CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215904Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Meeting Date: March 15, 2021 **Time:** 1:00 – 2:00 PM EST
Meeting Type: Type B/preNDA meeting
Sponsor: Marinus Pharmaceuticals, Inc.
Product: Ganaxolone (CCD 1042)
Proposed Use: The treatment of CDKL5 Deficiency Disorder (CDD).

Introductory Comment: This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for March 15, 2021 at 1:00 – 2:00 PM EST between Marinus Pharmaceuticals, Inc., and the Division of Neurology 2. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible. If any modifications to the development plan or additional questions for which you would like CDER feedback arise before the meeting, contact the RPM to discuss the possibility of including these items for discussion at the meeting.

SUMMARY OF QUESTIONS AND FDA PRELIMINARY RESPONSES

QUESTION 1: Does the FDA agree with the Sponsor's plans for providing datasets in the formats outlined in the Study Data Standardization Plan (see Appendix 3)?

FDA Preliminary Response

Overall, your plan for providing datasets for the studies listed appears appropriate.

See also the responses to Questions 12 and 13.

QUESTION 2: Does the FDA agree that based on results of in vitro drug interaction studies, and the data obtained from a clinical study of the effect of GNX on the CYP3A4 substrate midazolam, a clinical drug-drug interaction study with oral contraceptives is not needed?

FDA Preliminary Response

It is unclear to us that there is *in vivo* evidence of a lack of significant drug-drug interaction (DDI) potential with sensitive CYP3A4 substrate (midazolam) for the following reasons:

- The dose selected, 400 mg twice daily of ganaxolone, is lower than the proposed dosing regimen.

- The formulation (capsule) used has an 18% lower AUC and a 36% lower Cmax than those of the to-be-marketed formulation (suspension) in the fed state.

Therefore, the results from your completed *in vivo* DDI study with midazolam may underestimate the true DDI potential due to a lower exposure of ganaxolone than that expected from your proposed dosing regimen. The effect of ganaxolone suspension at the proposed dosing regimen on the CYP3A4 substrate midazolam remains unclear.

You need to provide an adequate rationale, based on your *in vitro* and *in vivo* studies, to support your request to waive a clinical DDI study with oral contraceptives.

QUESTION 3: Does the FDA agree to Marinus' request for a waiver from conducting a Phase 1 Alcohol-Induced Dose Dumping (AIDD) Study?

FDA Preliminary Response

We agree with your waiver proposal for the Phase 1 alcohol-induced dose dumping (AIDD) study; however, the corresponding appropriate labeling language would not be written until during the NDA review.

(b) (4)

QUESTION 4: Marinus has followed the recommendations set forth by the FDA and the applicable Guidance for Industry in its evaluation of the abuse- and physical dependence- potential of ganaxolone. Does CSS concur with the planned approach for presenting the abuse potential data of GNX, inclusive of the abuse- and physical dependence-related data obtained from nonclinical and clinical studies, as applicable? Does CSS agree with the sponsor's planned content, intended organization, and pooling strategy for abuse-related adverse event data?

FDA Preliminary Response

Yes, we agree that you have complied with the 2017 *Guidance for Industry: Assessment of Abuse Potential of Drugs* in terms of conducting the appropriate *in vitro*, animal, and human abuse-related studies requested by our Controlled Substance Staff.

We also agree with your planned content, intended organization, and pooling strategy for evaluating the abuse-related adverse event data from clinical studies with ganaxolone.

QUESTION 5: Marinus believes that Study 1042-CDD-3001 could serve as the single pivotal efficacy study to support the approval of ganaxolone for the treatment of CDKL5 Deficiency Disorder (CDD). The data from subjects with CDD in the recently completed double-blind portion of this Phase 3 Study, with supportive data from the open-label extension of Study 1042-CDD-3001 and the open-label Study 1042-0900, provides an adequate basis for filing and review of the NDA to support approval of GNX in the proposed indication as a treatment for CDD. Does the Agency agree?

FDA Preliminary Response

As stated in our Type C meeting response of January 8, 2021, the presentation of efficacy and safety data in your briefing document appears adequate for the filing of an NDA for review. The adequacy of these data to support approval of ganaxolone for the proposed indication will be a matter of NDA review.

Your application will also need to include a detailed discussion, as refered to in your Type C meeting package, with respect to the relevance of any negative trials with ganaxolone in other seizure disorders on the ability of Study 1042-CDD-3001 to serve as a single adequate and well-controlled trial in support of your proposed indication.

QUESTION 6: Marinus believes that patient exposure from the Phase 3 study 1042-CDD-3001 in addition to the extensive safety experience with GNX acquired through the clinical development program, via various indications, is sufficient to support the NDA filing? Does the Agency agree?

FDA Preliminary Response

The proposed safety exposure database appears generally adequate to support the filing of your application; however, see also our response to Question 13 regarding the studies to be included in your planned application. The adequacy of these data to support approval of ganaxolone for the proposed indication will be a matter of NDA review.

Your application should provide safety exposures as shown in sample Tables A and B in General Submission Contents, shown below.

QUESTION 7: Does the Agency agree with the proposed cut-off date of 24 February 2021 in anticipation of an NDA submission by 30 June 2021? Does the Agency agree with Marinus' plan to provide the safety update report 120 days following the NDA submission (28 October 2021)?

FDA Preliminary Response

Yes, the cut-off date and your plan to provide the safety update report are acceptable.

QUESTION 8: During data monitoring for Study 1042-CDD-3001, several duplicate seizure and medication diary entries were found. These were clearly distinguishable from the original entries which will be used in all analyses. Duplicate entries were coded as such, were filtered from the database and will not be summarized in the clinical study report or NDA. Does the Agency agree with the proposed strategy?

FDA Preliminary Response

In preparation for BIMO inspections, please provide all raw eDiary data as line listings, including duplicate entries. Please flag the duplicate entries that were not used in the efficacy analyses.

Provide a description of this issue in the NDA including the extent of the issue, what you mean by "several" duplicate entries (how many patients had duplicate entries and how many duplicates occurred per patient), when the duplicate entries were discovered, what the root cause of the duplicate entries was, and what corrective actions were taken. In each instance of duplicate entries, identify any discrepancies in the data between the duplicate entries and explain the root cause any such discrepancies.

QUESTION 9: Marinus intends to submit the study-level information, subject-level data line listings, and summary-level clinical site data for Study 1042-CDD-3001 in the format described in the draft FDA Guidance Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018).
For legacy studies, Marinus proposes to only submit raw datasets and analysis datasets. Does the Agency agree?

FDA Preliminary Response

Your plan to submit BIMO information for Study 1042-CDD-3001 is acceptable. BIMO data for legacy studies do not need to be submitted.

As noted in the response to Question 8, please include subject-level raw eDiary data listings including duplicate eDiary entries.

In the BIMO submission:

- Please describe how the self-reported seizure data were handled from the time of entry into the electronic diary device by the subjects until the data reached the study database. Include the roles of the clinical investigator, CRO/vendor (if any), and the sponsor in the process.

- Please describe the process for making any changes to these data after entry as well as whether audit trails and data clarification forms were in use.

- Please indicate if and how the self-reported seizure data from the electronic diaries were made available to the clinical investigator at their sites throughout the study and after study completion.

- Please submit the manual(s) for the electronic device used for the collection of self-reported seizure data.

- In preparation for BIMO inspections, please indicate the data available at the clinical investigator sites for verification of raw e-diary data listings. For example, are certified CDs (including audit trails) available and does the site have access to the web portal?

QUESTION 10: Data from one recently completed Phase 3 study (1042-CDD-3001) will provide the basis for the filing and review of the NDA, an ISE will not be provided in Module 5.3.5.3. However, a cross reference will be noted in Module 2.7.3, and Module 5.3.5.3 noting this omission. Does the Agency agree?

FDA Preliminary Response

This approach is acceptable.

QUESTION 11: Marinus considers the proposed content of the Integrated Summary of Safety, and pooling strategy, defined in the ISS SAP, adequate to allow for the review and evaluation of the safety profile of GNX in CDD. Does the Agency agree?

FDA Preliminary Response

The approach to analysis of the pooled CDD clinical studies appears acceptable.

QUESTION 12: Does the Agency agree with the proposed Data Standardization Plan and the presentation of electronic datasets and documentation in the NDA (see Appendix 3)?

FDA Preliminary Response

From a technical perspective (data standards and format but not content) SDSP is acceptable except that we note that some studies are completed but study start dates are TBD. CDISC standards are not required if a study started before December 17, 2016. Please see the responses to Questions 13 and 14 for further discussion of the required content of your NDA.

QUESTION 13: Does the Agency agree with the proposal to only provide SAS datasets for studies conducted by Marinus starting from 2006?

FDA Preliminary Response

The data that you plan to provide from the clinical studies that have been completed with ganaxolone are not fully specified. The legacy studies prior to 2006 must be complete with a full clinical study report (CSR) and data tables in PDF format. Clinical studies of migraine headache and postpartum depression, pediatric studies of partial onset seizures, and studies of PCDH19, infantile spasms, and Fragile X syndrome must be included as described in the General Clinical Safety Requests included below. There also appears to be no plan for submission of data from the Study 1042-0700 in PTSD. This study must also be included in the NDA safety dataset.

QUESTION 14: Marinus plans to submit the NDA in eCTD format according to Marinus' eCTD Table of Contents. A copy of the proposed eCTD Table of Contents has been provided in the briefing package (Appendix 6). Does the Agency agree that the eCTD Table of Contents is acceptable?

FDA Preliminary Response

The clinical components of Module 2 and Module 5 are acceptable except for the absence of Study 1042-0700 (see response to Question 13) and the need to address the General Clinical Safety Requests provided below.

QUESTION 15: Based on the high unmet medical need for treatments for CDKL5 deficiency disorder, Marinus intends to request priority designation for the NDA at the time of submission? Does the Agency agree with this proposal?

FDA Preliminary Response

A review designation for your application will be determined at the time of filing of the NDA.[1]

[1] https://www.fda.gov/media/86377/download

QUESTION 16: The entry into the aquatic environment (EIC) of ganaxolone is calculated to be (b) (4) ppb, which is below the threshold of 1 ppb. This concentration is likely lower as the compound undergoes potentially extensive metabolism (with only 20% of the active moiety being introduced into the environment unchanged). To our knowledge, no other extraordinary circumstances exist to require a full Environmental Assessment. Therefore, we intend to request a Request for Categorical Exclusion (RCE) under 21 CFR 25.31(b)?

FDA Preliminary Response

Your plan to submit a claim of categorical exclusion per 21CFR25.31(b) appears acceptable. This is based on the very low EIC and extensive metabolism; however, your statement of "no extraordinary circumstances" needs to be supported. Please refer to the Agency's recent publication (below) that addresses drugs with estrogenic, androgenic, or thyroid activity as a potential "extraordinary circumstance."

USFDA (2016). Environmental Assessment: Questions and Answers Regarding Drugs with Estrogenic, Androgenic, or Thyroid Activity. Center for Drug Evaluation and Research. https://www.fda.gov/downloads/Drugs/Guidances/UCM444658.pdf

QUESTION 17: As GNX was granted Orphan Designation on 28 June 2017 (#17-5780), Marinus intends to claim the orphan exemption upon completion and submission of the User Fee Cover Sheet, Form FDA 3397. As noted in FDA Guidance for Industry, Prescription Drug User Fee Act Waivers, Reductions, and Refunds for Drug and Biological Products (October 2019), Marinus plans to include the User Fee Cover Sheet with the NDA along with a brief statement claiming the orphan exception in the cover letter. Does the Agency agree that the waiver request for the filing fee is appropriate for Marinus?

FDA Preliminary Response

Your proposal is acceptable.

QUESTION 18: Does the Agency intend to include an Advisory Committee Meeting during the review of this NDA?

FDA Preliminary Response

The need for an Advisory Committee meeting is determined during the NDA review.

General Clinical Safety Requests

Datasets:

1. Each individual subject should be assigned a single unique subject identifier across the entire application (e.g., including open label extensions of the trials). Include the unique subject identifier in the ISS and individual studies' datasets.

2. Submit datasets for all Phase 1, Phase 2, Phase 3 studies (including open-label extension studies), including the Phase 2 and 3 studies performed for indications other than the one proposed for this application.

For additional guidance refer to the FDA webpage on Study Data Standards Resources.

General Submission Contents:

1. Follow the requirements noted in 21CFR 314.50 (d)(5)(vi), Summary of Safety Information and the Guideline for the Format and Content of the Clinical and Statistical Sections of an Application.

2. Provide an assessment of safety as per the FDA Guidance for Industry: Premarketing Risk Assessment.

3. Include a copy of each clinical study protocol as well as each amended protocol. Provide a list of the inclusion and exclusion criteria for each of the studies, including those introduced as part of protocol amendments. Please submit all versions of the protocols (and Statistical Analysis Plan) and the date when changes were implemented. Please ensure that a Summary of Changes for each version is included.

4. In addition to the comprehensive analyses performed for the pivotal trials, the ISS should also comprehensively integrate safety analyses for all other study group pools for treatment-emergent adverse events (TEAEs), deaths, serious adverse events, discontinuations for TEAEs, TEAEs of special interest, subgroups, and vital sign/laboratory/ECG measurements.

5. Submit a table detailing all of the tables and figures featured in the clinical efficacy and safety sections of the application. The table should contain the following:

    a. Title of the table or figure in the application
    b. A hyperlink to the location of the table or figure with page number
    c. A hyperlink to the SAS code used to create the table or figure (including information regarding the datasets that were used)

6. Format the tables of the ISS according to examples in FDA's Reviewer Guidance – Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review.

7. Include active hyperlinks from the lists of references to the referenced article.

8. Provide DSMB meeting minutes (including any data/slides presented). For those meetings that were cancelled or meetings where no minutes were taken, please include a place holder for that meeting noting such and signed by a member of the clinical team. Please also ensure that these packages come with a table of contents and are bookmarked by date.

9. Include information regarding important regulatory actions in other countries and foreign labeling (translated, if applicable).

10. Submit an annotated version of the pre-NDA meeting minutes that include hyperlinks, when applicable, to the analysis and/or documents requested.

11. Provide the following tables related to exposure:

Sample Table A: Safety Population, Size, and Denominators

Safety Database for the Study Drug[1] Individuals exposed to any treatment in this development program for the indication under review N= (N is the sum of all available numbers from the columns below)			
Clinical Trial Groups	New Drug (n=)	Active Control (n=)	Placebo (n=)
Healthy volunteers			
Controlled trials conducted for this indication[2]			
All other trials conducted for this indication[3]			
Controlled trials conducted for other indications[4]			
All other trials conducted for other indications			

[1] *Study drug* means the drug being considered for approval.
[2] to be used in product's labeling
[3] If placebo arm patients switch to study drug in open label extension, then the sample n should count those patients only once; do not count twice patients who go into extension

from randomized study drug arm
[4] Include n in this row only if patients exposed to the study drug for indication(s) other than that in the marketing application have been included in the safety database under review.

Sample Table B. Duration of Exposure

Dosage	Number of patients exposed to the study drug:				
	>= 1 dose	>=6 months[1]	>=12 months	>=18 months	18 months or longer
Dose 1	N=	N=	N=	N=	N=
Dose 2, etc.	N=	N=	N=	N=	N=

[1] These time interviews are provided as a sample. Time interval and cumulative treatment duration selected for this table will vary among products and should be based on experience with a specific product under review

12. Provide a list that includes the NCT number (for the ClinicalTrials.gov site) for each trial included in the submission.

Adverse events:

1. Follow the coding rules for MedDRA in the ICH-endorsed "MedDRA Term Selection: Points to Consider" document accessible at MedDRA
2. For each of the studies, the submitted datasets should contain both the verbatim terms and the MedDRA coding with all levels of the MedDRA hierarchy. For each adverse event, MedDRA coding should be provided for the primary MedDRA path as well as the alternative MedDRA coding paths.
3. Provide a summary table of the original AE coding dictionaries that were used in each of the trials.
4. The preparation of the adverse event dataset for the ISS should include MedDRA Preferred Terms from a single version of MedDRA.
5. Ensure that all adverse events are presented, and not only events deemed "drug-related."
6. Provide a table of treatment-emergent adverse events reported in ≥ 2% of subjects (after rounding) in any drug treated dose group (and greater than placebo) sorted by MedDRA SOC (in alphabetical order) and then by MedDRA Preferred Term.
7. Provide a table which summarizes the outcomes of all pregnancies. Provide a table which summarizes all known adverse events in subject offspring.

Narratives and Case Report Forms (CRFs):

1. Provide narratives and case report forms for deaths, adverse events leading to drug discontinuation, SAEs, pregnancies, and AEs of special interest. You should be prepared to supply any additional CRFs or narratives with a rapid turnaround upon request. Narratives should be integrated. For subjects who had more than one event

requiring a narrative (whether in the same trial or in the core study and an extension) present a single narrative (rather than separate narratives for the various events).

2. Include a word file (and excel spreadsheet) that indicates those subjects for whom you submitted a case report form and/or narrative. This file should include an indicator for whether each item was submitted and the reason why it was submitted along with hyperlinks to the narrative and CRF.
3. Provide reports for any autopsies conducted during any of the studies.
4. Provide a line listing, narrative, and case report form for all subjects who fit the Hy's Law laboratory criteria.
5. Note that CRFs should include all clinical documents collected about the patient regardless of whether you label them "CRFs", e.g., Medwatch/CIOMS forms, event fax coversheets, SAE or event worksheets, narrative worksheets, data queries, etc.
6. Provide a tabular listing of all subjects with all discontinuations, sorted by reason. The table should include columns for study number, treatment group, unique subject ID, primary reason for drug or study discontinuation. For reasons including Lost to follow-up, Other, Physician/investigator decision, withdrew consent, and Patient decision, provide more specific information regarding the discontinuation. The Division may want to request selected narratives/CRFs from some of these patients, but they do not need to be submitted at the time of the initial NDA/BLA submission.
7. Narrative summaries should provide a complete synthesis of all available clinical data and an informed discussion of the case. The narratives should be comprehensive enough for the reader to come to a reasonable conclusion regarding the subject and the adverse event. The following items should be included (but not limited to):
    a) Patient age and gender
    b) Adverse event onset and stop dates (presented as relative Study Day number)
    c) Signs and symptoms related to the adverse event being discussed
    d) An assessment of the relationship of exposure duration to the development of the adverse event
    e) Pertinent medical history
    f) Concomitant medications with start dates relative to the adverse event
    g) Pertinent physical exam findings
    h) Any abnormal vital sign measurements
    i) Pertinent test results (e.g., lab data, ECG data, procedures, biopsy data, autopsy results)
    j) Discussion of the diagnosis as supported by available clinical data
    k) For events without a definitive diagnosis, a list of the differential diagnoses
    l) Treatment provided
    m) Re-challenge results (if performed)
    n) Outcomes and follow-up information

Laboratory and Vital Sign Measurements:

1. Refer to the following FDA webpage for the CDER position on use of SI units for lab tests: SI Units.
2. Provide the normal reference ranges for every laboratory value.

3. Clearly list the normal values, as well as the thresholds for analysis of outliers, for outlier analyses of laboratory data, vital signs, and ECG data.
4. When possible, use the latest version of the National Institutes of Health (NIH) Common Terminology Criteria for Adverse Events (CTCAE) for toxicity grades and shift analyses.
5. Summarize the protocols for collecting ECG data. Summarize the frequency of post-treatment QTc >450 ms, >480 ms, and >500 ms.

Other requests:

1. Patient profiles
   Submit individual patient profiles containing all laboratory and other study results in a single place for each patient. Provide this information for patients who died, had a serious adverse event, discontinued from the trial due to an adverse event, or had a medically significant event for which a narrative is submitted. Include all the information recorded for that patient, including but not limited to:
   a) Age
   b) Sex
   c) Dates of screening, randomization and starting therapy
   d) Whether the patient completed or did not complete the study, with dates and reason for withdrawal
   e) Adverse events (reported term, preferred term, start and stop date [with relative study day], seriousness, outcome, whether it resolved or not and action taken with drug)
   f) Prior medications and concomitant medications with dates of start and end
   g) Vital signs and laboratories, sorted by date, with reference ranges *
   h) Autopsy reports for all deaths. (If an autopsy report is not available, explicitly state this.)
   i) Full reports for radiologic studies, ECG, MRI, pathology results, special studies and procedures with dates and reference ranges
   j) Provide relevant results obtained outside of clinical trial visits, including those obtained during hospitalization or emergency room visits, in each patient file. Also include baseline study results.
   k) For patients who had IND safety report(s), include dates when the initial and follow up safety reports were submitted.

   Create a PDF file for each patient and a table of contents with links to each assessment for each patient.

2. Please submit for Division comments an example narrative from a patient who had more than one serious adverse event and participated in the controlled and extension studies prior to submitting your NDA.
3. We request that you submit a sample integrated summary of safety datasets (with data definition file) for Division comments prior to submitting the NDA. This process

could help to identify and resolve any potential issues of navigability or interpretability that could impact the review of your application.

Condition Specific Requests: Epilepsy

1. Clarify what criteria were used to categorize a seizure as an adverse event (versus lack of efficacy.)

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/

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