CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215904Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	March 17, 2022
Requesting Office or Division:	Division of Neurology 2 (DN 2)
Application Type and Number:	NDA 215904
Product Name and Strength:	Ztalmy (ganaxolone) suspension, 50 mg/mL
Applicant/Sponsor Name:	Marinus Pharmaceuticals, Inc.
OSE RCM #:	2021-1470-3
DMEPA 2 Safety Evaluator:	Justine Kalonia, PharmD
DMEPA 2 Acting Team Leader:	Stephanie DeGraw, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised Instructions for Use (IFU) labeling received on March 15, 2022 for Ztalmy. The Division of Neurology 2 (DN 2) requested that we review the revised IFU labeling for Ztalmy (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review and memorandums. [a, b, c]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Kalonia, J. Label and Labeling Review for Ztalmy (NDA 215904). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2021 NOV 23. RCM No.: 2021-1470.
[b] Kalonia, J. Label and Labeling Review for Ztalmy (NDA 215904). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2022 FEB 11. RCM No.: 2021-1470-1.
[c] Kalonia, J. Label and Labeling Review for Ztalmy (NDA 215904). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2022 FEB 25. RCM No.: 2021-1470-2.

APPENDIX A. LABELING RECEIVED ON MARCH 15, 2022

- Instructions for use, available from: \\CDSESUB1\evsprod\nda215904\0049\m1\us\114-labeling\draft\labeling\instruct-for-use-tracked.docx

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/s/

JUSTINE H KALONIA
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STEPHANIE L DEGRAW
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	March 9, 2022
To:	Tina Chhabra Regulatory Project Manager **Division of Neurology II (DNII)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Nyedra W. Booker, PharmD, MPH Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Sapna Shah, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG) and Instructions for Use (IFU)
Drug Name (established name):	ZTALMY (ganaxolone)
Dosage Form and Route:	oral suspension, CXX
Application Type/Number:	NDA 215904
Applicant:	Marinus Pharmaceuticals, Inc.

1 INTRODUCTION

On July 20, 2021, Marinus Pharmaceuticals, Inc. submitted for the Agency's review, a New Drug Application (NDA) 215904 and Request for Priority Review for ZTALMY (ganaxolone) oral suspension, CXX.

The proposed indication for ZTALMY (ganaxolone) oral suspension is for the treatment of seizures associated with Cyclin-dependent Kinase-like 5 Deficiency Disorder (CDD).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Neurology II (DNII) on July 29, 2021, and July 30, 2021, respectively for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for ZTALMY (ganaxolone) oral suspension.

2 MATERIAL REVIEWED

- Draft ZTALMY (ganaxolone) oral suspension MG and IFU received on July 20, 2021, revised by the Review Division throughout the review cycle, and received by DMPP on February 24, 2022.
- Draft ZTALMY (ganaxolone) oral suspension MG and IFU revised by the Review Division throughout the review cycle and received by OPDP on March 7, 2022.
- Draft ZTALMY (ganaxolone) oral suspension Prescribing Information (PI) received on July 20, 2021, revised by the Review Division throughout the review cycle, and received by DMPP on February 22, 2022.
- Draft ZTALMY (ganaxolone) oral suspension Prescribing Information (PI) revised by the Review Division throughout the review cycle and received by OPDP on February 22, 2022.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG and IFU we have:

- simplified wording and clarified concepts where possible

- ensured that the MG and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG and IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.

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/s/

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SAPNA SHAH
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SHARON W WILLIAMS
03/09/2022 03:06:15 PM

MARCIA B WILLIAMS
03/09/2022 03:17:20 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: March 7, 2022

To: Steve Dinsmore, M.D.
Division of Neurology Products II (DN II)

Tina Chhabra, Regulatory Project Manager, (DN II)

Tracy Peters, Associate Director for Labeling, (DN II)

From: Sapna Shah, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Aline Moukhtara, Team Leader, OPDP

Subject: OPDP Labeling Comments for ZTALMY® (ganaxolone) oral suspension, CXX (pending controlled substance scheduling)

NDA: 215904

In response to DN II's consult request dated July 30, 2021, OPDP has reviewed the proposed product labeling (PI), Medication Guide, Instructions for Use (IFU), and carton and container labeling for the original NDA submission for ZTALMY® (ganaxolone) oral suspension, CXX (pending controlled substance scheduling) (Ztalmy).

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DN II on February 22, 2022 and are provided below.

Medication Guide/Instructions for Use: A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed Medication Guide/IFU will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on February 23, 2022, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Sapna Shah at (240) 402-6068 or Sapna.Shah@fda.hhs.gov.

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SAPNA SHAH
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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	February 25, 2022
Requesting Office or Division:	Division of Neurology 2 (DN 2)
Application Type and Number:	NDA 215904
Product Name and Strength:	Ztalmy (ganaxolone) suspension, 50 mg/mL
Applicant/Sponsor Name:	Marinus Pharmaceuticals, Inc.
OSE RCM #:	2021-1470-2
DMEPA 2 Safety Evaluator:	Justine Kalonia, PharmD
DMEPA 2 Acting Team Leader:	Stephanie DeGraw, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on February 23, 2022 for Ztalmy. The Division of Neurology 2 (DN 2) requested that we review the revised container label and carton labeling for Ztalmy (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review and memorandum.[a, b]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Kalonia, J. Label and Labeling Review for Ztalmy (NDA 215904). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2021 NOV 23. RCM No.: 2021-1470.
[b] Kalonia, J. Label and Labeling Review for Ztalmy (NDA 215904). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2022 FEB 11. RCM No.: 2021-1470-1.

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/s/

JUSTINE H KALONIA
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STEPHANIE L DEGRAW
02/25/2022 05:55:09 PM

Clinical Inspection Summary

Date	2/18/2022
From	Cara Alfaro, Pharm.D., Clinical Analyst Phillip Kronstein, M.D., Team Leader Kassa Ayalew, M.D., M.P.H., Division Director; (Acting) Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Tina Chhabra, Regulatory Project Manager Steven Dinsmore, M.D., Medical Officer Philip Sheridan, M.D., Team Leader Division of Neurology 2 Office of Neuroscience
NDA #	215904
Applicant	Marinus Pharmaceuticals
Drug	Ganaxolone
NME	Yes
Proposed Indication	Treatment of seizures associated with cyclin-dependent kinase-like 5 deficiency disorder
Consultation Request Date	9/1/2021
Summary Goal Date	1/20/2022, extended to 2/18/2022
Priority/Standard Review	Priority
Action Goal Date	3/18/2022
PDUFA Date	3/20/2022

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Drs. Bahi-Buisson, Demarest, and Pestana-Knight were inspected in support of this NDA, covering Protocol 1042-CDD-3001. Despite some protocol deviations noted at Dr. Bahi-Buisson's site, the study appears to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.

Two of five enrolled subjects at Dr. Bahi-Buisson's site did not meet eligibility criteria. These two subjects, both randomized to placebo, did not meet the inclusion criterion of having at least 16 seizures in each month of the two months prior to screening per historical seizure diary data. The primary efficacy endpoint was the percent change in 28-day primary seizure frequency through the end of the 17-week, double-blind treatment phase relative to the 6-week prospective baseline period. The seizure frequency in the baseline period for these two subjects was in the range of baseline seizures for all subjects randomized to placebo. It is unlikely that inclusion of these two subjects would impact the overall efficacy analysis.

For Protocol 1042-CDD-3001, subjects/caregivers/legal authorized representatives (LARs) entered seizure data into an electronic diary (eDiary). The eDiary allowed parents/caregivers/LARs the ability to retroactively enter and/or edit seizures within a 7-day window. Any updates outside that 7-day window required a Data Clarification Form (DCF) and/or proxy entry into the eDiary by site personnel or into the eDiary database by the vendor, Signant Health. For proxy data entry and DCFs, sites were instructed to file hard copy source data with subject study records.

Upon request, the sponsor provided additional information regarding proxy data entry. The sponsor stated that a total of 2695 seizures for 38 subjects at 22 sites were entered by proxy entry; this accounted for approximately 4% of all seizures. Retrospective proxy data entry occurred, on average, 187 days after the study day of missing data. The sponsor described multiple types of source available at the sites to support proxy data entry. Without access to the source data, it is difficult to discern which proxy data entry was reliable and which was not.

In their response, the sponsor included datasets that identified (flagged) proxy and DCF data. The sponsor also included an additional efficacy analysis excluding all proxy and DCF data. We recommend that the FDA statisticians confirm the sponsor's sensitivity analysis.

II. BACKGROUND

Ganaxolone suspension for oral administration is being developed under NDA 215904 (IND 044020) for the treatment of seizures associated with Cyclin-dependent Kinase-like 5 (CDKL5) Deficiency Disorder (CDD). The sponsor has submitted one Phase 3 study to support the efficacy and safety of ganaxolone for the treatment of seizures associated with CDD.

Protocol 1042-CDD-3001

Title: "A double-blind, randomized, placebo-controlled trial of adjunctive ganaxolone treatment in children and young adults with cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) followed by long-term open-label treatment"

Subjects: 101

Sites: 36; United States (17), Western Europe (10), Eastern Europe (5), Australia (3), and Middle East/Central Asia (1)

Study Initiation and Double-Blind Completion Dates: 6/30/2018 – 7/31/2020; long-term open label phase of study is ongoing

Double-Blind Database Lock: 9/1/2020

This was a double-blind, randomized, placebo-controlled trial of adjunctive ganaxolone treatment in children and young adults with cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD). The long-term, open-label phase of this study is ongoing. Included were male or females 2 through 21 years (inclusive); molecular confirmation of a pathogenic or likely pathogenic CDKL5 variant; early onset, difficult to treat seizures, and neurodevelopmental impairment (genetic mutations were confirmed by a central lab); failure to control seizures despite trial of ≥2 anti-seizure medications at therapeutic doses; have at least 16 seizures of primary seizure types (bilateral tonic, generalized tonic-clonic, bilateral clonic, atonic/drop, or focal to bilateral tonic-clonic) per 28 days in each 4-week period in the 8-week period prior to screening; approved to participate by sponsor and or designee (i.e., Epilepsy Consortium); and on a stable regimen of 0 to 4 anti-seizure medications for ≥1 month prior to screening visit. Subjects with surgically implanted vagal nerve stimulator were also eligible.

The study was comprised of three phases:

Screening/Baseline Phase
There were two screening visits. At the first screening visit, an 8-week daily historical seizure calendar was reviewed to determine eligibility based on seizure frequency. This was followed by a second screening visit. Subjects without this calendar were asked to return to the clinic for the screening visit after they had maintained an 8-week daily historical seizure calendar. To be eligible for the study, subjects had to have at least 16 seizures per 28 days in each 4-week period of this 8-week period.

This phase then included a 6-week prospective baseline period in which subjects recorded seizure information daily in the eDiary.

Double-Blind Phase
Subjects were randomized (1:1) to one of the following study arms:

- Ganaxolone: administered three times daily (TID) and titrated to 63 mg/kg/day (max dose 1800 mg/day) over 4 weeks and then maintained at that dose for an additional 13 weeks. There were different titration regimens for subjects weighing ≤28 kg and subjects >28 kg.

- Placebo TID for 17 weeks

Subjects were stratified into two groups based on baseline seizure frequency. Subjects recorded seizure information daily in an eDiary during the double-blind period.

Open-Label Phase
After completing the double-blind period, all subjects were treated with ganaxolone (63 mg/kg/day) in the long-term open-label period of this study. Any subject who

discontinued the study early had to undergo a 2-week taper, unless otherwise medically indicated, and return to the site 2 weeks later for safety follow-up assessments. Subjects continued to record seizure information in the eDiary during this open-label period. The open-label period was to continue until drug approval or until the study was stopped by the sponsor.

The *primary efficacy endpoint* was the percent change in 28-day primary seizure frequency through the end of the 17-week double-blind treatment phase relative to the 6-week prospective baseline period.

Rationale for Site Selection

The clinical sites were chosen primarily based on risk ranking in the site selection tool, numbers of enrolled subjects, site efficacy, and prior inspectional history.

III. RESULTS

1. **Nadia Bahi-Buisson, M.D.**
   Site #701
   Hopital Universitaire Necker-enfants Malades
   149 Rue de Sevres
   Porte H2, Niveau 1
   Paris 75015
   France
   Inspection Dates: 11/15/2021 – 11/19/2021

   At this site for Protocol 1042-CDD-3001, 6 subjects were screened, randomized, and completed the double-blind phase of the study. Two subjects continued in the open-label phase of the study.

   Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records for all subjects was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IEC/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, and primary efficacy endpoint data (seizures).

   Subjects, parents, or legal authorized representatives (LARs) entered seizure data into an eDiary, called the TrialMax Touch. During the inspection, the FDA field investigator was given read-only access to TrialManager, the eDiary database. Seizure data from the TrialManager database was verified against the sponsor data line listings; no discrepancies were noted. There was no evidence of under-reporting of adverse events.

During the inspection, it was noted that two subjects did not meet eligibility requirements based on the number of seizures recorded in the 8-week historical seizure calendar that the clinical investigator was to have reviewed during the screening/baseline period. According to inclusion criterion #5, subjects must have "at least 16 seizures of primary seizure types…per 28 days in each 1-month period in the 2-month period prior to screening" – a total of at least 32 seizures for the 28-day period. The subjects' historical seizure calendars were not available for review at the site, but the site recorded the total number of seizures experienced per month and the type of seizure on a paper source document.

While Subject # (b) (6)'s historical seizure frequency was only one seizure too few for eligibility, Subject # (b) (6) experienced 12 seizures in the first four weeks and 7 seizures in the second four weeks of the 8-week historical seizure period (see Table 1). The clinical investigator stated that she had interpreted the inclusion criterion as 16 seizures during the 8-week historical seizure period and not 16 seizures for each of the two months.

Inclusion criterion #6 of the protocol states that subjects "must be approved to participate by sponsor and/or designees (i.e., Epilepsy Consortium) after review of medical history, genetic testing, seizure classification, and historical seizure calendars." Both subjects were deemed eligible for enrollment into the study by the Epilepsy Consortium. These eligibility protocol deviations were not included in the sponsor's protocol deviation line listing.

Table 1. Eligibility Protocol Deviations: 8-Week Historical Seizure Calendar

Subject	Treatment Arm	Number of Seizures	
		1st 4 Weeks	2nd 4 Weeks
(b) (6)	Placebo	15	16
	Placebo	12	7

Reviewer's comments: Per protocol, neither of these subjects met inclusion criterion #5 with respect to the frequency of seizures during the 8-week historical seizure period prior to screening. Despite not meeting this criterion, both subjects were deemed eligible for enrollment by the Epilepsy Consortium. The statistical periods of interest in this study were the 17-week double-blind period compared to the 6-week prospective baseline period. The protocol did not define a minimum seizure frequency for the 6-week prospective baseline period.

According to the clinical study report, the mean number of seizures in the prospective baseline period for subjects in the placebo group was 104 with a median of 49 seizures and a range from 0.7 – 1021. The number of seizures in the prospective baseline period for Subjects # (b) (6) (b) (6) was 29 and 21. Although the baseline number of seizures for these two subjects was lower than the mean and median, they were within the range of seizures for subjects in the placebo group.

2. Scott Demarest, M.D.
Site #104
University of Colorado School of Medicine
Children's Hospital Colorado
3123 E 16th Avenue
Aurora, CO 80045
Inspection Dates: 11/15/2021 – 11/18/2021

At this site for Protocol 1042-CDD-3001, 5 subjects were screened, 4 were randomized, and 3 subjects completed the double-blind phase of the study. Subject # (b) (6), randomized to placebo, discontinued due to an adverse event (seizure). The narrative for this discontinuation due to adverse events was not included in the NDA submission. Two subjects continued in the open-label phase of the study.

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records for all subjects was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, and primary efficacy endpoint data (seizures).

Subjects, parents, or LARs entered seizure data into an eDiary, called the TrialMax Touch. During the inspection, the FDA field investigator was given read-only access to TrialManager, the eDiary database. Seizure data from the TrialManager database was verified against the sponsor data line listings; no discrepancies were noted. There was no evidence of under-reporting of adverse events.

Reviewer comments: According to the sponsor's adverse event line listing, Subject # (b) (6) who was randomized to placebo, experienced an increase in seizures on (b) (6) and study drug was discontinued. The narrative for this event was not included in the NDA.

3. Elia Pestana-Knight, M.D
Site #105
Cleveland Clinic Foundation
Neurological Institute, Epilepsy Center
9500 Euclid Avenue, Suite S52
Cleveland, OH 44195
Inspection Dates: 9/27/2021 – 10/4/2021

At this site for Protocol 1042-CDD-3001, 12 subjects were screened, 10 were randomized, and 9 subjects completed the double-blind phase of the study. Subject # (b) (6), randomized to ganaxolone, discontinued due to adverse events (increased seizures, excessive somnolence).

The narrative for this discontinuation due to adverse events was included in the NDA submission. Nine subjects continued in the open-label phase of the study.

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records for all subjects was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, and primary efficacy endpoint data (seizures).

Subjects, parents, or LARs entered seizure data into an eDiary, called the TrialMax Touch. During the inspection, the FDA field investigator was given read-only access to TrialManager, the eDiary database. Seizure data from the TrialManager database was verified against the sponsor data line listings, no discrepancies were noted. There was no evidence of under-reporting of adverse events.

Electronic Diaries and Proxy Data Entry

Upon request, the sponsor included information about the electronic diary (eDiary) used in Protocol 1042-CDD-3001. The eDiary, called TrialMax Touch, was provided by the vendor, Signant Health. Subjects, caregivers, or legally authorized representatives (LARs) were to enter seizure data directly into the eDiary. The eDiary allowed parents/caregivers/LARs the ability to retroactively enter and/or edit seizures within a 7-day window. Any updates outside that 7-day window required a Data Clarification Form (DCF) and/or proxy entry as per Signant Health SOPs. Proxy data entry included data entry by study staff using TrialMax Touch. For proxy data entry and DCFs, sites were instructed to file hard copy source data with subject study records.

In the sponsor's 11/29/2021 response to an information request, the sponsor stated that at the time of double-blind database lock, a total of 2164 seizures were entered via proxy entry by study staff for 35 subjects at 21 sites. This accounted for <4% of all seizures.

On 12/15/2021, another information request was sent to the sponsor for additional information about proxy data entry including, but not limited to, time of proxy data entry relative to missing seizure data (retrospective data entry), personnel entering data by proxy, source data supporting proxy data entry, and whether proxy data entry was flagged in datasets submitted to the NDA. In the sponsor's 1/14/2022 response, the number of proxy entries was corrected to 2695 for 38 subjects at 22 sites; this accounted for approximately 4% of all seizures. Proxy entry was made by the site using the eDiary device (1838 seizures) or entry by the vendor, via DCF, into the eDiary database (857 seizures).

A review of the proxy data entry noted the following:

- The types of data entered by proxy included seizure (yes/no), seizure description and clinical term, number of seizures, seizures beyond 30 minutes (yes/no).
- Retrospective proxy data entry was, on average 187 days (median 162 days) after the study day of missing data, with a range of 0 to 609 days. Approximately 80% of retrospective data entry was >100 days after the study day of missing data.
- There was a time lag in the vendor's awareness of missing eDiary data. On average, the vendor was aware of missing data 150 days (median 158 days) after the date of missing data, with a range of 0 to 509 days. Approximately 50% of missing data was not identified by the vendor for 100 to 200 days after the study day of missing data.
- Per the sponsor, a description of the source data available at the site to support proxy data entry into the eDiary included "paper diary excel template given to site by parent/caregiver," "paper diary given to site by parent/caregiver," "diary log from caregiver," "parent sent email of source after forgetting to complete diary," "parent recorded seizures in cell phone and wrote the dates of missed entries on back of a questionnaire," "parent keeps electronic seizure diary via seizuretracker.com," "screenshot of text message from mother/paper seizure record", and "interviewed parents of subject and filled in missing data entries on log prior to proxy entry".

The review division did not have detailed information about the proxy data entry at the time the clinical investigator site inspections were conducted. Of the three site inspections, only Site #105 had proxy data entry; however, this was not known at the time of the inspection.

In their 1/14/2022 response, the sponsor submitted a dataset identifying proxy and DCF data entry. In this response, the sponsor also submitted an analysis of the primary efficacy endpoint excluding all data entered by proxy and DCF. The results of this sensitivity analysis were reportedly similar to the overall efficacy results in the clinical study report.

Reviewer comments: There appears to have been delays in the vendor's and sponsor's awareness of missing eDiary data that were later entered by proxy. The number of proxy entries was stated to be 2695 seizures for 38 subjects at 22 sites; this accounted for approximately 4% of all seizures. The sponsor noted multiple different types of source supporting proxy data entry and DCFs; however, without access to these sources, it is difficult to discern which proxy data entry was reliable and which was not.

The sponsor included a dataset that identified (flagged) data entered by proxy and DCF. The sponsor also provided a sensitivity analysis excluding all data entered by proxy and DCF, which they claimed did not change the overall efficacy results as stated in the clinical study report. We recommend that the FDA statisticians confirm the sponsor's sensitivity analysis.

{See appended electronic signature page}

Cara Alfaro, Pharm.D.
Clinical Analyst
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Phillip Kronstein, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H
Division Director and (Acting) Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:

Central Document Room/NDA 215904
Division of Neurology 2/(Acting) Division Director and Deputy Director/Teresa Buracchio
Division of Neurology 2/Medical Team Leader/Philip Sheridan
Division of Neurology 2/Medical Officer/Steven Dinsmore
Division of Neurology 2/Project Manager/Tina Chhabra
OTS/OB/DBI/Statistical Reviewer/Xiang Ling
OTS/OB/DBI/Statistical Team Leader/John Lawrence
OSI/Office Director/David Burrow
OSI/Office Deputy Director/Laurie Muldowney
OSI/DCCE/Division Director and Acting GCPAB Branch Chief/Kassa Ayalew

OSI/DCCE/GCPAB/Team Leader/Phillip Kronstein
OSI/DCCE/GCPAB/Reviewer/Cara Alfaro
OSI/GCPAB Program Analyst/Yolanda Patague

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M E M O R A N D U M
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date:	February 15, 2022
To:	Nicholas Kozauer, M.D., Director Division of Neurology 2 (DN2)
Through:	Dominic Chiapperino, Ph.D., Director Chad Reissig, Ph.D., Supervisory Pharmacologist Controlled Substance Staff
From:	Katherine Bonson, Ph.D., Senior Pharmacologist Controlled Substance Staff
Subject:	NDA 215904 (IND 044020) Ganaxolone oral suspension, 50 mg/ml (proposed tradename, ZTALMY) **Indication:** [redacted] (b) (4) for the treatment of cyclin-dependent, kinase-like 5 (CDKL5) deficiency disorder (CDD) in patients aged 2 years and older **Sponsor:** Marinus Pharmaceuticals, Inc.
Materials reviewed:	NDA 215904 (submitted July 20, 2021) Statistical review of human abuse potential study (Wei Liu, Ph.D., Office of Biostatistics, February 8, 2022)

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I. EXECUTIVE SUMMARY

1. Background

The Division of Neurology 2 (DN2) consulted the Controlled Substance Staff (CSS) to request an abuse potential assessment of the preclinical and clinical studies conducted with ganaxolone (tradename ZTALMY) under NDA 215904 (IND 044020), submitted by Marinus Pharmaceuticals, Inc.

Ganaxolone is proposed for (b) (4) for the treatment of cyclin-dependent, kinase-like 5 (CDKL5) deficiency disorder (CDD) in patients aged 2 years and older. CDD produces early onset seizures with severe encephalopathy. Ganaxolone solution is provided as a cherry flavored suspension at a concentration of 50 mg/mL (110 mL per bottle; 5500 mg per bottle). The proposed therapeutic dosing with epileptic patients is based on body weight.

In patients weighing more than 28 kg (>61 pounds), drug administration begins at 150 mg three times daily (450 mg/day) on Days 1 to 7, increasing to 300 mg three times daily (900 mg/day) on Days 8 to 14, then 450 mg three times daily (1350 mg/day) on Days 15 to 21. From Day 22 onwards, patients will receive 600 mg three times daily (1800 mg/day; maximum recommended daily dose at this weight class).

In patients weighing 28 kg or less (≤61 pounds), dosing is determined on a mg/kg basis. Drug administration begins at 6 mg/kg three times daily (18 mg/kg/day; up to 504 mg/day) on Days 1 to 7, increasing to 11 mg/kg three times daily (33 mg/kg/day; up to 924 mg/day) on Days 8 to 14, then 16 mg/kg three times daily (48 mg/kg/day; up to 1344

mg/day) on Days 15 to 21. From Day 22 onwards, patients will receive 21 mg/kg three times daily (63 mg/kg/day; up to 1764 mg/day; maximum recommended daily dose at this weight class).

Ganaxolone is a neurosteroid that acts as a positive allosteric modulator of $GABA_A$ receptors. It has a chemical structure and mechanism of action that is similar to alfaxalone, an anesthetic, and to brexanolone (also known as allopregnanolone), a treatment for postpartum depression. Both alfaxalone and brexanolone are controlled in Schedule IV under the federal Controlled Substances Act.

CSS was consulted on ganaxolone throughout the IND stage and provided feedback on abuse-related preclinical study designs and resultant data, culminating in the requirement of a human abuse potential (HAP) study.

In the NDA, the Sponsor concludes that ganaxolone should be proposed for placement in Schedule IV of the Controlled Substances Act (CSA) on the basis of "a thorough evaluation of the abuse-related preclinical and clinical data." They specifically highlight the generalization of ganaxolone to midazolam (Schedule IV) in a rat drug discrimination study, and the ability of ganaxolone to produce self-administration less than that of methohexital (Schedule IV).

The Sponsor proposes the following text for Section 9 of the drug label:

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

ZTALMY contains (b) (4) ganaxolone. (b) (4)

9.2 Abuse

Abuse is the intentional, non-therapeutic use of a drug, even once, (b) (4) psychological or physiological effects.

In a human abuse potential study, ZTALMY (400, 800, and 2000 mg) (b) (4) compared to lorazepam 6 mg and placebo. ZTALMY at all doses was shown to have lower abuse potential than lorazepam. (b) (4)

9.3 Dependence

Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug.

(b) (4)

[redacted]

2. Conclusions

- CSS has reviewed the nonclinical and clinical abuse-related data submitted in NDA 212904 for ganaxolone and concludes that the drug has abuse potential and should be recommended for placement in Schedule V of the CSA. This conclusion is based on the data described below:

- Ganaxolone has a chemical structure that is similar to alfaxalone, an anesthetic agent, and to brexanolone (also known as allopregnanolone), a treatment for postpartum depression.

- In receptor binding and functional studies, ganaxolone has highly selective activity as a positive allosteric modulator at GABA-gated chloride channels.

- In a general behavior tests in rats (Irwin study, rotorod performance, open field locomotor test), ganaxolone produced dose-dependent increases in sedative behavior, as shown by decreases in locomotion and muscle coordination.

- In a drug discrimination study in rats, ganaxolone produced full generalization to midazolam, as would be expected from the binding data showing activity at $GABA_A$ receptors.

- In a self-administration study in rats, ganaxolone produce a low rate of self-administration that was statistically significantly greater than placebo but numerically similar to placebo. This suggests that ganaxolone produces a low degree of rewarding properties.

- In a physical dependence study in rats, chronic administration of ganaxolone produced a mild withdrawal syndrome compared to diazepam. This suggests that ganaxolone produces physical dependence, but to a degree that is less than that of a benzodiazepine.

- In a human abuse potential study with subjects experienced with sedatives, ganaxolone produced only slight signals of abuse potential at the 2000 mg supratherapeutic dose on positive subjective measures such as VAS for Drug Liking, Overall Drug Liking, Good Drug Effects, High, or Take Drug Again. On the VAS for Drug Similarity, ganaxolone did not produce a meaningful score of similarity for benzodiazepines except at the 2000 mg dose. Although ganaxolone dose-dependently produced euphoria as an AE, the absolute number of subjects who experienced euphoria was only slightly greater following therapeutic and supratherapeutic doses of ganaxolone than following placebo, and this number was 2-3 times less than that reported after lorazepam administration. These data suggest that ganaxolone has an abuse potential that is less than that of benzodiazepines.

- An assessment of abuse-related adverse events in Phase 1 and Phase 2/3 studies showed no clinically meaningful signals for euphoria. However, ganaxolone did produce other CNS-related AEs, especially somnolence. In the absence of a euphoria signal, however, this is not considered to be a sign of abuse potential.

- A human physical dependence evaluation could not be conducted following chronic administration of ganaxolone to epileptic patients because of medical and ethical considerations involved in abrupt discontinuation of antiepileptic medication. Additionally, all subjects in Phase 2/3 clinical studies with ganaxolone were allowed to take other antiepileptic drugs during the studies, which confounds interpretation of any withdrawal signs or symptoms. Healthy subjects who participated in Phase 1 clinical studies were not assessed for physical dependence.

1. If approved, the approval of ganaxolone will be under section 505(x) of the Food, Drug, and Cosmetic Act and the approval will only be in effect as of the date the Drug Enforcement Administration issues an Interim Final Rule to place ganaxolone in Schedule V of the CSA. At that time, prescribing information and carton and container labeling may be updated by the Sponsor via a supplementary NDA submission to reflect the control status of ganaxolone.

3. Recommendations

CSS has determined that ganaxolone has an abuse potential less than that of drugs in Schedule IV and recommends that:

- Ganaxolone should be recommended for placement in Schedule V under the CSA.

- If approved, the ganaxolone product label should include Section 9 (Drug Abuse and Dependence), with the following text:

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

ZTALMY contains ganaxolone. (Controlled substance schedule to be determined after review by the Drug Enforcement Administration.)

9.2 Abuse

Ganaxolone has potential for abuse. Abuse is the intentional non-therapeutic use of a drug, even once, to achieve a desired psychological or physiological effect. In a human abuse potential study, 400, 800, and 2000 mg oral ZTALMY were compared to 6 mg oral lorazepam administration and placebo. On positive subjective measures of "drug liking," "overall drug liking," "high," "good drug effects," and "take drug again," the 400 and 800 mg doses of ZTALMY produced mean scores that within or just outside of the acceptable placebo range and were statistically (b) (4) to placebo. The 2000 mg dose of ZTALMY produced responses on these positive subjective measures that were slightly greater than the acceptable placebo range and were statistically (b) (4) to placebo. Scores on these positive subjective measures for all three doses of ZTALMY were statistically significantly lower than those produced by lorazepam.

9.3 Dependence

Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug. (b) (4) . It is recommended that ZTALMY be tapered according to the dosage recommendations, unless symptoms warrant immediate discontinuation [see Dosage and Administration (2.2), Warnings and Precautions (5.1)].

II. DISCUSSION

1. Chemistry

1.1 Drug Substance

Ganaxolone is a new molecular entity identified by CAS registry number: 38398-32-2. Chemically, ganaxolone is a neurosteroid that is an analogue of allopregnanolone (also known as brexanolone), with an additional methyl group at the 3β position that is purported by the Sponsor (b) (4) . The chemical

formula of ganaxolone is 3α-hydroxy-3β-methyl-5α-pregnan-20-one. It has a molecular formula of $C_{22}H_{36}O_2$ and a molecular weight of 332.53. It is a white to off-white crystalline, nonhygroscopic powder with a melting point of 190-198°C. It is virtually insoluble in water, slightly soluble in methanol, ethanol, isopropanol, ethyl acetate, and toluene (5 to 25 mg/mL at 20°C), and soluble in N,N-dimethylacetamide.

1.2 Drug Product

Ganaxolone Oral Suspension, 50 mg/mL is a white to off-white immediate release oral suspension, packaged in 4 fl. oz. (135 mL) bottles. Hypomellose and polyvinyl alcohol are present as (b) (4), sodium lauryl sulfate is the (b) (4) methylparaben, propylparaben, and sodium benzoate are (b) (4) citric acid (b) (4) and sodium citrate (b) (4) thicone emulsion is the (b) (4) The solution (b) (4) with sucralose and flavored with cherry flavoring.

2. Nonclinical Abuse-Related Studies

2.1 Receptor Binding and Functional Studies (Study # #100055032 and 1042-231-020)

In a series of receptor binding studies, ganaxolone was found to have high affinity at GABA-gated chloride channels (96% inhibition, Ki value not calculated). When ganaxolone was tested at 47 receptors, ion channels, steroid sites, and enzymes, at a concentration of 10 μM, no other site produced binding inhibition >50%. The sites tested included abuse-related sites such as dopamine (D_1 and D_2), serotonin ($5HT_{1A}$, $5HT_{2A}$, and $5HT_{2C}$), GABA (A, B, and glycine), cannabinoid (CB_1 and CB_2), opioid (mu, kappa, and delta), glutamate (NMDA, AMPA, phencyclidine, glycine, kainate), transporters (dopamine, serotonin, norepinephrine).

Functional studies of GABA agonism were also conducted with ganaxolone. These studies showed the following results:

- Addition of ganaxolone to a preparation of rat brain membranes inhibited the binding of radiolabeled [^{35}S]tetra-butylbicyclo-phosphorothionate (TBPS), a $GABA_A$ chloride channel ligand, in a concentration-dependent manner (IC_{50} = 80 nmol/L).

- Addition of ganaxolone to a preparation of rat brain membranes enhanced the binding of radiolabeled ligands [^{3}H]flunitrazepam (a benzodiazepine ligand; EC_{50}=125 nmol/L) and [^{3}H]muscimol (a GABA ligand; EC_{50}=86 nmol/L)

- Addition of ganaxolone to a preparation of rat brain cortical synaptoneurosomes potentiated GABA-stimulated radiolabeled ^{36}Cl-uptake in a concentration-dependent manner. Similar results were obtained with the addition of the progesterone-derived neurosteroid, allopregnanolone.

- In human recombinant $GABA_A$ receptor subtypes ($\alpha1\beta1\gamma2L$, $\alpha2\beta1\gamma2L$, $\alpha3\beta1\gamma2L$), ganaxolone enhanced GABA-evoked currents. Ganaxolone also directly activated these subtypes when they were expressed in *Xenopus* oocytes.

- In human $GABA_A$ receptors expressed in in *Xenopus* oocytes, nanomolar concentrations of ganaxolone potentiated chloride currents evoked by GABA. In contrast, ganaxolone alone did not evoke these currents until micromolar concentrations were applied.

- In hippocampal neurons that contain synaptic $GABA_A$ receptors, as well as in dentate gyrus neurons that contain extrasynaptic $GABA_A$ receptors, ganaxolone increased the depolarization evoked by GABA.

These data show that ganaxolone is a positive allosteric modulator at $GABA_A$ sites.

2.2 Animal Behavioral Studies

a. Behavioral Observations During Animal Toxicology Studies

i. Rat Irwin Test (Study #8396690, 11042.RT.Irwin.oral.10019), Rotorod Test (Study #1042.221.00320, 1042.221.00521, 1042.221.00722), Open Field Test (Study #1042.221.01323 and 1042.221.01424)

Irwin Test

In an Irwin study conducted in female rats (8 rats/sex/group), ganaxolone was administered through oral gavage at doses of 0, 10, 20, and 40 mg/kg. A functional observational battery (FOB) assessment was conducted up to 24 hours after drug administration. The FOB included assessment of behavior (observational, physiological, autonomic, neuromuscular, and sensorimotor functioning) while animals were in the home cage, upon removal of animals from the home cage, while animals were in hand, and during placement of animals in an open field cage. Body temperature was also assessed.

There were no differences between ganaxolone-treated and saline-treated animals with regard to general behavioral activity, restlessness, aggression, alertness, reactivity to handling, vocalization, involuntary movements, extensor thrust, eye closure, bar test, waxy rigidity, grip strength, proprioception, palpebral reflex or pupil status.

However, ganaxolone did produce the following behavioral changes:

- An ”abnormal visual response,” which was time dependent, was observed at 4 hours postdose in one animal in each of the 20 and 40 mg/kg GNX groups; therefore, it was considered test article-related.

- Abnormal gait (ataxia), grasping loss, and abnormal righting reflex that were time-dependent (occurring within 6 hours postdose) and observed with GNX doses of 20 or 40 mg/kg, but mainly with 40 mg/kg.

- Low carriage was observed with 40 mg/kg and it was time-dependent (occurring within 6 hours postdose);

- GNX at all doses (10, 20, 40 mg/kg) was associated with lower body temperature (by up to -0.9°C) within the first 8 hours postdose. The lower body temperature was considered test article-related because the changes were consistent with GNX's PK profile and were statistically significant.

Rotarod Performance Test

The rotorod performance test evaluates motor coordination by placing a rat's forepaws on a slowly rotating bar a few inches off the ground so that the animal must continue to grip the bar to avoid falling off. Three rotorod studies were conducted in rats that received intraperitoneal administration of ganaxolone (5 to 50 mg/kg), ethosuximide (100 to 600 mg/kg), or valproate (100 to 600 mg/kg) were used and the animals were tested at a pre-specified time.

Ganaxolone produced a dose-dependent increase in the number of rats that failed to maintain themselves on the rotorod, greater than that produced over the dose range of the positive control drugs, demonstrating that ganaxolone interferes with motor coordination. This drug-induced impairment was coincident with a loss of righting reflex.

Open-field Locomotor Test

Open field locomotor tests evaluate the impact of drugs on normal behaviors of rats in an open cage (e.g., moving about freely, distance travelled, etc.). Two open field locomotor tests were conducted in rats with ganaxolone (5 to 50 mg/kg; test at 30 and 60 minutes after drug administration) in comparison to two anticonvulsants, ethosuximide (200 to 1200 mg/kg; test at 10 minutes after drug administration) and valproate (200 to1200 mg/kg; test at 10 and 30 minutes after drug administration). All three drugs produced a dose-dependent decrease in locomotor activity, as well as a loss of righting reflex. Ganaxolone produced a greater impairment on each parameter than the positive control drugs at the doses tested.

b. Abuse-Related Behavioral Studies

i. Drug Discrimination Study with Ganaxolone (Study #RS1974)

Drug discrimination is an experimental method of determining whether a test drug produces physical and behavioral responses that are similar to a training drug with specific pharmacological effects. Any centrally-acting drug can serve as the training

drug. When the training drug is a known drug of abuse, drug discrimination in animals serves as an important method for predicting whether the effects of a new drug will similarly have abuse potential. Drugs that produce a response similar to known drugs of abuse in animals are also likely to be abused by humans.

In drug discrimination, an animal learns to press one bar when it receives the training drug and another bar when it receives a placebo. Once responding to the training drug and placebo is stable, an animal is given a challenge session with the test drug. A test drug is said to have "full generalization" to the training drug when the test drug produces bar pressing ≥80% on the bar associated with the training drug.

Method

A drug discrimination study was conducted in female rats evaluating whether ganaxolone generalizes to the midazolam interoceptive cue. The use of female rats is justified in the protocol by stating that female animals are weight-stable as adults and thus easier to handle and dose. The study included three phases: pharmacokinetic (PK), dose-finding, and generalization.

In the dose-finding phase, half-log oral doses of ganaxolone (10, 30, and 100 mg/kg) were tested in rats (n = 40) to determine if these doses interfere with operant responding for sweetened condensed milk in the discrimination chamber. Animals were monitored at 30, 60, 120 and 180 minutes after ganaxolone administration. Overt behaviors indicative of CNS activity (sedation, ataxia/rolling gait, hunched posture (sitting or walking), subdued, head weaving, Straub tail, prostration, seizures, head shakes, body tone, locomotor activity, sterotypy, vacuous chewing movements, writhing, tremors, and any other abnormal signs) were also monitored. This study showed that ganaxolone produced a dose-dependent interference with behavioral performance, such that the 10 mg/kg dose did not affect behavior, the 30 mg/kg dose impaired some animals, and the 100 mg/kg does impaired performance in all animals. In terms of overt behaviors, a dose-dependent ataxia/rolling gait was the main observable change following ganaxolone administration.

In the generalization phase, rats (n = 40) were trained to discriminate between intraperitoneally-administered midazolam (0.50 mg/kg initially, increasing to 0.75 mg/kg) and saline using sweetened condensed milk in a 2-choice lever-pressing model. The Sponsor states, “In this variant of the drug discrimination technique, rats were rewarded with sweetened milk on a FR5 schedule of reinforcement on either the midazolam or vehicle lever throughout the 10-minute test sessions. To prevent lever bias in test sessions, sweetened milk rewards were delivered after 5 presses on either lever, and in addition, these 5 presses were not required to be consecutive for the delivery of a reward.” In order to participate in the challenge sessions with the test drugs, rats had to attain at least 75% accuracy on the drug and saline levers.

Following training, rats were challenged with oral administration of the training drug, midazolam (0.3, 0.5, 0.75 and 1.0 mg/kg), oral ganaxolone (3, 5, 10 and 30 mg/kg) as

well as oral administration of two other GABA-acting sedatives, alprazolam (0.125, 0.375, 0.5 and 0.75 mg/kg), and sodium pentobarbital (2, 5, 7.5 and 10 mg/kg). The doses of these sedatives were selected on the basis of company history with the drugs in previously-conducted drug discrimination studies. All drugs were tested at the time of Cmax following oral administration. Oral administration was justified on the basis of the clinical development of ganaxolone for oral administration. There was at least 72 hours between drug administrations.

Full generalization in this study was defined as ≥ 75% responding on the midazolam-associated lever, partial generalization is defined as 26-74% responding on the midazolam-associated lever, and no generalization is defined as ≤ 25% responding on the midazolam-associated lever.

In the pharmacokinetic satellite testing, plasma levels of ganaxolone were determined following oral administration of 3, 5, 10, and 30 mg/kg doses to female rats (n = 6 per group). These doses parallel those administered in the drug discrimination study. Blood sampling occurred at 15, 30, 60, 90, 120, and 180 minutes after ganaxolone administration (n = 3 per timepoint, per group).

Results

In challenge tests with rats that had been trained to discriminate intraperitoneal midazolam from saline:

Midazolam

- Full generalization (97%) to the training dose of intraperitoneal midazolam (0.5-0.75 mg/kg)
- No generalization (4%) to vehicle
- No generalization (12-19%) to oral midazolam at 0.3 and 0.5 mg/kg
- Partial generalization (66%) to oral midazolam at 0.75 mg/kg
- Full generalization (88%) to oral midazolam at 1 mg/kg

Alprazolam

- No generalization (10%) to i.p. midazolam from oral alprazolam at 0.125 mg/kg
- Partial generalization (68%) to i.p. midazolam from oral alprazolam at 0.375mg/kg
- Full generalization (range of 78-92%) to i.p. midazolam from two oral alprazolam doses (0.5 and 0.75 mg/kg)

Sodium Pentobarbital

- No generalization (17%) to i.p. midazolam from oral sodium pentobarbital at 2 mg/kg
- Partial generalization (39%) to i.p. midazolam from oral sodium pentobarbital at 5 mg/kg
- Full generalization (range of 80-99%) to i.p. midazolam from two oral sodium pentobarbital doses (7.5 and 10 mg/kg)

Ganaxolone

- No generalization (18%) to i.p. midazolam from oral ganaxolone at 3 mg/kg (equivalent to 0.4X of plasma levels produced by human oral therapeutic dose of 1600 mg)
- Partial generalization (30%) to i.p. midazolam from oral ganaxolone at 5 mg/kg (equivalent to 0.7X of plasma levels produced by human oral therapeutic dose of 1600 mg)
- Full generalization (range of 85-91%) to i.p. midazolam from two oral ganaxolone doses (10 and 30 mg/kg; equivalent to 0.9X to 1.4X of plasma levels produced by human oral therapeutic dose of 1600 mg)

Conclusions

Oral ganaxolone produced full generalization to i.p. midazolam at doses equivalent to 0.9X to 1.4X of the human oral therapeutic dose, demonstrating that it produces an interoceptive cue that is similar to that of a benzodiazepine.
Although we typically request plasma exposures of the test drug of 2X to 3X relative to the therapeutic dose, this is not necessary when a lower exposure produces full generalization to the comparator drug of abuse.

The data from ganaxolone were similar to the full generalization produced the GABA-acting drugs, midazolam and alprazolam, and sodium pentobarbital.

ii. Self-Administration Studies in Rats with Ganaxolone (Study #RS1973 and RS2224)

A self-administration study evaluates whether a test drug has rewarding properties that are sufficient to produce reinforcement (i.e., the likelihood that an animal will repeatedly self-administer the test drug after initial exposure). Animals are first trained to press a bar in the test cage in order to receive a food reward. After animals consistently bar-press in response for food, they begin to receive an intravenous dose of a known drug of abuse (training drug) as the reward, instead of food. They are also tested with vehicle to ensure that bar-pressing is not maintained for a substance without rewarding properties. Once animals stably bar-press (self-administer) the training drug, they are then allowed to self-administer intravenous doses of the test drug. If the test drug produces a high level of self-administration compared to vehicle, there is a good probability that the drug will produce rewarding properties in humans that are supportive of drug abuse.

The Sponsor conducted two self-administration studies in rats with ganaxolone. Both studies have exactly the same methodological design, with the report for Study #RS1973 dated November 24, 2020, and the report for Study #RS2224 dated January 14, 2021. It is unclear why two studies of the same design were conducted two months apart. The report for Study #RS2224 only mentions Study #RS1973 with regard to selection of doses based on pharmacokinetic data.

However, the replication of this study may be related to the following statement in the report for Study #1973 regarding the 0.1 mg/kg/injection dose:

"Due to the reasons listed below, the decision was taken to exclude all data from the 0.1 mg/kg/injection group in the main self-administration experiment as the validity of results cannot be assured:

- The formulation analysis report highlights that the formulation samples for the 0.1 mg/kg/injection group in the self-administration experiment were outside of specification in both the original samples and the duplicate samples.
- As it is not possible to confirm the accuracy of the formulation for the 0.1 mg/kg/injection samples, data from the 0.1 mg/kg/injection group is not discussed as part of the main study as reliable conclusions cannot be drawn from this data."

Study #R1973

Methods

Training for Self-Administration

Male rats (n = 52) were first trained to self-administer heroin (0.050 mg/kg/injection as the initial training dose and then the dose was reduced to 0.015 mg/kg/injection as final training dose, i.v.) using an FR3 schedule of reinforcement. The use of male rats in this study contrasts with the proposed use of female rats in the drug discrimination and physical dependence studies.

Immediately prior to each training session, rats received a single, non-contingent i.v. ("priming") injection of heroin. The protocol states that, "The objective is to establish robust and consistent responding for heroin (0.015 mg/kg/injection final dose) under a FR3 schedule of drug reinforcement, with a mean of $\geq$12 injections/session over 3 consecutive sessions."

Rats were allowed up to 20 injections in a 2-hour session. Each injection was followed by a 30-second time-out period to prevent overdose. The acceptance criterion for positive reinforcement with heroin during acquisition was defined as 3 consecutive sessions where the mean number of injections was $\geq$ 12. The acceptance criterion for non-reinforcement with saline was defined as 3 consecutive sessions where the mean number of injections was $\leq$ 6. After rats stably self-administered heroin, they underwent an extinction procedure to ensure that self-administration of i.v. saline using FR3 produced $\leq$ 6 injections/session over three consecutive sessions.

Once training on heroin and saline was completed, rats (n = 6/drug dose) were challenged with access to ganaxolone and methohexital. Doses of methohexital were selected based on those used in recently conducted rat i.v. self-administration studies. Ganaxolone doses were selected following the conclusion of a dose-finding study.

Ganaxolone Dose-Finding Phase

Four acute doses of ganaxolone (0.1, 0.3, 1.0 and 3.0 mg/kg, i.v.; n = 4/dose) and vehicle (n = 10) were evaluated during a 1 hr session in which rats were allowed to lever press for food pellets using an FR3 schedule of reinforcement. Rats were monitored for suppression or enhancement of lever pressing for food rewards as well as for general behavioral effects. Sessions ended after 1 hr or the delivery of 50 food pellets. The highest dose of ganaxolone (3.0 mg/kg) was only given to one rat because of its profound behavioral depression effects (91% reduction in lever pressing). Ganaxolone at the lowest two doses (0.1 and 0.3 mg/kg) had no effect on the rate of active lever pressing for food rewards or general behavior. The 1.0 mg/kg dose did not produce an effect on lever pressing but did cause ataxia in 3 of 4 animals.

Challenge Sessions with Ganaxolone and Methohexital

Once the doses of ganaxolone were identified, challenge sessions with ganaxolone (0.05, 0.1, 0.25 and 0.5 mg/kg/injection, n = 8-9/dose) and methohexital (0.0025, and 0.005 mg/kg/injection, n = 9/dose) were initiated. Immediately prior to each test session, rats received a priming injection of the test drug at the dose to which they would have access during the test session. Doses of ganaxolone and methohexital were tested from low to high.

Ganaxolone and methohexital were tested for at least 6 sessions until stable responding was achieved, or for a total of 10 sessions if responding was not stable. The definition of stable responding was "when the number of inj/session taken by an individual rat did not vary by more than ± 25% of the mean of the 3 previous sessions and where there was no obvious increasing or decreasing trend in self-administration, or 3 consecutive sessions where the number of injections was ≥ 12, or 3 consecutive sessions where the number of injections was ≤ 6." If any dose of ganaxolone or methohexital produced responding, 3-4 test sessions with saline were given prior to the next dose of ganaxolone or methohexital, to avoid conditioned responding.

Positive reinforcement for the test compound and reference comparators were defined as "when the mean number of test compound or reference comparator infusions was significantly greater than the mean number of vehicle infusions." Non-reinforcement was defined "where the mean number of infusions of the test compound and reference comparators was not significantly greater than the mean number of vehicle infusions."

Pharmacokinetic Study

Following the conclusion of the self-administration study, a PK study was conducted in male rats (n = 15-18) to evaluate the plasma levels produced by the cumulative doses of each drug that were self-administered by the rats, as well as the cumulative doses that included the initial priming dose. Blood samples were collected at 5 min, 15 min, 30 min, 1 hour, 2 hours and 4 hours after ganaxolone administration.

Results and Conclusions

Over the course of the study, self-administration of heroin (0.015 mg/kg/inj) in the rats was maintained at a level at least 3.7X greater (~19 injections/session) than that produced by saline (~4-5 injections/session) over the course of the study. This confirms that rats were still familiar with the training procedure and would work for a rewarding substance but would not work for a non-rewarding substance. This also validates the study, since heroin serves not only as the training drug, but as a positive control.

Methohexital at the lowest dose (0.0025 mg/kg/injection) produced self-administration at a level similar to that produced by saline (8 injections/session). At the higher dose (0.005 mg/kg/injection), methohexital produced a slightly greater level of self-administration (10 injections/session), but this was statistically significantly greater than saline. This also validates the study, although the results are barely outside the placebo range.

Ganaxolone at the three doses evaluated (0.05, 0.25 and 0.5 mg/kg/injection) produced levels of self-administration (5-7 injections/session) that were similar to those produced by saline. This suggests that ganaxolone does not produce rewarding properties that would lead to reinforcement. As noted above, the 0.1 mg/kg/injection dose was identified as suspect and therefore not reported in the results.

Since this was an unexpected response, given that ganaxolone has $GABA_A$ agonist properties, rats were subsequently challenged again with both heroin (0.015 mg/kg/injection) and saline. The results from this second challenge were similar to those from the training sessions (heroin = 17 injections/session and saline = 4 injections/session), confirming that the rats were still familiar with the training procedure and would work for a rewarding substance, but would not work for a non-rewarding substance.

However, when the pharmacokinetic evaluation of ganaxolone was conducted, it showed that a single administration of each of the individual doses used in the self-administration study produced drug plasma levels relative to human therapeutic plasma levels that were 11% from the 0.05 mg/kg dose, 49% from the 0.25 mg/kg dose, and 108% from the 0.5 mg/kg dose. Thus, two highest doses are likely too high for use in a self-administration study, since they are likely to lead to satiation if the drug has rewarding properties.

When the cumulative amount of ganaxolone resulting from the 0.5 mg/kg dose during self-administration was evaluated, it showed that plasma levels were 456% relative to the human therapeutic plasma levels. This strongly suggests that animals may have been satiated with even small numbers of self-administered injections, since the plasma levels quickly would have accumulated to 0.8X of human therapeutic levels at the 0.05 mg/kg/injection dose (11% x 7 injections) and to 4.5X at the 0.5 mg/kg/injection dose. Thus, this study does not support the conclusion that ganaxolone does not produce rewarding properties.

Study #RS2224

This study is an exact replication of Study #RS1973. Although the study report does not state so, it appears this study was conducted to improve the response from the second positive control condition using methohexital. In Study #RS1973, methohexital produced self-administration responses at 0.0025 and 0.005 mg/kg/injection that were similar to those produced by saline (although data from the higher dose was statistically significantly different from saline). In the present study, the self-administration responses produced by the same doses of methohexital were 15 injections/session for each of the two doses, both of which were statistically significantly greater than saline.

However, in formal terms, this replication was not necessary, since the first positive control, heroin, was self-administered at a rate that was statistically significantly different from saline throughout Study #RS1973 (as well as in the present study).

Methods

Training for Self-Administration

Male rats (n = 52) were first trained to self-administer heroin (0.050 mg/kg/injection as the initial training dose and then the dose was reduced to 0.015 mg/kg/injection as final training dose, i.v.) using an FR3 schedule of reinforcement. The use of male rats in this study contrasts with the proposed use of female rats in the drug discrimination and physical dependence studies.

Immediately prior to each training session, rats received a single, non-contingent i.v. ("priming") injection of heroin. The protocol states that, "The objective is to establish robust and consistent responding for heroin (0.015 mg/kg/injection final dose) under a FR3 schedule of drug reinforcement, with a mean of $\geq$12 injections/session over 3 consecutive sessions."

Rats were allowed up to 20 injections in a 2-hour session. Each injection was followed by a 30-second time-out period to prevent overdose. The acceptance criterion for positive reinforcement with heroin during acquisition was defined as 3 consecutive sessions where the mean number of injections was $\geq$ 12. The acceptance criterion for non-reinforcement with saline was defined as 3 consecutive sessions where the mean number of injections was $\leq$ 6. After rats stably self-administered heroin, they underwent an extinction procedure to ensure that self-administration of i.v. saline using FR3 produced $\leq$ 6 injections/session over three consecutive sessions.

Once training on heroin and saline was completed, rats (n = 6/drug dose) were challenged with access to ganaxolone and methohexital. Doses of methohexital were selected based on those used in recently conducted rat i.v. self- administration studies. Ganaxolone doses were selected following the conclusion of a dose-finding study.

Challenge Sessions with Ganaxolone and Methohexital

Based on the dose-finding study with ganaxolone conducted previously in Study #RS1973 (see above), challenge sessions were conducted with ganaxolone (0.05, 0.1, 0.25 and 0.5 mg/kg/injection, n = 8-9/dose) and methohexital (0.0025, and 0.005 mg/kg/injection, n = 9/dose). Immediately prior to each test session, rats received a priming injection of the test drug at the dose to which they would have access during the test session. Doses of ganaxolone and methohexital were tested from low to high.

Ganaxolone and methohexital were tested for at least 6 sessions until stable responding was achieved, or for a total of 10 sessions if responding was not stable. The definition of stable responding was "when the number of inj/session taken by an individual rat did not vary by more than ± 25% of the mean of the 3 previous sessions and where there was no obvious increasing or decreasing trend in self-administration, or 3 consecutive sessions where the number of injections was ≥ 12, or 3 consecutive sessions where the number of injections was ≤ 6." If any dose of ganaxolone or methohexital produced responding, 3-4 test sessions with saline were given prior to the next dose of ganaxolone or methohexital, to avoid conditioned responding.

Positive reinforcement for the test compound and reference comparators were defined as "when the mean number of test compound or reference comparator infusions was significantly greater than the mean number of vehicle infusions." Non-reinforcement was defined "where the mean number of infusions of the test compound and reference comparators was not significantly greater than the mean number of vehicle infusions."

Pharmacokinetic Study

Following the conclusion of the self-administration study, a PK study was conducted in male rats (n = 15-18) to evaluate the plasma levels produced by the cumulative doses of each drug that were self-administered by the rats, as well as the cumulative doses that included the initial priming dose. Blood samples were collected at 5 min, 15 min, 30 min, 1 hour, 2 hours and 4 hours after ganaxolone administration.

Results and Conclusions

Over the course of the study, self-administration of heroin (0.015 mg/kg/inj) in the rats challenged with ganaxolone and methohexital was maintained at a level at least 3.7X greater (~19 injections/session) than that produced by saline (~4-5 injections/session). This difference between bar pressing for heroin and saline was statistically significant. These data confirm that rats were still familiar with the training procedure and would work for a rewarding substance but would not work for a non-rewarding substance. This also validates the study, since heroin serves not only as the training drug, but as a positive control. These data are similar to those from Study #RS1973.

Methohexital at both doses (0.0025 and 0.005 mg/kg/injection) produced self-administration at a level statistically significantly above that produced by saline (15

injections/session for each dose). This validates the study. Notably, when these same doses of methohexital were tested previously in Study #RS1973 (using exactly the same self-administration protocol), they produced self-administration that was either similar to that of saline (8 injections/session for 0.0025 mg/kg/injection) or only slightly greater than saline but statistically significantly different (10 injections/session for 0.005 mg/kg/injection). Thus, there was a more robust response for this positive control condition than in the previous study, which provides more confidence in the results from ganaxolone. However, this second positive control was not necessary scientifically, since heroin also serves as a positive control by demonstrating that animals will self-administer a drug with rewarding properties.

Ganaxolone produced the following levels of self-administration at the doses tested: 5 injections/session for the 0.05 mg/kg/injection dose, 8 injections/session for the 0.10 mg/kg/injection dose, 8 injections/session for the 0.25 mg/kg/injection dose, and 6 injections/session for the 0.50 mg/kg/injection dose. These data are similar to those from Study #RS1973. The self-administration produced by ganaxolone was much less than that produced by methohexital (15 injections/session) and heroin (19 injections/session and was numerically similar to that produced by saline (5 injections/session). Although the 0.05, 0.25 and 0.50 mg/kg/injection doses of ganaxolone produced self-administration that was statistically similar to saline, the 0.10 mg/kg/injection dose of ganaxolone did produce self-administration that was statistically significantly greater than saline. However, levels of self-administration from ganaxolone were lower than those produced by methohexital or heroin.

Since it was unexpected that a positive allosteric modulator at $GABA_A$ receptors like ganaxolone would produce self-administration that was numerically similar to saline at all doses tested, there was concern that the rats had lost training over the course of the study. Thus, rats were subsequently challenged again with both heroin (0.015 mg/kg/injection) and saline. The results from this second challenge were similar to those from the training sessions (heroin = 17 injections/session and saline = 4 injections/ session), confirming that the rats were still familiar with the training procedure and would work for a rewarding substance, but would not work for a non-rewarding substance.

However, when the pharmacokinetic evaluation of ganaxolone was conducted as part of Study #RS1973, it showed that a single administration of each of the individual doses used in the self-administration study produced drug plasma levels relative to human therapeutic plasma levels that were 11% from the 0.05 mg/kg dose, 49% from the 0.25 mg/kg dose, and 108% from the 0.5 mg/kg dose. Pharmacokinetic data were not collected for the 0.10 mg/kg dose of ganaxolone. Thus, these data from Study #RS1973 show that the two highest doses are likely too high for use in a self-administration study, since they are likely to lead to satiation after only a few injections, if the drug has rewarding properties.

When the cumulative amount of ganaxolone resulting from the 0.5 mg/kg dose during self-administration was evaluated, it showed that plasma levels were 456% relative to the human therapeutic plasma levels. This strongly suggests that animals may have been

satiated with even small numbers of self-administered injections, since the plasma levels quickly would have accumulated to 0.8X of human therapeutic levels at the 0.05 mg/kg/injection dose (11% x 7 injections) and to 4.5X at the 0.5 mg/kg/injection dose.

Thus, this study does not support the conclusion that ganaxolone does not produce rewarding properties.

Overall Conclusion from Both Self-Administration Studies

The high doses of ganaxolone used in the two studies produced plasma levels after only a few self-administrations that were similar to, and more than 4X greater than those produced in humans at the therapeutic dose. Thus, the low numbers of injections at these doses suggests that animals may have been satiated too quickly. It is unclear why the lowest dose, which produces plasma levels in rats 1/10th that of those produced in humans at the therapeutic dose, did not engender greater self-administration. However, during the dose-finding study, mild ataxia and general subdued behavior were observed as the dose increased, so it is possible that the cumulative dose after several self-administrations of the lowest dose produced behavioral impairment.

2.3 Physical Dependence Studies in Animals

a. Rat Physical Dependence Study with Ganaxolone (Study# RS1975)

A physical dependence study was conducted in rats to determine if chronic administration of ganaxolone produces a withdrawal syndrome upon drug discontinuation, compared to diazepam and vehicle.

Methods

An animal physical dependence study was conducted in which female rats (n = 10/group) received twice-daily oral doses of diazepam, ganaxolone, or vehicle for 28 days.

Over the course of the 28-day dosing period, the twice-daily oral doses of diazepam increased from 10 mg/kg (20 mg/kg/day, Days 1-5) to 15 mg/kg (30 mg/kg/day, Days 6-18), and finally to 20 mg/kg (40 mg/kg/day, Days 19-28).

The oral doses of ganaxolone chosen for this study were 20 and 40 mg/kg, twice daily (40 and 80 mg/kg/day). For ganaxolone, a dose-finding study showed that oral doses of 10-40 mg/kg for 28 days produced dose-dependent ataxia, prostration, and unresponsiveness in rats. Unlike the diazepam dosing, the ganaxolone doses were steady across the drug administration period. The Sponsor notes that a pharmacokinetic analysis of these doses of ganaxolone showed that they produced drug Cmax plasma levels relative to those produced by human therapeutic doses that ranged from 0.5X to 0.8X for the 20 mg/kg dose and 0.6X to 1.1X at the 40 mg/kg dose. Although the 2017 FDA guidance for industry: *Assessment of Abuse Potential of Drugs* suggests that Sponsors use doses that produce plasma levels that are 2-3X relative to those produced by the

human therapeutic dose, the use of higher doses of ganaxolone would have caused impairment in the animals during the dosing period, including sedation and sleep.

At the end of the dosing period, rats were abruptly discontinued from treatment and were monitored for 7 days for withdrawal signs. This is an appropriate observation period, since the half-life of oral ganaxolone in rats is 12 hours and animals should be monitored for 5 half-lives (12 hours X 5 = 60 hours = 2.5 days). Standard behavioral signs indicative of withdrawal, body weight, food and water intake, and body temperature measurements were measured twice daily during the withdrawal phase.

Results

Diazepam produced a standard benzodiazepine withdrawal syndrome during the drug discontinuation period, which validates the study. Observed changes included decreases in daily change in body weight, decreases in food and water intake, increased body temperature. Behaviors observed during the discontinuation period that did not occur during drug administration included decreased locomotor activity, drooping abdomen, teeth chattering. Some of the behaviors observed during drug administration were increased during drug discontinuation including hunched posture, rearing, increased reaction to sound, and piloerection. These changes were pronounced on the first two days of drug discontinuation and continued to decline over the course of the observation period.

Ganaxolone administration at both doses induced a decrease in body weight but no corresponding decrease in food or water intake. Both doses of ganaxolone also produced a slight increase in body temperature. Behavioral changes during ganaxolone administration included ataxia, rearing (40 mg/kg only), escape attempts from the cage, increased body tone, increased locomotor activity, increased reaction to sound, explosive movements (20 mg/kg only), piloerection (40 mg/kg only). Tolerance developed rapidly to changes in ataxia, but other behaviors persisted over the dosing period. Following ganaxolone discontinuation, there were decreases in body weight, food and water intake, and increased body temperature. Observed behaviors in at least 5 of 10 rats during the discontinuation period included increased locomotor activity, increased reaction to sound, hunched posture, and piloerection, to a degree greater than that during drug administration.

These data show that ganaxolone produces a withdrawal syndrome, indicating that it produces physical dependence. The Sponsor asserts that this syndrome is less than that observed from diazepam, but this is likely a function of the much greater dose of diazepam administered relative to the lower dose of ganaxolone used during drug administration. As noted above, the highest rat dose used only produced plasma levels equivalent to those produced by the proposed human dose.

3. Pharmacokinetics of Ganaxolone in Animals and Humans (Study # SC93005715, SC93018316, 1245-00617, 1245-006; # CA042-9402.01,1042-GNX.AME-1001)

Rat Pharmacokinetics

In rats, acute oral administration of ganaxolone at doses ranging from 10 to 40 mg/kg produced a time to peak plasma concentrations (Tmax) of 1.5 to 2.0 hours. However, in one study that evaluated an oral dose of 80 mg/kg, the Tmax did not occur until 4 hours. When multiple oral doses of ganaxolone were administered, there was a dose-dependent increase in Cmax and AUC(0-t), with female animals producing higher ganaxolone levels than males. Following oral administration, ganaxolone is distributed across most organs and tissues, including the brain.

Human Pharmacokinetics

In humans, ganaxolone has a time to plasma concentration (Tmax) of 2.0 to 3.0 hours, showing that it is rapidly absorbed. With repeated administration, steady state levels of ganaxolone are reached after 2 to 3 days. The bioavailability of ganaxolone following oral administration is ~10% due to first pass metabolism. As in rats, ganaxolone in humans is distributed across most organs and tissues, including the brain. Oxy-dehydro-ganaxolone (M60b) is the only major metabolite (>10% of parent) of ganaxolone identified in human plasma. Further characterization of M60b for behavioral effects did not occur. The terminal half-life (t½) for ganaxolone at steady state is ~8-10 hours.

4. Clinical Abuse-Related Studies with Ganaxolone

4.1 A Randomized, Double-Blind, Placebo- and Active-Controlled Crossover Study to Evaluate the Abuse Potential of Oral Ganaxolone in Recreational Central Nervous System Depressant Users (Study #1042-HAP-1001)

This was a randomized, double-blind, double-dummy, placebo-controlled, 5-way crossover study that evaluated the oral abuse potential, safety, tolerability, and pharmacokinetics of ganaxolone compared to placebo and lorazepam in healthy nondependent recreational depressant users. The study consisted of 2 parts: Dose Finding (Part A) and the Main Study (Part B). Dose Finding was comprised of 3 phases: Screening, Dose Escalation, and Follow-up. The Main Study consisted of 4 phases: Screening, Qualification, Treatment, and Follow-up.

Subjects

Subjects

Subjects were healthy male and female adults, between 18 and 55 years of age, inclusive, who are non-dependent, non-treatment seeking recreational depressant users and have a body mass index (BMI) ranging from 18-34 kg/m^2.

Eight subjects were randomized in the Dose Finding Phase and 6 completed this portion of the trial.

In the Main Study, 94 subjects were randomized to the Qualification Phase. From this population, 46 subjects proceeded to the Treatment Phase and 44 subjects completed the study.

Inclusion Criteria for participation are standard but include the following criteria that are relevant for a human abuse potential study:

- The subject is a current CNS depressant user who has used CNS depressants (e.g., benzodiazepines, barbiturates, zolpidem, eszopiclone, zopiclone, propofol, fospropofol, gamma-hydroxybutyrate) for recreational, non-therapeutic reasons at least 10 times in his or her lifetime.

- The subject had at least 1 non-therapeutic experience with CNS depressants in the 12 weeks prior to Screening.

Exclusion Criteria are standard but include the following criteria that are relevant for a human abuse potential study:

- Subject has a history of substance or alcohol dependence (excluding nicotine and caffeine) within the past 2 years, as defined by the Diagnostic and Statistical Manual of Mental Disorders 4th edition, text revision (DSM-IV-TR).

- Subject has ever been in treatment for substance use disorder(s) (except smoking cessation) or is currently seeking treatment for substance use disorder(s).

- Positive urine drug screen (UDS) for substances of abuse at admission to the Dose Escalation, Qualification or Treatment Phases, excluding tetrahydrocannabinol (THC). If a subject presents with a positive UDS at any admission, the subject may be rescheduled at the discretion of the Investigator. If THC is positive, a cannabis intoxication evaluation was performed at check-in. Inclusion was at the discretion of the Investigator.

- Subject has a history or presence of any clinically significant psychiatric or neurological disorder.

- Subject has active or recent suicidal ideation or suicidal behavior (within the past year), as assessed by the Columbia-Suicide Severity Rating Scale (C-SSRS).

- Subject is a heavy smoker (>20 cigarettes per day) and/or is unable to abstain from smoking or use of prohibited nicotine-containing products for at least 1 hour before and 6 hours after study drug administration.

Dose Finding Phase and Main Study:

The Dose Finding Phase occurred prior to initiation of the Main Study. Subjects that participated in the Dose Finding Phase were not be allowed to participate in the Main Study.

The Main Study consisted of a Qualification Phase and a Treatment Phase. Subjects were required to pass the following criteria in the Qualification Phase to be eligible to enter the Treatment Phase:

1. Peak score in response to lorazepam 6 mg greater than that of placebo by at least 15 points on the bipolar Drug Liking visual analog scale (VAS), with peak score of at least 65 points for lorazepam.

2. Acceptable placebo response based on Drug Liking VAS score, between 40 and 60 points, inclusive.

3. Acceptable overall responses to lorazepam and placebo on the subjective measures, as judged by the Investigator or designee.

4. Able to tolerate the 6 mg dose of lorazepam, as judged by an Investigator, including no episodes of vomiting during the first 3 hours post-dose. Subjects with unarousable sedation within the first 4 hours post-dose were not be eligible for the Treatment Phase (based on the Modified Observer's Assessment of Alertness/Sedation [MOAA/S]).

5. General behavior suggests that the subject could successfully complete the study, as judged by the investigational site staff.

Subjects received a standardized breakfast approximately 1 hour prior to the start of study drug administration.

Subjects were asked not to consume more than 6 servings (1 serving is approximately equivalent to 120 mg of caffeine) of coffee, tea, cola, or other caffeinated beverages per day from 1 week prior to admission to the Dose Escalation or Qualification Phase until after discharge from the Dose Escalation or Treatment Phases. Subjects were not permitted to consume caffeine-containing beverages during inpatient stays at the clinical site.

Subjects were required to abstain from smoking or use of nicotine-containing products for at least 1 hour prior to study drug administration. Smoking or use of nicotine-containing products was permitted at short breaks (approximately 10 minutes in duration) after the 6-hour post-dose procedures, at the clinical site's discretion.

Oral Drug Doses

Dose Finding Phase:

The Dose Finding Phase was planned to ensure that the dose of ganaxolone used in the Treatment Phase would not produce sedative effects that prevent completion of the study measures. The study was designed to compare three doses of ganaxolone to placebo, in a sequential fashion. If any administered dose of ganaxolone produced behavioral impairment or adverse events, the next higher dose would not be tested.

Subjects were randomized to receive either ganaxolone (n = 7) or placebo (n = 1) as an oral suspension in three separate periods:

- Ganaxolone 1000 mg vs. Placebo
- Ganaxolone 1500 mg vs. Placebo
- Ganaxolone 2000 mg vs. Placebo

The half-life of ganaxolone ranges from 8-10 hours. There was a washout period of at least 5 days in between treatments (equivalent to 5 half-lives), when concentrations of ganaxolone were expected to be <5% of maximum plasma concentration [Cmax] by 72 hours post-dose).

Three subjective measures (Alert/Drowsy VAS, Any Drug Effect VAS, and Modified Observer's Assessment of Alertness/Sedation (MOAA/S) were taken at baseline, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, and 24 hours after drug administration. Immediately following subjective measures, pharmacokinetic assessments were taken at the same timepoints.

Results

Following administration of 1000, 1500, and 2000 mg doses of ganaxolone, there was no behavioral impairment in subjects that prevented them from completing all of the subjective measures. Notably, there was not a dose response effect as the dose of ganaxolone increased from 1000 to 2000 mg in terms of pharmacokinetics (Cmax and AUC), appearance of AEs, or subjective responses. Thus, the Sponsor concluded that administration of the 2000 mg dose of ganaxolone in the Treatment Phase would be safe.

Main Study

Qualification Phase (single blinded)

The following treatments were administered orally:

- Lorazepam 6 mg (three 2 mg lorazepam tablets, over-encapsulated)
- Placebo capsule

The half-life of lorazepam is 12 hours. At the conclusion of the Qualification Phase, there was a 72-hour (3 day) washout period before initiation of the Treatment Phase. This washout period is acceptable because it accounts for 6 lorazepam half-lives.

Treatment Phase (double-blind)

The following treatments were administered orally:

- Ganaxolone 400 mg suspension + 1 placebo capsule
- Ganaxolone 800 mg suspension + 1 placebo capsule
- Ganaxolone 2000 mg suspension + 1 placebo capsule
- Lorazepam 6 mg (three 2 mg lorazepam tablets, over-encapsulated) + 20 ml placebo suspension
- Placebo capsule + 20 ml placebo suspension

Dose Justification

Ganaxolone

The Sponsor chose to utilize an oral suspension rather than an oral capsule for ganaxolone administration for this study, based on the known pharmacokinetics of each formulation. The suspension produces a Tmax of ~1 hour, compared to a Tmax of 3-5 hours produced by the capsule. Additionally, the suspension provides a less variable pharmacokinetic profile relative to the capsule.

The lowest dose of ganaxolone used in this study was 400 mg, which is slightly less than the cumulative dose of ganaxolone on the first day of therapeutic drug administration (150 mg TID; 450 mg/day). The 450 mg/day dose is proposed for the first week of ganaxolone dose escalation in adults and in children who weigh more than 61 kg. The middle dose of 800 mg is ~2 times greater than both the lowest dose in this HAP study and the lowest cumulative therapeutic daily dose during the first week of ganaxolone administration.

The highest dose of ganaxolone used in this study was 2000 mg, which is 5 times greater than the lowest dose used in this HAP study and 4.4 times greater than cumulative daily dose during the first week of therapeutic drug administration (450 mg/day). The 2000 mg dose is also slightly greater than the 1800 mg/day cumulative therapeutic dose resulting from the 600 mg TID dose administered at the end of the three-week dose escalation phase for adults and for children who weigh more than 61 kg.

The dose of ganaxolone was not increased beyond 2000 mg because that would have likely resulted in levels of sedation that would have impaired participation in the HAP study.

Lorazepam

The Sponsor justifies the proposed dose of lorazepam in the following statement:

A single dose of lorazepam (6 mg) has been selected within the range that has previously demonstrated abuse potential in human studies (Funderburk et al., 1988; Schoedel et al., 2011; Troisi et al., 1993). Because of the lack of dose-response within this range of doses observed with lorazepam (Schoedel et al., 2011) and other benzodiazepines, only a single dose of the positive control will be included in the current study.

The half-life of ganaxolone ranges from 8-10 hours and the half-life of lorazepam is 12 hours. There was a washout period of at least 5 days in between treatments (which exceeds 5 half-lives of ganaxolone), when concentrations of ganaxolone are expected to be <5% of maximum plasma concentration [Cmax] by 72 hours post-dose).

Pharmacodynamic Variables

During the Qualification Phase, subjective endpoints were assessed at baseline, 1, 2, 3, 4, 6, 8, 10, 12, and 23 hours, except for VAS for Overall Drug Liking and Take Drug Again, which were assessed at 10 and 23 hours, and Drug Similarity at 10 hours.

During the Treatment Phase, all subjective endpoints were assessed at baseline, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, and 24 hours after drug administration, except for VAS for Overall Drug Liking and Take Drug Again, which were assessed at 12 and 24 hours, and Drug Similarity at 12 hours.

Primary Measure:

Drug Liking VAS (Emax)

Secondary Measures:

Balance of effects:
- Drug Liking VAS
- Overall Drug Liking VAS
- Take Drug Again VAS

Positive and negative effects:
- High VAS
- Good Effects VAS
- Bad Effects VAS

Sedative effects:
- Alertness/Drowsiness VAS

Other drug effects:
- Any Effects VAS
- Drug Similarity VAS

Safety Variables

- Adverse events
- Clinical laboratory parameters
- Vital signs measurements
- 12-lead ECG
- Temperature
- Continuous SpO_2^m
- Physical examination findings
- Columbia Suicide Severity Rating Scale (C-SSRS) examination
- Concomitant medication usage.

Pharmacokinetic Evaluation

During the Treatment Phase, blood samples were collected immediately after subjective measures are completed, at baseline, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, and 24 hours after drug administration.

Results

Primary Measure: Study Validation and Other Statistical Comparisons

As shown in Table 1, the positive control drug, lorazepam (6 mg), produced the expected increase in positive subjective response on the primary measure of Drug Liking (79 out of 100, respectively), which is outside the acceptable placebo range (40-60 out of 100 on a bipolar scale). Ganaxolone at 400, 800, and 2000 mg produced a slight dose-dependent response (60, 62, and 66 out of 100, respectively) on the bipolar scale that was just outside of the acceptable placebo range. Placebo produced a score of 56 out of 100 that was within the acceptable placebo range. The statistical analysis evaluated three comparisons for the primary measure:

- **Comparison of lorazepam to placebo**: In this test, the null hypothesis presumes that the positive control drug **is similar** to placebo and does **not** have abuse potential unless the null hypothesis is rejected. Thus, a p value that is significant indicates that the null hypothesis has been rejected and that there is a **difference** between lorazepam and placebo.

  As stated by Dr. Wei Liu, Ph.D., DBVI/OB in his statistical evaluation of this HAP study (DARRTS, 2/8/22), "The validation test for comparing the mean Drug Liking VAS Emax between lorazepam 6 mg and placebo was statistically significant; the lower 95% confidence limit (one-sided) of the mean difference was greater than the test margin of 15 points." Thus, the HAP study was validated.

- **Comparison of lorazepam to ganaxolone**: In this test, the null hypothesis presumes that the test drug **is similar** to the positive control drug and does have abuse potential unless the null hypothesis is rejected. Thus, a p value that is

significant indicates that the null hypothesis has been rejected and that there is a **difference** between lorazepam and ganaxolone.

As stated by Dr. Liu in his statistical evaluation, "For the relative abuse potential of ganaxolone, the mean Emax of Drug Liking VAS to the treatment of lorazepam 6 mg was statistically significantly greater than that of each ganaxolone dose (400 mg, 800 mg, and 2000 mg), suggesting that ganaxolone at above doses was less liked than lorazepam 6 mg at a level of 0.05 (one-sided) in healthy, male and female, non-dependent, recreational CNS depressant users."

- **Comparison of ganaxolone to placebo**: In this test, the null hypothesis for a safety evaluation like abuse potential presumes that the test drug **is not similar** to placebo and does have abuse potential unless the null hypothesis is rejected. Thus, a p value that is significant indicates that the null hypothesis has been rejected and that there is **similarity** between placebo and ganaxolone.

  As stated by Dr. Liu in his statistical evaluation, "For the absolute abuse potential of ganaxolone, the null hypothesis of the mean Emax of Drug Liking VAS to ganaxolone response being at least 11 points higher than that of placebo was rejected for the dose 400 mg and dose 800 mg, respectively, suggesting that drug liking of ganaxolone at the two low doses was not significantly different from that of placebo. However, there was not sufficient evidence to reject the null hypothesis for ganaxolone 2000 mg – placebo because of the upper 95% confidence limit greater than 11, suggesting that ganaxolone 2000 mg may have abuse potential."

Table 1: Effects of Oral Placebo, Lorazepam (6 mg), and Ganaxolone (400, 800, and 2000 mg) on Subjective Measures (VAS) – E_{max} Scores (scale 0-100, least squared mean and standard error) (n = 44)

	Placebo	Lorazepam (6 mg)	Ganaxolone 400 mg	Ganaxolone 800 mg	Ganaxolone 2000 mg
Drug Liking (bipolar)	56 ± 2	79 ± 2 !!	60 ± 2 ^^^ **	62 ± 2 ^^^ *	66 ± 2 ^^^
Overall Drug Liking (bipolar)	56 ± 2	78 ± 3 !	61 ± 3 ^^^ *	63 ± 2 ^^^	67 ± 3 ^^^
Take Drug Again (bipolar)	57 ± 3	80 ± 3 !!	61 ± 3 ^^^ *	63 ± 3 ^^^	68 ± 4 ^^
High (unipolar)	9 ± 3	61 ± 4 !!!	18 ± 4 ^^^ *	19 ± 3 ^^^ *	30 ± 4 ^^^
Good Drug Effects (unipolar)	10 ± 3	61 ± 4 !!!	18 ± 4 ^^^ *	21 ± 3 ^^^ *	30 ± 4 ^^^
Bad Drug Effects (unipolar)	3 ± 2	19 ± 4 !!!	2 ± 2 ^^^	3 ± 1 ^^^	5 ± 2 ^^^
Alert/Drowsy (bipolar)	43 ± 2	22 ± 2 !!!	37 ± 2 ^^^	35 ± 2 ^^^	30 ± 2 ^^
Any Drug Effects (unipolar)	12 ± 3	63 ± 4 !!!	20 ± 4 ^^^ **	21 ± 3 ^^^ **	34 ± 4 ^^

Comparison of lorazepam to placebo: ! = $p < 0.05$ compared to lorazepam, !! = $p \leq 0.001$ compared to lorazepam, !!! = $p \leq 0.0001$ compared to lorazepam.

Comparison of lorazepam to ganaxolone: ^ = $p < 0.05$ compared to lorazepam, ^^ = $p \leq 0.001$ compared to lorazepam, ^^^ = $p \leq 0.0001$ compared to lorazepam.

Comparison of ganaxolone to placebo: * = $p < 0.05$ compared to placebo, ** = $p \leq 0.001$ compared to placebo, *** = $p \leq 0.0001$ compared to placebo. ***Note, as described above, a significant p value indicates a <u>similarity</u> between ganaxolone and placebo, as shown for certain subjective measures in response to the 400 and 800 mg doses of ganaxolone, but not in response to the 2000 mg dose.***

Secondary Measures

Dr. Liu also evaluated secondary endpoints and concluded, "The results of the primary analysis were supported by the analysis of key secondary endpoints. Additional supportive results come from the consistent positive dose response in the mean Emax of the primary and key secondary endpoints." The comparative means for each of these secondary measures are described below:

Overall Drug Liking and Take Drug Again

- On the Overall Drug Liking measure, ganaxolone at 400, 800, and 2000 mg produced a slight dose-dependent response (61, 63, and 67, respectively) on the bipolar scale that was just outside of the acceptable placebo range (40-60 out of 100). Placebo produced a score of 56 that was within the acceptable placebo range. In contrast, lorazepam produced a score of 78 out of 100.

- For Take Drug Again, ganaxolone at 400, 800, and 2000 mg produced a slight dose-dependent response (61, 63, and 68 out of 100, respectively) that was just outside of the acceptable placebo range for a bipolar scale (40-60 out of 100) and similar to that produced by placebo (57 out of 100). Lorazepam produced a score (80 out of 100) that was outside of the acceptable placebo range.

High, Good Drug Effects, Bad Drug Effects, and Any Drug Effects

- For High, ganaxolone at 400, 800, and 2000 mg produced a dose-dependent response (18, 19, and 30 out of 100, respectively) on a unipolar scale that was outside of the acceptable placebo range (0-20 out of 100 on a unipolar scale). However, these scores are numerically half or more than half of that produced by lorazepam (61 out of 100). Placebo produced a score of 9 out of 100.

- For Good Drug Effects, ganaxolone at 400, 800, and 2000 mg produced a dose-dependent response (18, 21, and 30 out of 100, respectively) on a unipolar scale that was either inside the acceptable placebo range (0-20 out of 100 on a unipolar scale) or just outside of this range. However, these scores are numerically half or more than half of that produced by lorazepam (61 out of 100). Placebo produced a score of 10 out of 100.

- For Bad Drug Effects, ganaxolone at 400, 800, and 2000 mg produced a slight increase in response (2, 3, and 5 out of 100, respectively) that was within the acceptable placebo range (0-20 for unipolar scales). Placebo and lorazepam also produced scores that were within the acceptable placebo range (3 and 19 out of 100, respectively).

- For Any Drug Effect, ganaxolone at 400 and 800, produced responses (20 and 21 out of 100, respectively) that were within or slightly greater than the acceptable placebo range (0-20 for unipolar scales), similar to the response from placebo (12 out of 100). The 2000 mg dose of ganaxolone produced a score that was outside of the acceptable placebo range (34 out of 100) indicating that there was a moderate drug effect. In contrast, lorazepam produced scores (63 out of 100, respectively) that indicate a strong drug response.

Alert/Drowsy

- For Alert/Drowsy, ganaxolone at 400, 800, and 2000 mg produced a slight dose-dependent response (37, 35, 30 out of 100, respectively) that was just outside of the acceptable placebo range for a bipolar scale (40-60 out of 100). These data demonstrate a dose-dependent increase in drowsiness with increasing dose of ganaxolone. Placebo produced an expected score (43 out of 100). Lorazepam produced a score (22 out of 100) that was outside of the acceptable placebo range, indicating that it produces greater drowsiness than any dose of ganaxolone.

Drug Similarity

For the Drug Similarity VAS measure, subjects were asked at the 12 hour time point whether the session treatment produced effects that were similar to benzodiazepines, barbiturates, sedatives, cannabinoids ("THC"), opioids, heroin, codeine, ethanol, cocaine, amphetamine, pseudoephedrine, MDMA, LSD, psilocybin ("mushrooms"), phencyclidine, ketamine, and placebo.

Subjects were required to have had experience with the specific drug class in order to rate its similarity. Overall, there was a full response by all subjects (n = 44) on only three of the survey drug classes: benzodiazepines, cannabinoids, and placebo. There was substantial participation for three other classes: opioids (n = 36), ethanol (n = 31), and cocaine (n = 27), with less than half of subjects responding on the remaining drug classes: MDMA (n = 19), amphetamine (n = 15), codeine (n = 6), sedatives (n = 2), LSD (n = 1), phencyclidine (n = 1), barbiturates (n = 0), heroin (n = 0), ketamine (n = 0), pseudoephedrine (n = 0). When the participation on a specific drug class query was low, it indicates that a low number of subjects had past experience with that drug class. Thus, the only data that will be discussed below will be for those drug classes where more than 30 of 44 subjects responded to the query (benzodiazepines, cannabinoids, opioids, ethanol, and placebo), based on having a history of using that drug class.

Subjects rated lorazepam as similar to benzodiazepines (score of 68 out of 100), slightly similar to an opioid (score of 32 out of 100), but dissimilar to other drug classes (<25 out of 100). Subjects rated placebo as similar to placebo (55 out of 100), but dissimilar to any of the drug classes (<25 out of 100).

For the lower two doses of ganaxolone (400 and 800 mg), subjects rated these treatments as slightly similar to placebo (36 and 31 out of 100, respectively) and benzodiazepines (28 and 30 out of 100, respectively), but dissimilar to other drug classes (<20 out of 100).

However, the 2000 mg dose of ganaxolone produced a score of 49 out of 100 in similarity to a benzodiazepine, but dissimilar to other drug classes (scores <25 out of 100). This suggests that at a supratherapeutic dose of ganaxolone, there was some similarity to a benzodiazepine, but that it was much less than lorazepam (68 out of 100), an actual benzodiazepine. These data show that ganaxolone does not produce effects that are similar to other known drugs of abuse, including opioids.

Adverse Events

The data in Table 2 show the incidence of abuse-related AEs that were reported for more than 2 subjects during the HAP study. All AEs in Table 2 were mild, with the exception of 3 of 26 subjects reporting somnolence following administration of 6 mg lorazepam who had moderate somnolence.

Table 2: Summary of Abuse-Related Adverse Events Reported by Two or More Subjects During the Treatment Phase (Completer Population; N (%))

	Placebo (n = 45)	**Lorazepam (6 mg) (n = 45)**	**Ganaxolone 400 mg (n = 46)**	**Ganaxolone 800 mg (n = 45)**	**Ganaxolone 2000 mg (n = 45)**
Euphoric mood	4 (9%)	16 (36%)	5 (11%)	6 (13%)	7 (16%)
Somnolence	5 (11%)	26 (58%)	12 (26%)	17 (38%)	13 (29%)
Fatigue	2 (4%)	1 (2%)	3 (7%)	3 (7%)	4 (9%)
Feeling abnormal	0 (0%)	3 (7%)	0 (0%)	1 (2%)	3 (7%)

For the AE of euphoric mood, there was a 9% incidence following placebo administration (n = 4) and an incidence of 36% after lorazepam administration (n = 16). There was a very slight dose-response in euphoric mood as the dose of ganaxolone increased, such that the 400 mg dose produced an incidence of 11% (n = 5), the 800 mg dose produced an incidence of 13% (n = 6), and the 2000 mg dose produced an incidence of 16% (n = 7). Thus, euphoric mood was reported following administration of any dose of ganaxolone by only 1-3 more subjects (n = 5-7) than was reported following administration of placebo (n = 4). In contrast, euphoric mood was reported following lorazepam administration 4 times more often than after placebo administration (n = 16 vs. 4,

respectively) and 2-3 times more than after ganaxolone administration at any dose (n = 16 vs. 5-7).

Notably, responses on the positive subjective measures with each of the three doses of ganaxolone, the scores on VAS for Drug Liking, Good Drug Effects, High, or Take Drug Again were barely outside the acceptable placebo range. Thus, both the euphoria rate and the subjective responses are just slightly greater than those reported for placebo.

For somnolence, there was an 11% incidence following placebo administration (n = 5) and an incidence of 58% after lorazepam administration (n = 26). As the dose of ganaxolone increased, the 400 mg dose produced an incidence of somnolence of 26% (n = 12), the 800 mg dose produced an incidence of 38% (n = 17), and the 2000 mg dose produced an incidence of 29% (n = 13). Thus, there was not a dose dependent somnolence response with ganaxolone, although it was greater than placebo and less than that produced by lorazepam.

Fatigue was observed following placebo administration at an incidence of 4% (n = 2) and an incidence of 2% after lorazepam administration (n = 1). As the dose of ganaxolone increased, the 400 and 800 mg doses each produced an incidence of fatigue of 7% (n = 3), while the 2000 mg dose produced an incidence of 9% (n = 3). Thus, each dose of ganaxolone produced a similar incidence of fatigue that was greater than that reported with placebo or lorazepam.

Feeling abnormal was not reported following placebo administration (0%, n = 0) but was reported at an incidence of 7% after lorazepam administration (n = 3). Feeling abnormal was also not reported following administration of the 400 mg dose of ganaxolone (0%, n = 0), but the 800 mg dose produced an incidence of 2% (n = 1), and the 2000 mg dose produced an incidence of 7% (n = 3). Thus, there was a slight dose dependent increase in feeling abnormal with ganaxolone, which was slightly greater than placebo and equivalent to that produced by lorazepam at the highest dose of ganaxolone.

Safety: Vital Signs

There were no clinically meaningful changes from baseline in vital signs (blood pressure, pulse rate, oxygen saturation, and respiratory rate) following administration of ganaxolone at the three doses administered.

Pharmacokinetics

Table 3 shows the results of the pharmacokinetic analysis of ganaxolone at the three doses administered during the HAP study (400, 800, and 2000 mg).

Table 3: Pharmacokinetic Parameters (Cmax, Tmax, AUC) Following Ganaxolone Administration (400, 800, and 2000 mg) in the Treatment Phase

	Ganaxolone 400 mg (n = 46)	Ganaxolone 800 mg (n = 45)	Ganaxolone 2000 mg (n = 45)
Cmax (ng/ml)	59.1	88.4	133.5
Tmax (hours)	1.0	1.5	1.5
AUC(0-t) (h*ng/ml)	287.7	435.5	653.6
AUC(0-inf) (h*ng/ml)	338.0	534.2	762.9

An examination of peak plasma level (Cmax) values shows that ganaxolone levels did not increase in a dose-proportional manner as the dose doubled from 400 mg (59.1 ng/ml) to 800 mg (88.4 ng/ml), nor when it increased by 5X to 2000 mg (133.5 ng/ml). In fact, the plasma levels only approximately doubled when the dose of ganaxolone increased from 400 mg to 2000 mg. A similar profile was observed for AUC(0-t) and AUC(0-inf) where both parameters did not show dose proportionality and approximately doubled when the dose of ganaxolone increased from 400 mg to 2000 mg.

These data suggest that there may be a limited increase in abuse potential of ganaxolone when the dose of ganaxolone is increased to supratherapeutic levels.

Overall Conclusions

In a human abuse potential study with subjects experienced with sedatives, ganaxolone did not produce meaningful signals of abuse potential on positive subjective measures such as VAS for Drug Liking, Overall Drug Liking, Good Drug Effects, High, or Take Drug Again. On the VAS for Drug Similarity, ganaxolone at therapeutic and 2X therapeutic doses did not produce scores indicating similarity to benzodiazepines or other drug classes. Although the highest (4X dose) of ganaxolone was rated as slightly similar to a benzodiazepine, this may be the result of sedative effects. Although ganaxolone dose-dependently produced euphoria as an AE, the absolute number of subjects who experienced euphoria was only slightly greater at therapeutic and supratherapeutic doses of ganaxolone compared to placebo and was 2-3 times less than that reported after lorazepam administration.

Overall, these data suggest that ganaxolone does not appear to have clinically meaningful abuse potential, even at supratherapeutic doses.

4.2 Abuse-Related Adverse Events in Clinical Studies

Forty-two clinical studies were conducted with ganaxolone:

Phase 1 Studies:

- PK studies – Healthy Adults (21 studies)

Phase 2/3 Studies:

- Epilepsy – Adults (6 studies)
- Epilepsy – Pediatric (7 studies)
- Fragile X– Pediatric (1 study)
- Post-Partum Depression (PPD) – Adults (2 studies)
- Migraine – Adults (3 studies)
- Post-traumatic stress disorder (PTSD) – Adults (1 study)
- HAP study – Recreational Drug Users - Adults (1 study)

a. Phase 1 Clinical Studies (Study # 9505, 9403, 0401, 9407, 0403, 0118, 0400, 0405, 9405, 0106, GNX AME, 0404, 0402, 0115, 9505, 0111, 9301, 1001, 9401, 9302, 9402, 9404, HAP1001)

During drug development, there were 405 healthy individuals who received ganaxolone at any dose in 23 Phase 1 PK studies. Of these 23 studies, there were only 8 studies in which euphoria-related AEs were reported (n = 165 who received ganaxolone, n =29 who received placebo), with the other 15 studies reporting no euphoria-related AEs (n = 197 who received ganaxolone, n =14 who received placebo). Of the 8 studies where euphoria-related AEs were reported following ganaxolone administration, 3 of these were repeat-dose studies and 5 were acute-dose studies.

In the 3 repeat-dose studies, euphoria-related AEs were reported by 24 of 64 subjects who received ganaxolone and by 0 of 17 subjects who received placebo. The euphoria-related AEs in these repeat-dose studies are described below in descending order of ganaxolone daily dose:

- Euphoria in 6 of 10 subjects (3 moderate, 3 severe) at 750 mg TID (2250 mg/day)
- Euphoria in 3 of 20 subjects (2 mild, 1 moderate) at 1000 mg BID (2000 mg/day)
- Euphoria in 2 of 20 subjects (2 moderate) at 800 mg BID (1600 mg/day)
- Euphoria in 1 of 10 subjects (1 mild) at 500 mg TID (1500 mg/day)
- Euphoria in 5 of 21 subjects (2 mild, 3 moderate) at 600 mg BID (1200 mg/day)
- Euphoria in 4 of 21 subjects (3 mild, 1 moderate) at 400 mg BID (800 mg/day)
- Thinking abnormal in 1 of 10 subjects (1 mild) at 250 mg TID (750 mg/day)
- Feeling drunk in 3 of 4 subjects (3 mild) at 500 mg/day
- Euphoria in 3 of 22 subjects (2 mild, 1 moderate) at 200 mg TID (400 mg/day)

In the 5 acute-dose studies, euphoria-related AEs were reported by 8 of 101 subjects who received ganaxolone and by 1 of 12 subjects who received placebo. The euphoria-related AEs in these acute-dose studies are described below in descending order of ganaxolone dose:

- Euphoria in 1 of 4 subjects (1 mild) at 1500 mg

- Euphoria in 2 of 10 subjects (2 mild) at 1200 mg
- Thinking abnormal in 2 of 8 subjects (2 mild) at 1200 mg
- Feeling drunk in 1 of 17 subjects (1 mild) at 900 mg
- Feeling drunk in 1 of 6 subjects (1 mild) at 750 mg
- Euphoria in 2 of 7 subjects (2 mild) at 400 mg
- Depersonalization in 1 of 4 subjects (1 mild) at 400 mg
- Euphoria in 1 of 16 subjects (1 mild) at 300 mg

Conclusions

Thus, in the 23 Phase 1 PK studies with ganaxolone, euphoria-related AEs were reported in 32 of 362 subjects who received ganaxolone (8.8%) compared to 1 of 43 subjects who received placebo (2.3%). The majority of the euphoria-related AEs following ganaxolone administration were mild in severity (n = 25 of 32 subjects, 78%), as was the single euphoria-related AE in the subject who received placebo. These data demonstrate that ganaxolone produces a variety of euphoria-related events, suggesting that it has abuse potential.

b. Phase 2/3 Clinical Studies (Study # PPD2002, PPD2003, 0117, 0112, 0116, 0700, 0104, 0603, 0600, 0601, 0603, 0602, 0604)

The rate of euphoria-related AEs cannot be determined from Phase 2/3 clinical studies conducted with ganaxolone in epilepsy patients because all subjects in these studies were concurrently taking other antiepileptic drugs. Since many antiepileptic drugs are known to produce euphoria and sedation, and are often controlled in schedule IV of the CSA, their presence in patients produces a confoundation for interpreting any euphoria-related AEs that may be reported during these clinical studies.

Similarly, the rate of euphoria-related AEs cannot be determined from Phase 2/3 studies conducted with ganaxolone in patients with post-traumatic stress disorder (PTSD), because subjects in these studies were allowed to take benzodiazepines at bedtime to treat insomnia. Since benzodiazepines are controlled in schedule IV because they produce euphoria and sedation, their presence in patients confounds our ability to interpret any euphoria-related AEs that may be reported during these clinical studies.

In 1 of 3 migraine studies, euphoria was reported in 3 of 163 subjects who received a single 750 mg oral dose of ganaxolone (1.8%, 2 moderate, 1 severe) and in 1 of 164 subjects who received placebo (0.6%, 1 mild). There were no reports of euphoria-related AEs in the other 2 migraine studies, in which ganaxolone was administered at a single dose of 20 to 1000 mg (n = 233).

Conclusions

In healthy individuals, ganaxolone produced an 8.8% incidence of euphoria-like AEs, including euphoria, thinking abnormal, feeling drunk, and depersonalization, across acute doses of 300 to 1500 mg/day and repeat doses of 400 to 2250 mg/day, compared to a

2.3% incidence of euphoria-related AEs following placebo administration. In a migraine patient population, an acute dose of 750 mg ganaxolone produced a 1.8% incidence of euphoria, compared to a 0.6% incidence after placebo administration. These data show that ganaxolone can produce AEs that are supportive of abuse potential.

4.3 Assessment of Human Physical Dependence (Study #1042-060344)

In a human evaluation of physical dependence, subjects are typically abruptly discontinued from the test drug and then observed for at least 5 half lives to determine if withdrawal-like signs or symptoms develop. Given that ganaxolone is proposed for the treatment of a seizure disorder, it is not ethical or medically sound to conduct an assessment of abrupt ganaxolone discontinuation in an epileptic patient population that participated in Phase 2/3 studies. Healthy subjects who participated in Phase 1 studies were not evaluated for physical dependence.

The Sponsor provided data from an evaluation of physical dependence that was conducted in adults with drug-resistant partial-onset seizures who had received chronic administration of ganaxolone in a Phase 2 study, followed by a 2-week drug tapering period. However, ganaxolone was administered as adjunctive treatment to subjects who were concurrently taking other antiepileptic drugs (AEDs), including levetiracetam, carbamazepine, and lamotrigine. Thus, these data are not informative of withdrawal signs and symptoms associated with ganaxolone, since the other AEDs confound attribution of any response during the drug discontinuation period to ganaxolone.

5. Regulatory Issues and Assessment

CSS has concluded from the in vitro, animal, and human study data submitted in the NDA for ganaxolone that the drug has abuse potential that is less than that of benzodiazepines (Schedule IV) and similar to that of drugs in Schedule V.

Thus, it will be necessary for CSS to prepare an Eight Factor Analysis that recommends the placement of ganaxolone in Schedule V and for the drug label for ganaxolone to include Section 9 (Drug Abuse and Dependence).

If approved, the approval of ganaxolone will be under section 505(x) of the Food, Drug, and Cosmetic Act and the approval will only be in effect as of the date the Drug Enforcement Administration issues an Interim Final Rule to place ganaxolone in Schedule V of the CSA. At that time, prescribing information and carton and container labeling may be updated by the Sponsor via a supplementary NDA submission to reflect the control status of ganaxolone.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KATHERINE R BONSON
02/15/2022 12:52:26 PM

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DOMINIC CHIAPPERINO
02/15/2022 04:21:48 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	February 11, 2022
Requesting Office or Division:	Division of Neurology 2 (DN 2)
Application Type and Number:	NDA 215904
Product Name and Strength:	Ztalmy (ganaxolone) suspension, 50 mg/mL
Applicant/Sponsor Name:	Marinus Pharmaceuticals, Inc.
OSE RCM #:	2021-1470-1
DMEPA 2 Safety Evaluator:	Justine Kalonia, PharmD
DMEPA 2 Acting Team Leader:	Stephanie DeGraw, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on February 1, 2022 for Ztalmy. The Division of Neurology 2 (DN 2) requested that we review the revised container label and carton labeling for Ztalmy (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised container label and carton labeling are unacceptable from a medication error perspective. The sponsor maintained the statement [redacted] (b) (4) this may still be misunderstood [redacted] (b) (4), so in Section 3 (below) we provide recommendations to the Sponsor to either remove it or revise it to state the total contents of the carton. Furthermore, the Sponsor did not add the linear barcode to the container label as we requested and as part of their rationale cited 21 CFR 201.25(b)(1)(ii). However, to obtain the exemption for the linear barcode requirement, they will need to submit a written request to the Office of Compliance (OC). We provide these recommendations for the Sponsor in Section 3 below.

[a] Kalonia, J. Label and Labeling Review for Ztalmy (NDA 215904). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2021 NOV 23. RCM No.: 2021-1470.

3 RECOMMENDATIONS FOR MARINUS PHARMACEUTICALS, INC.

We recommend the following be implemented prior to approval of this NDA:

A. On the 5-count carton labeling, we acknowledge that you have added the following statement "Package contains five bottles each containing 110 mL of ganaxolone." However, we note that the statement (b) (4) We maintain that this (b) (4) may be misinterpreted as (b) (4) Consider replacing the statement (b) (4) For example, revise to read (b) (4) Alternatively, remove the (b) (4) statement from your carton labeling.

B. We note that you did not add the linear barcode to the container label and provided the following rationale:

> "Ztalmy is a prescription drug intended for outpatient use by patients. Prescription fulfillment is performed by Specialty Pharmacy direct to Patients as such Ztalmy is not intended to be sold or used in hospitals; therefore, in accordance with 21 CFR 201. 25(b)(1)(ii) the bar code requirement does not apply."

If you have not already done so, please provide a written exemption request documenting how the container label meets the specific rationales outlined in 21 CFR 201.25(b)(1)(ii) for an exemption from the linear barcode requirement. Requests for an exemption should be sent to the Office of Compliance, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Silver Spring, MD 20993-0002.

2 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

JUSTINE H KALONIA
02/11/2022 10:23:07 AM

STEPHANIE L DEGRAW
02/13/2022 01:51:56 PM

Division of Hepatology and Nutrition Consultation

Drug-induced Liver Injury Team

NDA	215904
Consultation Issue	Drug-induced liver injury (DILI)
Drug Product	Ganaxolone
Indication	Seizures in CDKL5 deficiency disorder
Applicant	Marinus Pharmaceuticals, Inc.
Requesting Division	Division of Neurology-2 (DN2)
Primary Reviewer	Ling Lan, MD, PhD, Clinical Analysist, DILI Team, DHN
Secondary Reviewer	Paul H. Hayashi, MD, MPH DILI Team Lead, OND/DHN
Reviewer **Office of Pharmacoepidemiology**	Mark Avigan, MD, CM Associate Director, OPE/OSE
Signatory Authority	Joseph Toerner, MD, MPH Director, OND/DHN
Assessment Date	Jan 31, 2022

Context: Ganaxolone (GNX) is an oral neurosteroid felt to be a positive modulator of gamma-aminobutyric acid A (GABA-A) receptors thus lowering neuronal excitation. Such modulation mimics GABA's inhibitory tone in the central nervous system. This NDA is for treatment of cyclin dependent kinase like 5 (CDKL5) deficiency (CDD), a rare pediatric disease (1 in 42,000 births) leading to refractory seizures. While there was no drug-induced liver injury (DILI) issue in the randomized controlled trial of 101 CDD subjects, there was a fatality in a Phase 2a study for other pediatric seizure disorders. DILI causality for this case is unclear. The Division of Neurology 2 (DN2) requested the DILI Team's input regarding "further work-up and assessment of possible causality."

Executive Summary: We do not think this fatality should hold up approval for GNX treatment of the rare pediatric seizure disorder, CDD. The liver injury was only possibly related to GNX with cholestasis of sepsis competing as a reasonable alternate cause. If DILI occurred, the phenotype would be bland cholestasis, a phenotype that typically has a good prognosis upon holding the offending agent. However, this subject had recurrent infections making distinction between cholestasis of sepsis and bland cholestasis from DILI impossible. Moreover, we do not agree that the primary cause of death was liver failure based on near normal INR and albumin when the subject transitioned to comfort care. Indeed, cholestasis of sepsis is a more likely explanation of (b) (6) persistent jaundice, and recurrent severe infections are also a more likely proximal cause of death. In other words, this subject probably died with cholestasis rather than from it.

Consultation Sections:

Section 1.0 – Rationale (target disease and mechanism of action)

Section 2.0 - ADME pertinent to DILI
Section 3.0 - Non-clinical data pertinent to DILI.
Section 4.0 - Clinical data
Section 5.0 – Assessment & Recommendations

Abbreviations:
AP: alkaline phosphatase
ALT: alanine aminotransferase
AST: aspartate aminotransferase
CDD: CDKL5 deficiency disorder
CDKL5: cyclin dependent kinase like 5
CNS: central nervous system
CPK or CK: creatinine phosphokinase
DB: direct bilirubin
DILI: drug-induced liver injury
IDMC: Independent Data Monitoring Committee
GABA: gamma-aminobutyric acid
GGT: gamma-glutamyl transferase
GNX: ganaxolone
HAC: Hepatology Assessment Committee
IP: investigational product
LDH: lactate dehydrogenase
MOA: mechanism of action
MOD: mechanism of DILI
NOS: not otherwise specified
RS: Reye's Syndrome
TB: total bilirubin

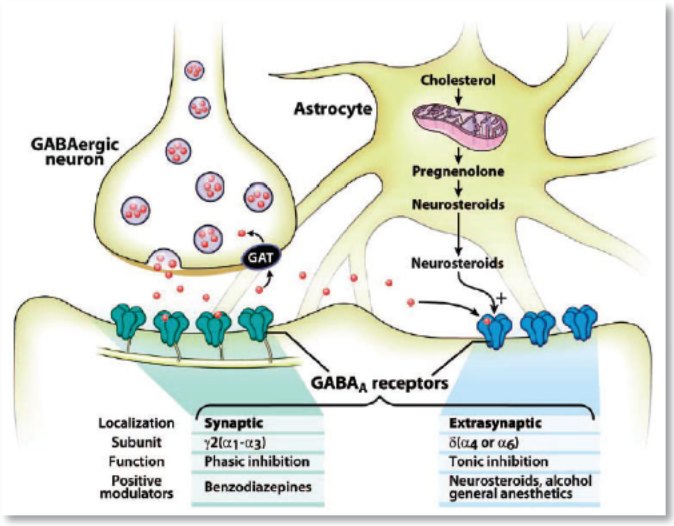
1.0 Rationale (Targeted Disease and Mechanism of Action)

1.1 Disease: Cyclin dependent kinase like 5 (CDKL5) deficiency (CDD) is a rare pediatric disease (1 in 42,000 births) causing refractory seizures and developmental disorders including impaired intellect and speech. There can also be hypotonia and cortical visual impairment. The CDKL5 gene is located on the X chromosome and encodes a serine-threonine kinase important to neuronal proliferation, migration and axonal growth. Onset of symptoms is typically in the first year of life. Genetic testing confirms the diagnosis with pathogenic mutations in the CDKL5 gene. The disease is more common in females but more severe in males.

1.2 Mechanism of Action: Ganaxolone (GNX) is an orally delivered neurosteroid, felt to be a positive modulator of gamma-aminobutyric acid A (GABA-A) receptors thus lowering neuronal excitation. GNX is similar to allopregnanolone, a neurosteroid approved for post-partum depression. GNX differs only by a 3-beta methyl group substitution [redacted (b) (4)] GNX retains its ability to allosterically and positively modulate GABA-A receptors. Such

modulation mimics GABA's inhibitory tone in the central nervous system. (Figure 1)[1]

Figure 1:

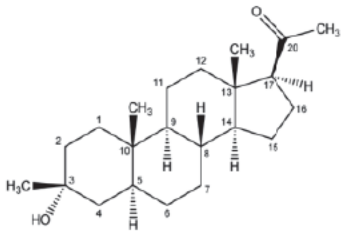


2.0 ADME Pertinent to DILI

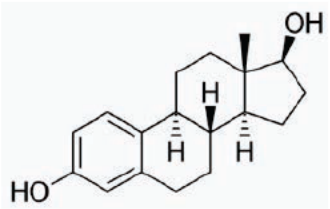
2.1 Structure: GNX is a neurosteroid structurally similar to estrogen. (Figure 2)

Figure 2:

Ganaxolone



Estrogen



2.2 Absorption: Oral absorption is rapid in mice, rats, and dogs. Tmax ranged from 0.5 to 3.5 hours.

2.3 Distribution: GNX is highly protein bound (>99%) and widely distributed in tissues across mouse, rat, and human studies. Volume of distribution = 9 L.

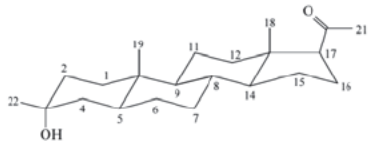
2.4 Metabolism: GNX is extensively metabolized according to mouse, rat, dog, and human microsome studies. Oxidation and glucuronidation are the major modifications. It is metabolized predominantly by CYP3A4 with the primary metabolite in plasma being 16 alpha-hydroxyganaxolone (M1), but a "large number of metabolites" (>19) including 3-beta-hydroxyganaxolone (Figure 3) are found in excreta, bile and urine of rats, dogs and humans. In vitro studies

[1] Benarroch EE. Neurology 2007

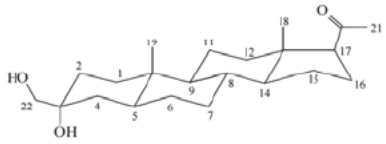
suggest GNX induces and inhibits CYP3A4, though clinical studies in healthy volunteers did not show significant PK effect on midazolam.

Figure 3: **Structures of ganaxolone, 3ß-Methyl-OH-ganaxolone and 16-OH-ganaxolone**

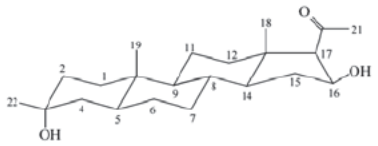
(a) ganaxolone



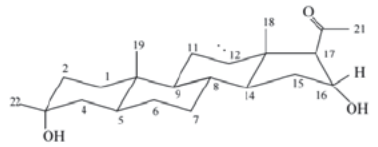
(b) 3ß-Methyl-OH-ganaxolone



(c) 16α -OH-ganaxolone



(d) 16ß-OH -ganaxolone



2.5 Excretion: Excretion by carbon labeling studies is predominantly via feces (64-94%) with the remainder found in urine. Accordingly, approximately 70% of radioactivity was found in bile and 10% in urine across all species.

3.0 Non-clinical data

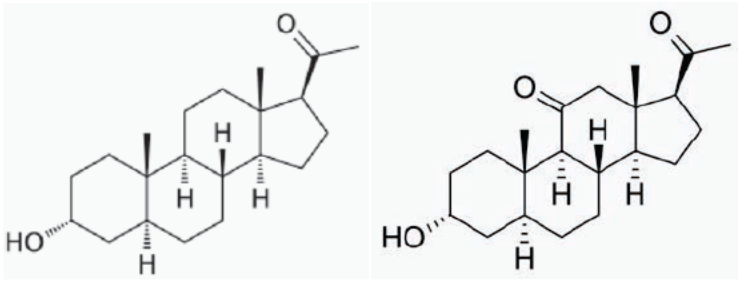
3.1 In vitro data: As mentioned in Section 2.0, microsomal studies indicate extensive metabolism by hepatocytes via oxidation and glucuronidation. It is not considered a substrate nor inhibitor of the major drug uptake or efflux transporters.

3.2 Animal data: Repeat dosing studies were done in mice, rats, and dogs across a total of 17 studies. No significant liver injury was seen. There was increased liver weights and hepatocellular hypertrophy in mice and rats, but not dogs.

4.0 Clinical data:

4.1 In class or near class data: There are two neurosteroids approved for non-seizure indications. (Figure 4) Brexanolone (allopregnanolone, Zulresso®; post-partum depression, approved Mar 2019) is listed as "E" on LiverTox® or an unlikely cause of liver injury. Alphaxalone (Alfaxan®) is approved for use in animals as a general anesthetic.

Figure 4:



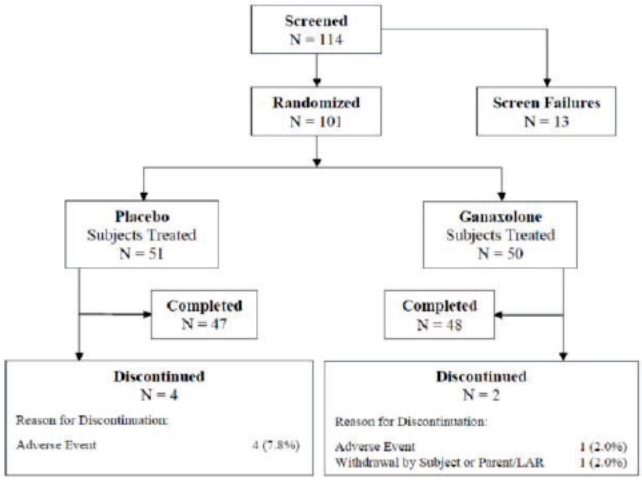
Allopregnanolone Alphaxalone

As noted in Section 2.1, GNX is structurally similar to and estrogen which have been associated with cholestasis and occasionally jaundice.[2],[3]

4.2 Study protocol(s):

a) The Marigold study (1042-CDD-3001) is serving as the registration trial: A Double-blind, Randomized, Placebo-Controlled Trial of Adjunctive Ganaxolone Treatment in Children and Young Adults with Cyclin-Dependent Kinase-Like 5 (CDKL5) Deficiency Disorder (CDD) Followed by Long-Term Open Label Treatment. (Figure 5)

Figure 5: **Subject Disposition (All Subjects)**



b) Study 1042-0900: A Multicenter, 26 week Open-Label Proof-of-Concept Trial of Ganaxolone in Children with PCDH19 Female pediatric Epilepsy and Other Rare Genetic Epilepsies Followed by 52 week Open-Label Treatment. The one fatality attributed to liver injury came from this trial. Just 30 subjects enrolled in this study. The DILI Team does not have access to this study's datasets. The Clinical Study Report from Mar 26, 2019 suggests no significant ALT, AST or bilirubin elevations through week 26. AP levels as high as 539 U/L are recorded. Median at baseline was 267. No GGT data are available. There is no control arm.

[2] LiverTox Estrogens and Oral Contraceptives - LiverTox - NCBI Bookshelf (nih.gov) (accessed Dec 7, 2021)

[3] LiverTox Progestins - LiverTox - NCBI Bookshelf (nih.gov) (accessed Dec 7, 2021)

4.3 Liver biochemistry scatterplots, summary tables and graphics for Study 1042-CDD-3001 (Marigold Study, registration trial for CDD indication).

a) Hepatocellular scatterplot (eDISH):

Figure 6a: Peak TB vs. peak ALT (both in x ULN)

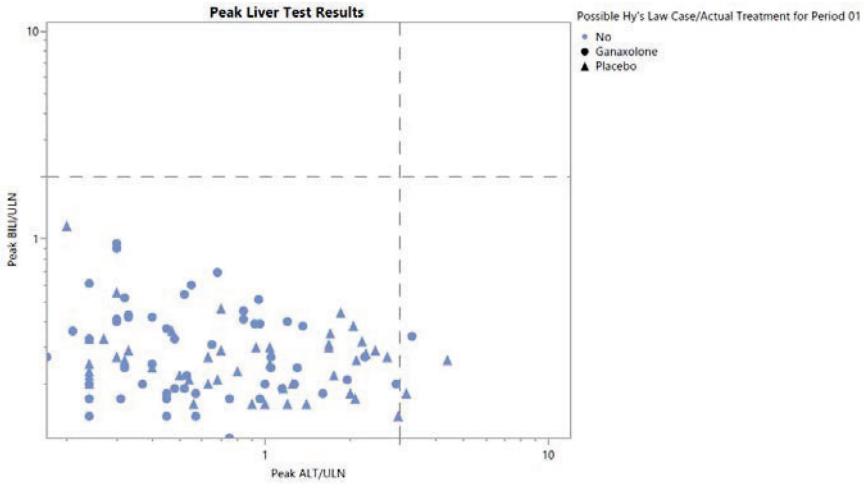
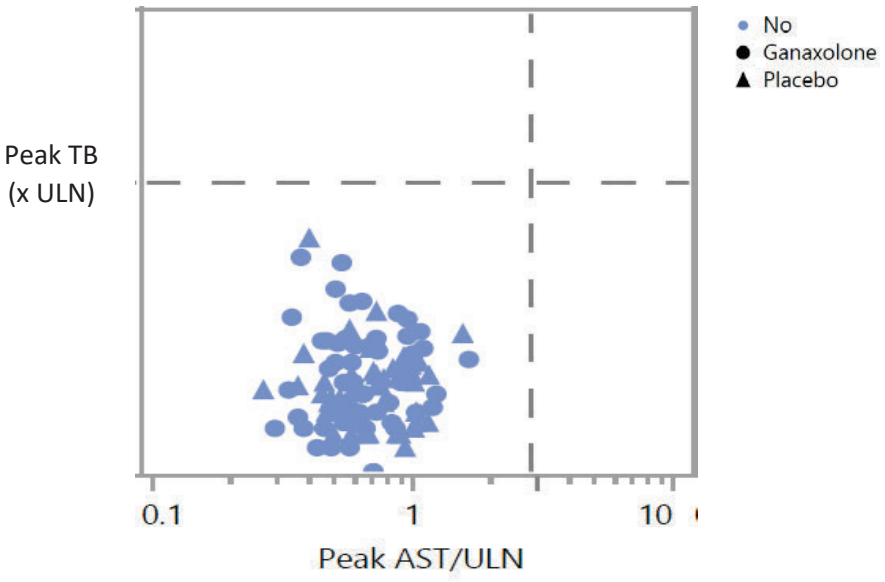
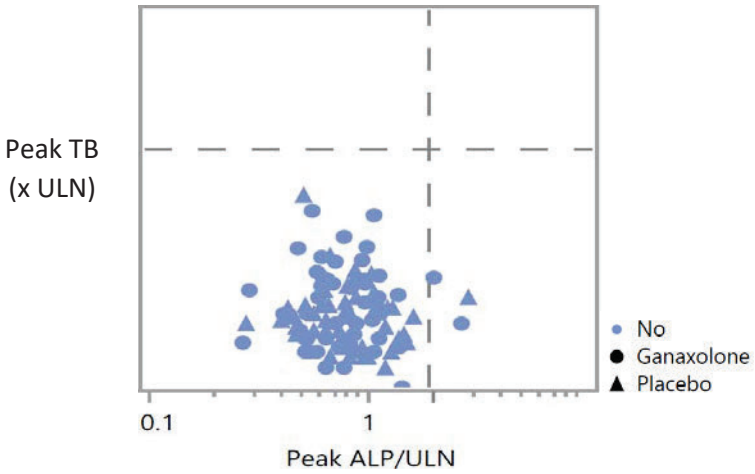


Figure 6b: Peak TB vs. peak AST (both in x ULN)



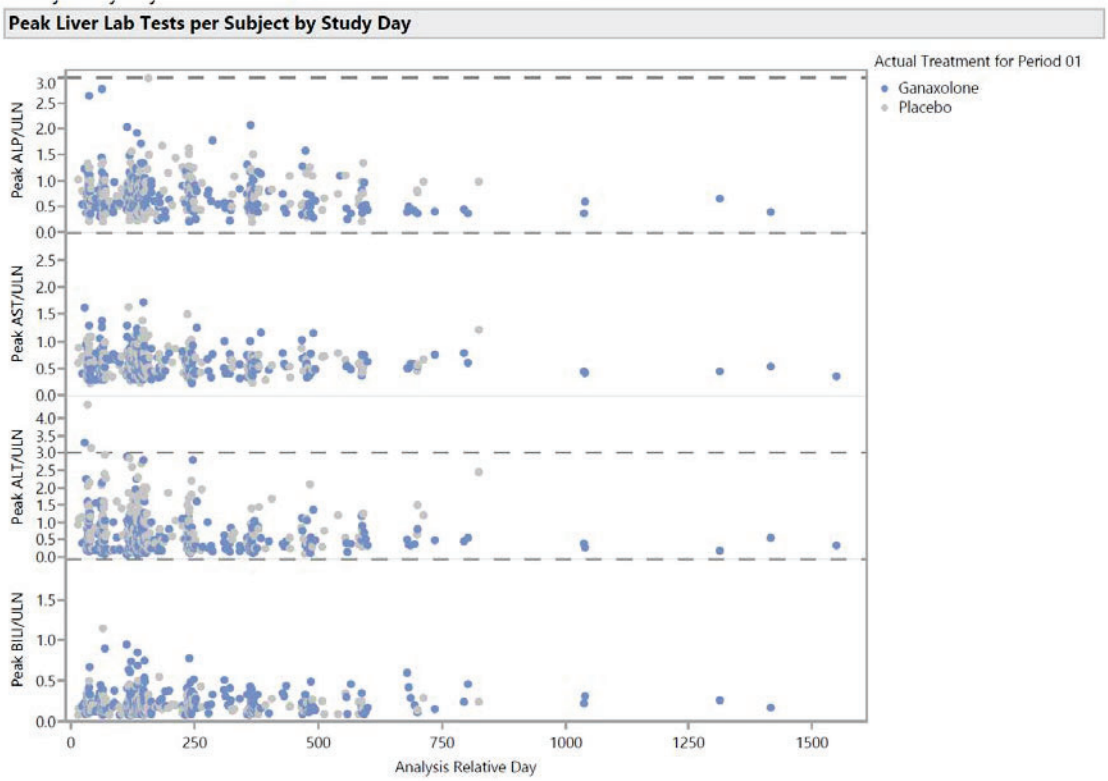
b) Cholestatic scatterplot:

Figure 7: Cholestatic scatterplot (peak TB vs. peak AP)



c) Liver biochemistries by study day: There was a modest imbalance in AP elevations with more occurring in the GNX treatment arm (Figure 8). There was a similar imbalance seen in bilirubin but the levels remained <ULN. Otherwise, liver enzyme changes over time were not obviously different between arms.

Figure 8: Liver tests over time.



4.4 GNX has been studied in other seizure disorders. The DILI Team made several attempts at loading these older datasets for analysis of liver biochemistries but were unsuccessful due to formatting incompatibilities with data analysis tools, missing critical variables and missing variable keys.

4.5 Case level analysis

a) There were no subjects with significant liver injury due to GNX in trial 1042 CDD 3001 (Marigold registration trial). No subject had an ALT or AST >5 x ULN and there were no cases of jaundice. Two subjects had peak AP between 2x and 3x ULN but no jaundice.

b) Summary of fatal case: Subject [redacted] from Study 1042-0900 is the crux of this consult. The sponsor suggests IgG4 cholangiopathy as causal. The cause of death is felt to be "liver failure" by the medical record review.

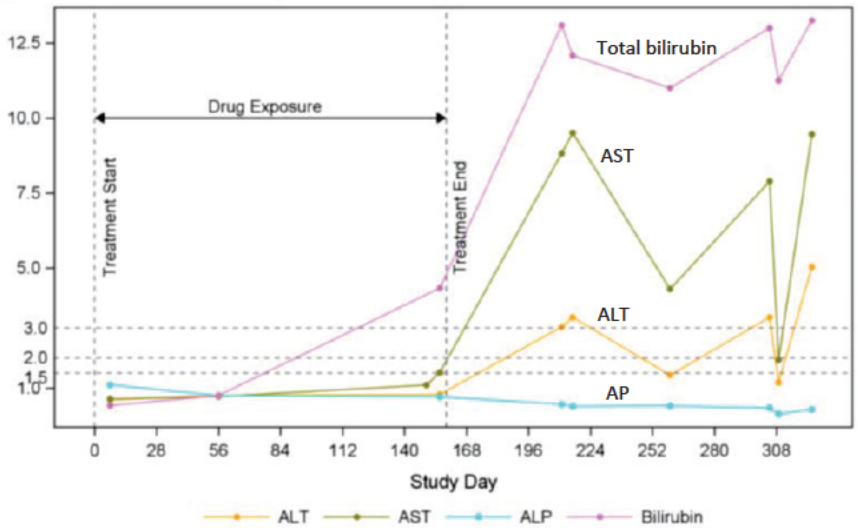
Summary: This subject is a [redacted] with PCDH19 related seizures (not CDD), who developed jaundice while on GNX and died without resolution of the jaundice.

At birth, [redacted] had necrotizing enterocolitis resulting in short gut syndrome. (gastrostomy, intestinal resection). At baseline, [redacted] had hypotonia of all extremities, urinary incontinence, developmental delay, and static encephalopathy due to anoxic brain injury with resultant seizure disorder. [redacted] was wheelchair-bound and non-verbal. Concomitant medications included a scopolamine patch, omeprazole, ondansetron, loperamide, ketotifen eye drops, artificial tears, topical mupirocin, phenobarbital (start [redacted]), topiramate ([redacted]), perm panel (anti-epileptic; DILI Likelihood Category E in LiverTox®) ([redacted]), clonazepam, and diazepam. Nutritional supplements, folic acid, budesonide, vitamins (NOS), tobramycin, cetirizine, albuterol, and vitamin D.

[redacted] started GNX (18/mg/kg/d) on [redacted] (Day 0). The dose had increased to 54 mg/kg/d by time of DILI onset but most recent dose increase was not specified. On [redacted] (Day 145), [redacted] had "jaundice" and GNX was stopped (no TB or enzymes results available for this day). On [redacted] (Day 148), [redacted] primary care provider prescribed unnamed antibiotics x 10 days for a buttocks infection. [redacted] worsened with mental status decline and was admitted to the ICU, [redacted] (Day 155). ALT was 22, AST 91, AP 247, TB 5.2 mg/dL (DB 4.3), NH3 94, INR 6.6. Intravenous ceftriaxone & vitamin K given. IgG was 1914 mg/dL (ULN 1229). MRCP and MRI were negative for acute changes. Liver biopsy on [redacted] (Day 162) showed "hepatocellular glycogen, microvesicular steatosis, mild portal fibrosis, mild pericholangitis, and mild cholestasis." Electron microscopy showed "glycogen accumulation and hepatocytes with enlarged vacuoles; the differential diagnosis included possible reactive process versus a mitochondrial disorder of fatty acid oxidation defect and that the findings were not consistent with obstruction." Anti-LKM, Hep A, B, CMV & EBV tests were negative. "Emory Cholestasis genetics panel" did not show any known hepatic transporter mutations.

(b) (6) was discharged but needed re-hospitalization for worsening jaundice on (b) (6) (Day 206). (b) (6) then went through a series of hospitalizations for infections and seizures. Jaundice persisted (last value 15.9 mg/dL; 12.8 direct), ALT and AST varied widely (Figure 9). IgG4 cholangiopathy was initially diagnosed but was based on incorrect IgG4 interpretation. Liver histology, history and MRCP did not support an IgG4 related diagnosis. Nevertheless, steroids were tried, but (b) (6) was intolerant due to "autonomic instability". (b) (6) would go on to die on comfort care status. Last INR was 1.49, albumin 3.4. Cause of death was "liver failure". (b) (6) died on (b) (6) (Day 354), 209 days after stopping GNX. No autopsy performed.

Figure 9: Ratio observed values to upper limits of the reference ranges for ALT, AST, alkaline phosphatase and total bilirubin.



Assessment: The highest attribution we could give for DILI was only possible, and we disagree with the primary cause of death being “liver failure”. We discuss this case in detail because it meets biochemical criteria for Hy’s Law, and recommendations for approval hinge on this case in this small, rare disease dataset.

Case complexity and lack of dechallenge hurts the case for GNX liver injury quite a bit. While ALT and AST were elevated, both fluctuated during (b) (6) liver injury, particularly the AST which fell to <2x ULN from >7.5x ULN, only to rebound to >8x ULN in a matter of days. Ongoing seizure activity is a better explanation for the wide swings. Indeed, AST was always 2-3x higher than ALT, suggesting possible muscle source. No CK data are available. Despite persistent jaundice with direct hyperbilirubinemia, (b) (6) ALT fluctuated between almost normal to just 3x ULN. Recurring severe infection likely contributed to the persistent jaundice (cholestasis of sepsis) and lack of resolution.

There are two possibilities to consider for GNX liver injury:

(1) Bland cholestasis from GNX is possible. GNX has a similar structure to estrogen (Section 2.1, Figure 2), which is well known to cause bland cholestasis. This DILI is typified by modest enzyme elevation and mild to no inflammation in the liver. The injury can cause significant jaundice, but it is usually benign, resolving with stopping the offending agent. There was only mild inflammation on biopsy, and ALT and AST were only 22 and 91 at presentation when (b) (6) bilirubin was already >5 mg/dL. AP levels are not that helpful in children because bone production makes setting population ULN values unreliable. GGT can be used, but only sporadic values are available, and they varied widely during the injury without correlation with TB. (GGT = 8x ULN when TB was 10.6; GGT = 2.5x ULN when TB was 20.) Cholestasis of sepsis would be indiscernible from bland cholestasis of DILI, and the former became an increasingly likely competing cause as (b) (6) infections piled on over the ensuing months.

(2). A DILI related Reye's Syndrome (RS) similar to valproate or intravenous tetracycline is considered because the electron microscopy showed "possible reactive process versus a mitochondrial disorder of fatty acid oxidation defect." RS is due to a mitochondrial defect in fatty acid oxidation. However, the clinical picture here does not fit RS. The mild ALT elevation and coagulopathy are consistent with RS, but deep jaundice is not. Typically, ammonia levels are much higher and there was no mention of metabolic acidosis which is classic for RS. RS also has a more acute course that does not span months. Lastly, the INR corrected with vitamin K. Thus, we think RS due to DILI is highly unlikely.

Finally, we do not agree that (b) (6) primary cause of death was liver failure. While (b) (6) bilirubin remained high, (b) (6) INR had fallen to 1.49 from 6.0. Moreover, (b) (6) ALT barely reached 5x ULN and only at transition to comfort care. For 20 weeks it remained normal to 3x ULN, and (b) (6) biopsy did not show necrosis. Hepatic encephalopathy was a poor indicator of liver failure due to (b) (6) "static encephalopathy" and non-verbal state at baseline. Thus, it is more likely (b) (6) had a multi-factorial death with infections and cholestasis of sepsis. Indeed, (b) (6) last hospitalization was for treatment of sepsis and meningitis which resolved, but (b) (6) transitioned to comfort care by the end of the hospitalization. (b) (6) last bilirubin was 15.9 mg/dL, but INR was down to 1.49, ALT 141 (highest level recorded), and albumin 3.4 mg/dL (lower limit of normal is 3.5 mg/dL).

5.0 Assessment & Recommendations

5.1 **Assessment:** Ganaxolone (GNX) is an orally delivered neurosteroid, felt to be a positive modulator of gamma-aminobutyric acid A (GABA-A) receptors thus lowering neuronal excitation. Such modulation mimics GABA's inhibitory tone in the central nervous system. This NDA is for GNX treatment of cyclin

dependent kinase like 5 (CDKL5) deficiency (CDD), a rare pediatric disease (1 in 42,000 births) characterized by refractory seizures, developmental disorders including impaired intellect and speech, and other neurologic impairments.

GNX is extensively metabolized in the liver and eliminated predominantly in bile and feces. Studies in mice, rats and dogs did not detect a liver injury signal. GNX is not approved for any other indications. Brexanolone (allopregnanolone) which is similar to GNX in chemical structure, is approved for post-partum depression and has no reported significant liver injury in trials or in post-marketing literature. Summary data of liver enzyme abnormalities for this BLA registration trial do not suggest significant DILI risk, but the number of subjects exposed is quite low due to the rarity of CDD.

Therefore, much of our assessment rests on this fatal case. We feel the liver injury and fatality are only possibly related to GNX. If GNX caused DILI, we suspect a benign cholestatic injury, but cholestasis of sepsis competes well and confounds the diagnosis. The maximum ALT was only 5x ULN, and the liver biopsy showed only mild inflammation without necrosis. This pattern of injury is consistent with bland or benign cholestasis due to drug or sepsis. Interestingly, GNX is structurally similar to estrogen which is associated with bland cholestasis and jaundice. We do not think this subject had a Reye's Syndrome liver injury.

We disagree that the cause of death was primarily liver failure. While (b) (6) bilirubin was high, (b) (6) INR had fallen to <1.5, and albumin was nearly normal before transitioning to comfort care. We suggest a multi-factorial death including a series of severe infections is more plausible. Cholestasis may have contributed to (b) (6) demise and the prolonged cholestasis was more likely due to repeated infections.

Thus, the data do not support a DILI risk that warrants disapproval of this NDA. While the data set is quite small, the fatal case is only a possible DILI and the primary cause of death is unlikely liver failure. While alkaline phosphatase elevations were higher in subjects on GNX compared to placebo, the fatal case did not have such elevations coincident with the liver injury. Moreover, AP levels are less specific for liver injury in children and no GGT levels were available for analysis to detect bland cholestasis. Labeling for enzyme monitoring or liver specific risk mitigation plan are not supported by this subject's demise nor the summary trial data.

5.2 Recommendations:

a) Approval should not be held up due liver injury risk.
b) No need for specific post-marketing requirements; routine post-marketing safety surveillance is sufficient.

Paul H. Hayashi -S

Digitally signed by Paul H. Hayashi -S
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Date: 2022.02.02 16:45:35 -05'00'

Paul H. Hayashi, MD, MPH
DILI Team Lead, Division of Hepatology and Nutrition
CDER/OND

Joseph G. Toerner -S

Digitally signed by Joseph G. Toerner -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300136263, cn=Joseph G. Toerner -S
Date: 2022.02.01 09:03:41 -05'00'

Joseph Toerner, MD, MPH
Director, Division of Hepatology and Nutrition
CDER/OND

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

PAUL H HAYASHI
02/02/2022 04:51:59 PM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	November 23, 2021
Requesting Office or Division:	Division of Neurology 2 (DN 2)
Application Type and Number:	NDA 215904
Product Name and Strength:	Ztalmy (ganaxolone) suspension, 50 mg/mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Marinus Pharmaceuticals, Inc.
FDA Received Date:	July 20, 2021, August 31, 2021, September 22, 2021, November 2, 2021, and November 9, 2021
OSE RCM #:	2021-1470
DMEPA 2 Safety Evaluator:	Justine Kalonia, PharmD
DMEPA 2 Acting Team Leader:	Stephanie DeGraw, PharmD

1 REASON FOR REVIEW

As part of the approval process for Ztalmy (ganaxolone) suspension, the Division of Neurology 2 (DN 2) requested that we review the proposed Ztalmy prescribing information (PI), instructions for use (IFU), medication guide (MG), container labels and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other – Information Request	E
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Ztalmy (ganaxolone) is proposed for the treatment of seizures associated with Cyclin-dependent Kinase-like 5 Deficiency Disorder (CDD) in patients 2 years of age and older. It will be supplied as an oral suspension in bottles containing 110 mL of product. In the initial proposed labels and labeling submitted to NDA 215904 on July 20, 2021, Marinus expressed the intent (b) (4) . At the initial phase of our review, we identified concerns with the proposed (b) (4) Thus, on August 18, 2021, we sent an information request (IR) to the Sponsor (b) (4) The Sponsor replied to our IR on August 31, 2021 (b) (4) As such, we followed up with the

[redacted] (b) (4)

[redacted] (b) (4)

Alternatively, we proposed [redacted] (b) (4)
On October 28, 2021 we sent another IR to communicate these options to the Sponsor. We received the Sponsor's response on November 2, 2021 indicating that they decided [redacted] (b) (4) Subsequently, on November 9, 2021, we received the revised labels and labeling for our review.

We provide our recommendations for the revised labeling in Sections 5 and 6 below.

4 CONCLUSION

The proposed prescribing information (PI), instructions for use (IFU), medication guide (MG), container label and carton labeling may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 5 for the Division and in Section 6 for Marinus Pharmaceuticals, Inc.

5 RECOMMENDATIONS FOR DIVISION OF NEUROLOGY 2 (DN 2)

Table 2. Identified Issues and Recommendations for Division of Neurology 2 (DN 2)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information, Medication Guide, and Instructions for Use – General Issues			
1.	We note that the dosage form statement on the proposed Medication Guide (MG) and Instructions for Use (IFU) is [redacted] (b) (4) However, this format is inconsistent with the USP Nomenclature Guidelines.	Per the USP Nomenclature Guidelines: "Generally, the dosage form title appears in the following format: [DRUG] [ROUTE OF ADMINISTRATION] [DOSAGE FORM]" The USP Nomenclature Guidelines are available from:	Revise the dosage form statement from [redacted] (b) (4) to read "oral suspension" wherever it appears in the labeling.

Table 2. Identified Issues and Recommendations for Division of Neurology 2 (DN 2)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		https://www.usp.org/sites/default/files/usp/document/usp-nomenclature-guidelines.pdf In addition to being inconsistent with the USP Guidelines, the current presentation appears cluttered.	
2.	Throughout the Prescribing Information (PI) labeling the frequency of administration is described as (b) (4) but it is unclear whether there is a specific time frame recommended between doses. Additionally, it is also unclear how soon a patient should take their next dose if they miss a dose.	Lack of clarity on frequency of dose administration may lead to "inappropriate schedule of product administration" errors resulting in either lack of efficacy or increased adverse events.	If applicable, consider providing information regarding the specific dosing interval, and how to approach missed doses in the PI, IFU, and MG. We defer to the review team as to whether to include a specific time frame between doses.
3.	We note the Sponsor recommends instructing patients to take this product (b) (4) (Section 2.3), or (b) (4) (Section 17) in the PI. Additionally, Section 12.3 in the PI states that (b) (4)	Conflicting information on when and how to take this product may lead to wrong technique in product administration errors, which may result in lack of efficacy.	Consider revising the instructions in the PI Sections 2.3, 12.3 and 17, and in the IFU for consistency. We defer to the review team to determine the most appropriate instructions for taking this product with food.

Table 2. Identified Issues and Recommendations for Division of Neurology 2 (DN 2)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	(b) (4) In the IFU, the Sponsor states that this product (b) (4)		
Highlights of Prescribing Information (HPI)			
1.	We note that the product title (b) (4) This format is inconsistent with the USP Nomenclature Guidelines.	Per the USP Nomenclature Guidelines: "Generally, the dosage form title appears in the following format: [DRUG] [ROUTE OF ADMINISTRATION] [DOSAGE FORM]" The USP Nomenclature Guidelines are available from: https://www.usp.org/sites/default/files/usp/document/usp-nomenclature-guidelines.pdf	Revise the product title to read "ZTALMY (ganaxolone) oral suspension".
2.	We note the Sponsor provides the usual recommended (b) (4) dosages in the statements: • Dosage for patients weighing 28 kg or less (b) (4) • Dosage for patients weighing over 28 kg is (b) (4)	Misinterpretation of these instructions may lead to incorrect dose administered errors.	Consider revising the HPI statements starting with "Dosage for patients weighing…" to state the recommended starting dosages for patients weighing 28 kg or less and patients weighing more than 28 kg (i.e., 6 mg/kg and 150 mg, respectively). Add a bullet below these to state that Ztalmy needs to be titrated. Also, for the statements "(63 mg/kg/daily)" and "(1800 mg daily)" consider specifying that they are the "total daily dose."

Table 2. Identified Issues and Recommendations for Division of Neurology 2 (DN 2)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	However, these dosages may be misinterpreted as the starting dosage. (b) (4) [redacted]		
3.	The total daily doses 1350 mg and 1800 mg do not have a comma in both the Dosage and Administration section of the HPI and Section 2 of the PI.	To improve readability, we recommend adding a comma for dose numbers at or above 1,000. Large doses without properly placed commas are listed as an error-prone dose designation on the Institute for Safe Medication Practice's (ISMP's) List of Error-Prone Abbreviations, Symbols, and Dose Designations Available from: http://www.ismp.org/tools/errorproneabbreviations.pdf.	Revise all dosages that are at or above 1,000 mg to contain the comma. Specifically revise 1350 mg and 1800 mg to read 1,350 mg and 1,800 mg.
Full Prescribing Information – Section 2 Dosage and Administration			
1.	The dosing information can be improved for clarity.	Stating the dosing in plain language may improve readability and comprehension.	Consider revising the paragraphs prior to tables 1 and 2, such that it is in a plain language format. For example, the first sentence of these paragraphs can both be revised to read (b) (4) [redacted]

Table 2. Identified Issues and Recommendations for Division of Neurology 2 (DN 2)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			(b) (4) [redacted] Alternatively, consider removing (b) (4) [redacted] above Tables 1 and 2 and instead revise the second sentence in section 2.2 to direct users to the appropriate dosage table as Tables 1 and 2 contain all necessary dosage and titration schedule information. We defer to the review team to determine the necessity of (b) (4) [redacted]
2.	Section 2.3 (Administration Instructions) in the PI does not state the route of administration.	The administration instructions can be improved by including the route of administration.	Consider adding the route of administration to the sentence about administering Ztalmy, such that it reads (b) (4) [redacted]
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	The strength statement can be improved for consistency. We note that throughout the PI labeling (and carton labeling and container label) the strength is stated as "50 mg/mL." However, in Section 16, instead of "50 mg/mL" it	This is not consistent with the rest of the labels and labeling.	We recommend adding the strength statement of "50 mg/mL" to Section 16 of the PI for consistency.

Table 2. Identified Issues and Recommendations for Division of Neurology 2 (DN 2)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	is described as (b) (4)		
2.	The net quantity statement can be improved for clarity. As presented, it states (b) (4)	This statement does not (b) (4)	Consider revising the statement to read "ZTALMY is a cherry flavored white to off-white suspension supplied in a 4 fl. oz (135 mL) round natural high density polyethylene (HDPE) bottle with a propylene child-resistant cap containing 110 mL of ZTALMY oral suspension" or a similar statement.
3.	We note that Section 16.2 of the PI states: "Store ZTALMY in its original bottle in an upright position".	This statement may be misinterpreted to mean dispense in the original container.	Please clarify the intention of this statement.
4.	We note that the NDC is (b) (4)	Per 21 CFR 201.57(c)(17), the NDC must be provided in Section 16 to facilitate identification of the dosage forms.	Revise (b) (4)
Instructions for Use (IFU)			
1.	The phrase (b) (4) can be improved for clarity.	Patients and caregivers may not understand this statement.	Revise this statement. For example, revise it to read: "Follow your healthcare provider's instructions for how to take (or give) the dose of ZTALMY."
2.	We note that the IFU states (b) (4)	Although pharmacies typically dispense an oral syringe with oral solutions	Consider revising the language (b) (4) to instead read:

Table 2. Identified Issues and Recommendations for Division of Neurology 2 (DN 2)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	(b) (4)	and suspensions, (b) (4)	"Supplies not included in the package: a press-in bottle adaptor and appropriately sized oral syringe(s) to take or give ZTALMY. You can get a press-in bottle adaptor and oral syringe from your pharmacy. Your pharmacist can help you select the correct items. Follow the instructions below to use the bottle adaptor and oral syringe to measure and administer ZTALMY."
3.	Step 2 does not provide an explanation for why users need to allow the bottle to stand for 1 minute.	Without this information, users may not understand why this is necessary and choose to ignore the direction.	Consider including the rationale for allowing the bottle to stand for 1 minute to Step 2 of the IFU, so that users can understand why this is necessary.
4.	Step 4 does not contain a corresponding image or explanation of the "induction seal."	Without an image, it may be unclear to the user what this instruction means.	Consider including an image or a description of the induction seal in Step 4 of the IFU.
5.	The image in step 10 on page 5 of the IFU may be misinterpreted as the opposite of the intended action, which according to the IFU, may cause choking.	The image (b) (4)	Consider revising the image to show the user placing the tip of the oral syringe against the inside of the cheek.

Table 2. Identified Issues and Recommendations for Division of Neurology 2 (DN 2)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
6.	As presented, the steps under the header "Prepare the bottle (b) (4) [redacted]	Users may misinterpret the order of steps. (b) (4) [redacted]	Consider combining the steps (b) (4) [redacted]

6 RECOMMENDATIONS FOR MARINUS PHARMACEUTICALS, INC.

Table 3. Identified Issues and Recommendations for Marinus Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label and Carton Labeling			
1.	The format for expiration date is not defined.	Clearly define the expiration date will minimize confusion and risk for deteriorated drug medication errors.	Identify the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
2.	As presented, the readability of the established name and dosage form may be compromised due to poor color contrast (b) (4)	Inability to read this important information may lead to product selection medication errors.	Please ensure the color contrast (b) (4) is sufficient to ensure adequate readability. Consider increasing the prominence of the established name and dosage form (b) (4) as needed to improve readability.

Table 3. Identified Issues and Recommendations for Marinus Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
3.	The placeholder for the controlled substance symbol appears in close proximity to the proprietary name, such that it might be misinterpreted as part of the proprietary name.	Misinterpretation of the proprietary name may lead to product selection medication errors.	Relocate the controlled substance symbol away from the proprietary name, so it is not misinterpreted as a part of the proprietary name (e.g., read as the letter 'c' or 'o'). Ensure placement of this symbol remains in accordance with 21 CFR 1302.04.
4.	As currently presented, the dosage form statement on the proposed labels and labeling is (b) (4) However, this format inconsistent with the USP Nomenclature Guidelines.	Per the USP Nomenclature Guidelines: "Generally, the dosage form title appears in the following format: [DRUG] [ROUTE OF ADMINISTRATION] [DOSAGE FORM]" The USP Nomenclature Guidelines are available from: https://www.usp.org/sites/default/files/usp/document/usp-nomenclature-guidelines.pdf In addition to being inconsistent with the USP Guidelines, the current presentation is more cluttered.	Revise the dosage form statement from (b) (4) to read "oral suspension" on the labels and labeling.
5.	We note that the PI states that this product should be stored "in its original bottle." However, there is no statement on the container label or carton	Per 21 CFR 201.100 (b)(7), the label should bear "A statement directed to the pharmacist specifying the type of container to be used in dispensing the drug product to maintain its	Please clarify the intent of the storage statement. If there is a specific reason this product should be dispensed (and therefore stored by the intended user [e.g., patient or caregiver]) in a specific type of

Table 3. Identified Issues and Recommendations for Marinus Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	labeling directing the pharmacist whether to dispense this product in the original bottle or another specific type of container.	identity, strength, quality, and purity."	container (e.g., its original container, or a tight, light-resistant container), then include this information on the labels and labeling.
6.	The storage statement contains hyphens and does not align with PI.	The storage statement terminology should be consistent across the labeling to mitigate risk of confusion, and the presentation of the storage statement should be clearly stated to avoid storage errors.	Replace the hyphen with the intended meaning. Consider revising (b) (4) (b) (4) to read
7.	The statement "Dispense the enclosed Medication Guide to each patient" is missing from the container label and carton labeling. As currently presented, it is not clear how the Medication Guide and IFU are provided in the carton.	This information is required per 21 CFR 208.24(d), which states: "The label of each container or package, where the container label is too small, of drug product for which a Medication Guide is required under this part shall instruct the authorized dispenser to provide a Medication Guide to each patient to whom the drug product is dispensed, and shall state how the Medication Guide is provided. These statements shall appear on the label in a prominent and conspicuous manner."	Ensure the statement "Dispense the enclosed Medication Guide to each patient" or a similar statement is prominently displayed on the PDP of the container label and carton labeling. In light of the carton presentation containing 5 bottles, we recommend you consider attaching a Medication Guide and IFU to each bottle within the carton containing 5 bottles.
Container Label			

Table 3. Identified Issues and Recommendations for Marinus Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	As currently presented, the container label is missing a linear barcode.	The drug barcode is often used as an additional verification during the medication use process; therefore, it is an important safety feature that should be part of the label.	Add the linear barcode to each individual container label for this product as required per 21 CFR 201.25(c)(2). Also, ensure that the barcode is surrounded by sufficient white space to allow scanners to correctly read the barcode in accordance with 21 CFR 201.25(c)(1)(i), and that the barcode is placed in an area where it will not be damaged in accordance with 21 CFR 201.25(c)(1)(ii).
2.	The (b) (4) statement can be improved.	To ensure consistency with the Physician Labeling Rule (PLR) formatted Prescribing Information Labeling.	We recommend you revise the usual dose statement from: (b) (4) to read: "Recommended Dosage: See prescribing information."
3.	We note you have (b) (4) on container label. (b) (4) Additionally, we note you did not provide this discard information on the single-count carton labeling.	(b) (4) may lead to confusion with users who are familiar with other oral solutions or suspensions (b) (4) Leaving this discard information off of the single-count carton labeling may also lead to expired	We recommend (b) (4) and include this discard information on both the container label and the single-count carton labeling. Alternatively, if the product is intended to be dispensed directly to the patient or their caregiver, then consider revising the discard statement on your container label and single-count carton labeling to read: "Date of first opening __/__/__. Discard unused

Table 3. Identified Issues and Recommendations for Marinus Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		product administered errors.	portion 30 days after first opening."
Carton Labeling			
1.	The net quantity statement on the Principal Display Panel (PDP) on the 5-count carton can be improved for accuracy. We note that the PDP states the quantity (b) (4)	This may cause confusion as to the contents of the package resulting in incorrect quantity dispensed errors.	Revise (b) (4) the PDP of the carton containing 5 bottles to state the total quantity in the carton, including the amount of product within each bottle. For example, you may revise it to read "five bottles each containing 110 mL of ganaxolone," or something similar.
2.	We note that next to the human readable product identifiers you have a placeholder for a (b) (4) If this is intended to be the machine-readable portion of the product identifier, then it is not an acceptable format for this product identifier.	Per the guidance (Product Identifiers Under the Drug Supply Chain Security Act Questions and Answers), a (b) (4)	Revise (b) (4) placeholder to be a 2D data matrix barcode that meets the requirements set forth by the DSCSA.

Table 3. Identified Issues and Recommendations for Marinus Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		(b) (4) * See GS1 General Specifications (Release 18, Ratified, January 2018), Section 2.1.6 Healthcare primary packaging (https://www.gs1.org/sites/default/files/docs/barcodes/GS1_General_Specifications.pdf). See our guidance available from: https://www.fda.gov/media/116304/download	
3.	It is unclear who the intended audience is for the following warning statement: "Do Not Accept If Tamper-Evident Seal on Box is Broken or Missing."	Lack of clarity for whom the intended audience is may lead to dispensing errors.	Please clarify the intended audience (e.g., pharmacists, patients) for this warning statement.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Ztalmy that Marinus Pharmaceuticals, Inc. submitted on July 20, 2021.

<table>
<tr><th colspan="2">Table 4. Relevant Product Information for Ztalmy</th></tr>
<tr><td>Initial Approval Date</td><td>N/A</td></tr>
<tr><td>Active Ingredient</td><td>ganaxolone</td></tr>
<tr><td>Indication</td><td>for the treatment of seizures associated with Cyclin-dependent Kinase-like 5 Deficiency Disorder (CDD)</td></tr>
<tr><td>Route of Administration</td><td>oral</td></tr>
<tr><td>Dosage Form</td><td>suspension</td></tr>
<tr><td>Strength</td><td>50 mg/mL</td></tr>
<tr><td>Dose and Frequency</td><td>(b) (4)
 
Table 1 ZTALMY Recommended Titration Schedule for Patients Weighing 28 kg or Less
<table><tr><th>Dose</th><th>Total Daily Dose</th><th>Days</th></tr><tr><td>6 mg/kg three times daily</td><td>18 mg/kg/day</td><td>1 to 7</td></tr><tr><td>11 mg/kg three times daily</td><td>33 mg/kg/day</td><td>8 to 14</td></tr><tr><td>16 mg/kg three times daily</td><td>48 mg/kg/day</td><td>15 to 21</td></tr><tr><td>21 mg/kg three times daily</td><td>63 mg/kg/day</td><td>22 to ongoing</td></tr></table>
(b) (4)
 
Table 2 ZTALMY Recommended Titration Schedule for Patients Weighing More Than 28 kg
<table><tr><th>Dose</th><th>mL per Dose</th><th>Total daily dose</th><th>Days</th></tr><tr><td>150 mg three times daily</td><td>3</td><td>450 mg</td><td>1 to 7</td></tr><tr><td>300 mg three times daily</td><td>6</td><td>900 mg</td><td>8 to 14</td></tr><tr><td>450 mg three times daily</td><td>9</td><td>1350 mg</td><td>15 to 21</td></tr><tr><td>600 mg three times daily</td><td>12</td><td>1800 mg</td><td>22 to ongoing</td></tr></table></td></tr>
</table>

How Supplied	ZTALMY is a cherry flavored white to off-white suspension supplied in a 4 fl. oz (135 mL) round natural high density polyethylene (HDPE) bottle with a propylene child-resistant cap containing 110 mL. [redacted] ZTALMY is packaged in a carton with 1 bottle, [redacted] (NDC 81583-100-01), or in a carton with 5 bottles [redacted](NDC 81583-100-05).
Storage	Store ZTALMY in its original bottle in an upright position, [redacted] Keep the cap tightly closed. Use within 30 days of first opening the bottle, then discard any remainder.
Container Closure	A 4 fl. oz (135 mL) round natural high density polyethylene (HDPE) bottle with a propylene child-resistant cap

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APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[c] along with postmarket medication error data, we reviewed the following Ztalmy labels and labeling submitted by Marinus Pharmaceuticals, Inc. received on November 9, 2021.

- Container label
- Carton labeling
- Instructions for Use, available from \\CDSESUB1\evsprod\nda215904\0026\m1\us\114-labeling\draft\labeling\instruct-for-use-tracked.docx
- Medication Guide, available from \\CDSESUB1\evsprod\nda215904\0026\m1\us\114-labeling\draft\labeling\med-guide-tracked.docx
- Prescribing Information (Image not shown), available from \\CDSESUB1\evsprod\nda215904\0026\m1\us\114-labeling\draft\labeling\uspi-tracked.docx

F.2 Label and Labeling Images

Container label

[c] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

JUSTINE H KALONIA
11/23/2021 04:14:25 PM

STEPHANIE L DEGRAW
11/23/2021 04:37:25 PM