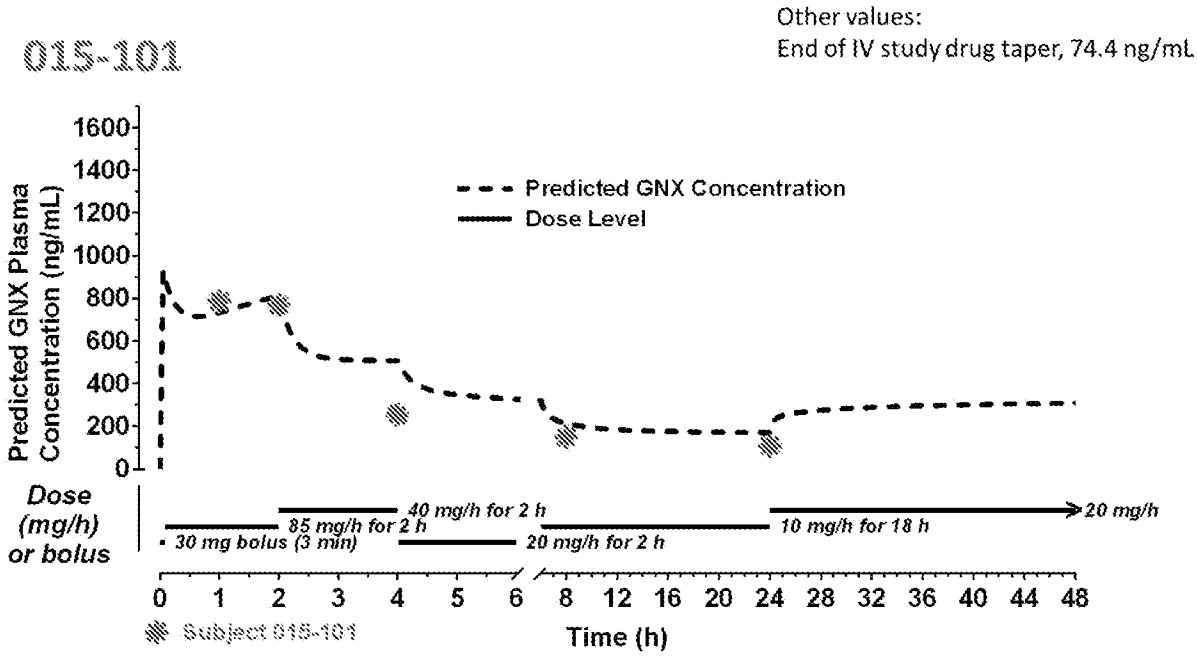


Figure 10

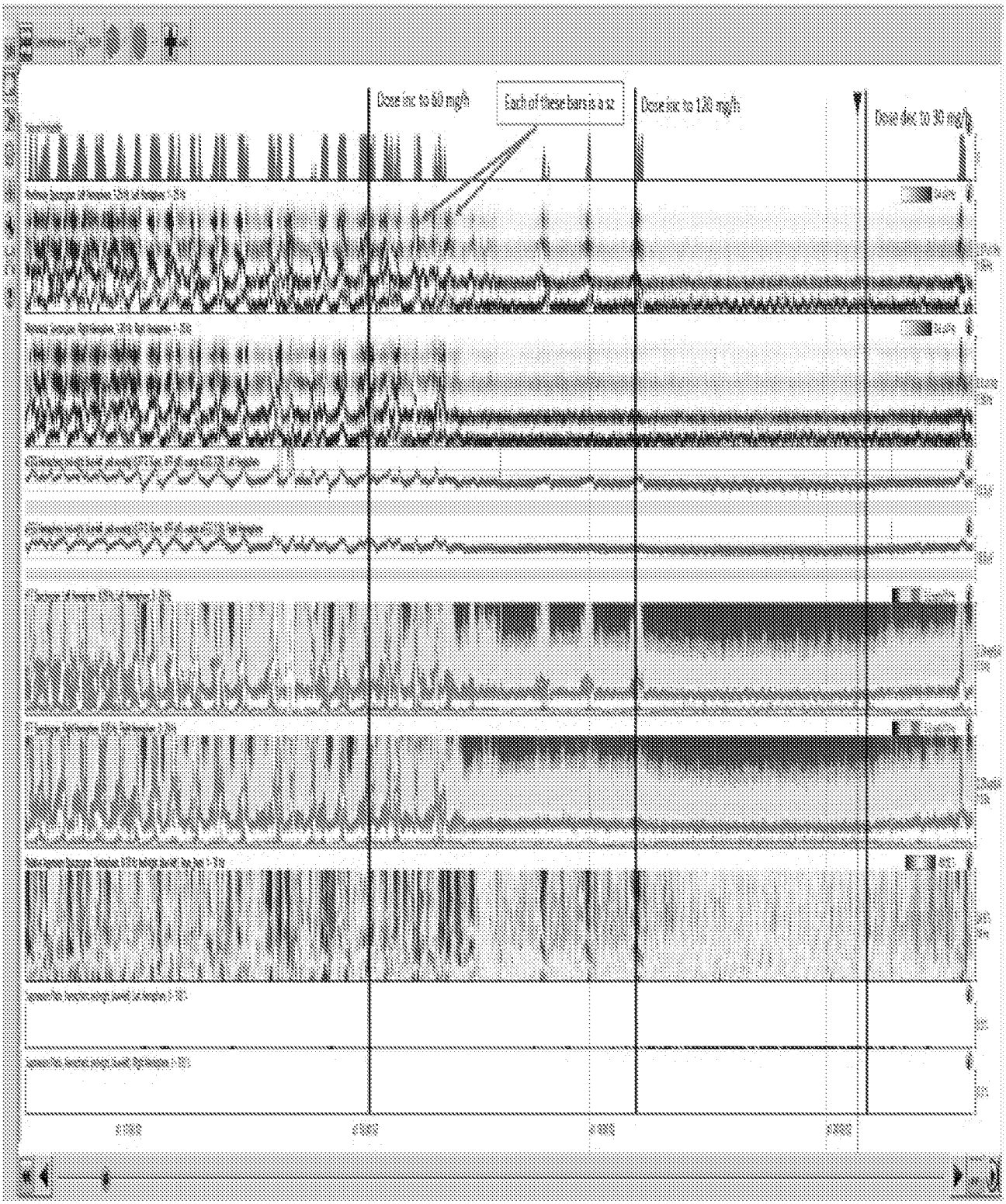


Figure 11

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| APPLICATION NUMBER | FILING or 371(c) DATE | GRP ART UNIT | FIL FEE REC'D | ATTY.DOCKET.NO | TOT CLAIMS | IND CLAIMS |
|---|---|---|---|---|---|---|
| 62/882,648 | 08/05/2019 | | 140 | 550.1013P | | |

**CONFIRMATION NO. 9952**

**FILING RECEIPT**

23280
Davidson, Davidson & Kappel, LLC
589 8th Avenue
16th Floor
New York, NY 10018

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Date Mailed: 09/13/2019

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Julia Tsai, Radnor, PA;

**Applicant(s)**

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**Power of Attorney:**
Oleg Ioselevich--56963

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The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 62/882,648**
**Projected Publication Date:** None, application is not eligible for pre-grant publication
**Non-Publication Request:** No

**Early Publication Request:** No
** **SMALL ENTITY** **
**Title**

GANAXOLONE FOR USE IN TREATMENT OF STATUS EPILEPTICUS

**Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications:** No

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