CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216718Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 122349

MEETING MINUTES

Reata Pharmaceuticals, Inc.
Attention: Andrea Loewen, MS, RAC
Vice President, Global Regulatory Affairs
5320 Legacy Drive
Plano, TX 75024

Dear Ms. Loewen:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for RTA 408 (omaveloxolone).

We also refer to the telecon between representatives of your firm and the FDA on August 31, 2021. The purpose of the meeting was to discuss the proposed content and format of a planned New Drug Application (NDA).

A copy of the official minutes of the meeting/telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, contact Brenda Reggettz, PharmD, Regulatory Health Project Manager, by email at Brenda.Reggettz@fda.hhs.gov or by phone at (240) 402-6220.

Sincerely,

{See appended electronic signature page}

Teresa Buracchio, MD
Deputy Director
Division of Neurology 1
Office of Neuroscience
Center for Drug Evaluation and Research

Enclosures:

- Meeting Minutes
- Attachments 1 and 2
- Sponsor meeting slides

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: August 31, 2021 at 4:00 p.m. (ET)
Meeting Location: Teleconference

Application Number: 122349
Product Name: RTA 408 (omaveloxolone)

Proposed Indication: Treatment of Friedreich's ataxia

Sponsor Name: Reata Pharmaceuticals, Inc.
Regulatory Pathway: 505(b)(1) of the Federal Food, Drug, and Cosmetic Act

FDA ATTENDEES

Office of New Drugs
Peter Stein, MD, Director

Office of Neuroscience
Billy Dunn, MD, Office Director
Eric Bastings, MD, Deputy Director; Director of DN1 (Acting)
Michelle Campbell, PhD, Stakeholder Engagement and Clinical Outcomes

Division of Neurology 1
Teresa Buracchio, MD, Deputy Director
Emily Freilich, MD, Clinical Team Leader
Veneeta Tandon, PhD, Clinical Reviewer
Tracy Peters, PharmD, Associate Director for Labeling

Division of Pharmacology and Toxicology-Neuroscience
Lois Freed, PhD, Director
David Carbone, PhD, Nonclinical Reviewer

Office of Clinical Pharmacology
Bilal AbuAsal, B.Pharm, PhD, Team Leader
Adarsh Gandhi, PhD, Reviewer
Manuela Grimstein, PhD, PBPK Reviewer
Yuching Yang, PhD, PBPK Co-lead

Michael Bewernitz, PhD, Pharmacometric Reviewer
Atul Bhattaram, PhD, Pharmacometric Team Leader

Office of Pharmaceutical Quality
Martha Heimann, PhD, CMC Lead for Neurology Products
Andrei Ponta, PhD, Reviewer, Division of New Drug Products

Office of Biostatistics
Kun Jin, PhD, Statistical Team Leader
Xiangmin Zhang, PhD, Reviewer

Division of Regulatory Operations-Neuroscience
Susan Daugherty, RN, BSN, Senior Regulatory Project Manager
Brenda Reggettz, PharmD, Senior Regulatory Health Project Manager
Terry Harrison, PharmD, Safety Regulatory Project Manager

Controlled Substances Staff
Chad Reissig, PhD, Team Leader
Edward (Greg) Hawkins, PhD, Reviewer

Division of Cardiology and Nephrology
Girish Bende, PhD, Scientific Co_Lead, QT/IRT

Division of Risk Management
Jacqueline Sheppard, PharmD, Team Leader
Lindsey Crist, PharmD, BCPS, Reviewer

Division of Pharmacovigilance
Charlene Flowers, PharmD, Safety Evaluator

Division of Medication Error Prevention and Analysis
Chad Morris, PharmD, MPH, Safety Evaluator

Division of Epidemiology
Chinenye Ugoji, PhD, MPH, BPharm, Reviewer

Division of Rare Diseases and Medical Genetics
Cynthia Welsh, MD, Rare Diseases Team

Office of Surveillance and Epidemiology
Casmir Ogbonna, PharmD, MBA, Safety RPM

SPONSOR ATTENDEES

Melanie Chin, Ph.D. Vice President, Product Strategy
Daren Denniston, M.S. Senior Manager, Regulatory Affairs
Angie Goldsberry, M.S. Vice President, Product Development
Warren Huff, J.D. Chief Executive Officer
Scott Hynes, Pharm. D., Ph.D. Associate Vice President, Clinical Pharmacology
Kevin Johnston, M.S., Chief Technical Officer
Seemi Khan, M.D. Chief Medical Officer
Andrea Loewen, M.S., RAC. Vice President, Global Regulatory Affairs
Masako Murai, M.D., Ph.D. Associate Vice President, Clinical Development
Colin Meyer, M.D. Chief Research and Development Officer
Scott Reisman, Ph.D., D.A.B.T. Director, Nonclinical Development
Lisa Semmens, M.S. Director, Regulatory CMC
Edward Tamer, Ph.D. Associate Vice President, Nonclinical Development
Min Young, Ph.D., RAC. Sr. Director, Global Regulatory Lead
(b) (4)

1.0 BACKGROUND

Reata Pharmaceuticals, Inc. is developing RTA 408 (omaveloxolone), an oral capsule for the treatment of Friedreich's ataxia (FA). The Agency granted orphan designation for omaveloxolone for the treatment of FA on June 19, 2017.

There have been many interactions between Reata and the Division to determine an efficacy endpoint that would support the submission of a New Drug Application (NDA). Due to the challenges of adequately powering a trial in FA using the ADL component of the Friedreich's ataxia rating scale (FARS) as a primary endpoint, the Division agreed in an email dated August 2, 2017, that a modified FARS (mFARS) would be an acceptable primary endpoint for their proposed study. The overall results of the clinical trial(s) on the various efficacy measures that are assessed to support the relevance to patients' daily functioning of any observed treatment effect on the mFARS would be evaluated to determine an appropriate regulatory pathway.

Reata completed Part 1 of their Phase 3 Study 408-C-1402, MOXIe, A Phase 3 Study of the Safety, Efficacy, and Pharmacodynamics of RTA 408 in the Treatment of FA; and Part 2 is ongoing for the extension study.

On February 26, 2021, Reata submitted a Type C meeting request to discuss additional analyses of data from Study 1402 Part 2, including the results of delayed-start analyses previously requested by the Division. After a preliminary review of the meeting package,

the Division notified Reata that a Pre-NDA meeting would be the most appropriate meeting type for a discussion of the development program for omaveloxolone in FA. Reata withdrew the Type C meeting request and submitted a Type B, Pre-NDA, meeting request on June 21, 2021.

The Agency's response to the questions presented in the Sponsor's background package dated July 30, 2021, are provided below.

FDA sent Preliminary Comments to Reata on August 27, 2021.

2.0 DISCUSSION

2.1. Clinical

Question 1: Primary and Secondary Efficacy Data Supporting NDA Submission

Does the Division agree with the proposed primary and supportive efficacy data for FA in the NDA submission?

FDA Response to Question 1:

On face, the proposed primary and supportive efficacy data appear reasonable for the NDA submission. The adequacy of the data and the determination of which data may be supportive of efficacy will be a matter of review of the application. Please clarify if you intend to seek standard approval or accelerated approval based on the mFARS as an intermediate clinical endpoint in your NDA submission.

Meeting Discussion:

The sponsor confirmed that it intends to provide sufficient clinical data to support standard full approval with the positive results of the MOXIE study (Study 1402), with supportive efficacy data coming from the delayed-start analysis and open-label extension study results. The Division noted that the ability of the data to support a standard approval would be a matter of review.

The Division clarified that although the delayed-start analysis was requested by the Division in an attempt to yield additional information from the available data, the analysis was viewed as exploratory, and the Division did not intend to imply a degree of endorsement that the delayed-start analysis would be adequate for providing supportive efficacy data. The Division noted that the determination of whether the available data constitute evidence of effectiveness supportive of full approval would be a matter of review. The sponsor expressed understanding of the context of these additional analyses requested by the Division. The sponsor also clarified that the support for a claim of disease modification will come from interpretation of the delayed-start analysis.

The sponsor sought clarification on the ability to request a rolling submission and proposed to submit a Fast-Track Designation Request in September 2021. The Division expressed openness to the proposal and noted that if Fast-Track Designation was granted, then a rolling review submission would be acceptable; however, a request for rolling review submission would still need to be formally submitted. The Division reiterated that all modules must be complete at the time of submission. The sponsor acknowledged that information and noted that the intent was to submit clinical and nonclinical modules at the end of 2021, but that CMC would be available at the end of February or March 2022.

Question 2: Module 5.3.5.3 ISE to Cross-Reference Module 2.7.3 SCE

Does the Division agree with the proposal to not include an Integrated Summary of Efficacy (ISE) in the NDA and to cross reference Module 2.7.3 in Module 5.3.5.3 ISE?

FDA Response to Question 2:

We agree with the proposal to not include an Integrated Summary of Efficacy (ISE) in the NDA and to cross reference Module 2.7.3 in Module 5.3.5.3 ISE.

Meeting Discussion: No discussion occurred.

Question 3: Proposed Safety Database

3a. Does the Division have any comment on the safety database and its adequacy to support an NDA submission for this rare disease?

FDA Response to Question 3a:

The proposed safety database appears adequate for NDA submission.
Please also see response to Q4.

Meeting Discussion: No discussion occurred.

3b. Can the Division confirm that inclusion of the CSRs and data from topical lotion or ophthalmic suspension clinical studies is not necessary in the NDA as the safety data from these studies are not considered supportive for the characterization of the oral administration safety in consideration of the negligible systemic exposure, as previously discussed with the Division.

FDA Response to Question 3b:

We agree that data from the topical lotion and the ophthalmic suspension clinical studies do not need to be included in the NDA submission.

Meeting Discussion: No discussion occurred.

Question 4: Plan for Integration of Safety

Does the Division agree with the proposed approach to present the product-specific safety data, including ISS analysis sets, pooling strategy, and data presentation plan, to support the safety review of the omaveloxolone NDA for the treatment of Friedreich's ataxia?

FDA Response to Question 4:

We agree with the proposed placebo-controlled Analysis Sets A and B.

We have the following recommendation for additional Analysis Sets for the ISS:

- An analysis set that includes all patients in the OLE study (N=149) by duration of treatment for 1, 2, ≥ 3 years, and overall.
- It appears that you have 43 drug-treated patients who completed Part 2 of the study and were enrolled in the OLE that can provide long-term safety beyond 48 weeks (up 2.5 years), and that you propose to analyze in Analysis set D. In addition, it appears that there are 43 placebo patients from Part 2 of the study that enrolled in the OLE and can also provide at least 1 year safety data on omaveloxolone treatment. Therefore, it appears there are 86 unique patients treated with omaveloxolone for at least 1 year. We recommend that you include a safety analysis set of all patients on treatment with at least one year exposure, regardless of their initial double-blind treatment.

We also have the following comments on the remaining proposed Analysis Sets:

- Analysis Set C (includes all drug-treated patients without regard to dose):
  You proposed to include 165 patients in this set, where 103 patients are from Part 1 and 2 of Study 1402, and 62 patients are from OLE. In your response to the information request dated August 9, 2021, you state that 62 patients from the OLE study had been randomized to placebo in the double-blind studies. However, you note that there were 69 patients randomized to placebo in Parts 1 and 2 of the study, which leaves 7 patients unaccounted for; all patients should be accounted for in safety analyses, and any discontinuations from Part 1 and 2 of the study should be clearly tabulated in a dispositions table, with patient IDs including reason for discontinuations. Analysis Set variables should be created in datasets.

- Analysis Set D (includes drug-treated patients that completed Study 1402 Part 2 and enrolled in OLE):
  You propose to include only 43 patients that enrolled in the OLE in the Analysis set. However, there were 51 drug-treated patients in Part 2 of the study, which

leaves 8 patients unaccounted for. As above, all of discontinuations should be tabulated, including reason for discontinuation.

- Analysis Set X (includes 225 patients from Study 1402 Parts 1 and 2 and mitochondrial myopathy study patients regardless of dose):
  We recommend that this analysis set only include drug and placebo-treated patients at the 150/160 mg doses, as the other doses are not relevant for evaluation of safety. However, you should also submit the Clinical Study Report for Study 1403 separately.

Please also refer to the standard Division of Neurology 1 pre-NDA safety requests in Attachment 1. We note that not all of the listed analyses may be appropriate for the FA study population; however, you should conduct that analyses that apply to your study population.

Meeting Discussion:

The sponsor clarified the number of patients in each of the proposed Analysis Sets (see attached slides). The Division acknowledged the clarification and further clarified that the intent of requesting that all subjects be accounted for was not to include them in each analysis subset, but rather to ensure that there were clear disposition tables for each analysis set within the NDA submission, accounting for all subjects and their disposition, including reason for discontinuation, and how the total "n" was achieved for each analysis set. The sponsor agreed to provide this information in the submission.

The sponsor also sought clarification on the additional analysis set requested by the Division that includes all patients in the OLE study (N=149) by duration of treatment for 1, 2, ≥ 3 years, and overall. Rather than "at least 1-year of exposure", the sponsor proposed "at least 48-weeks of continuous exposure" to align with Study 1402 visit schedule. Further, the sponsor proposed summarizing by 48-week exposure intervals (48, 96, ≥144 weeks) instead of 1-year intervals. The Division agreed to the proposal of exposure intervals to be included in the analysis.

Question 5: Method for Addressing Abuse Potential Requirement

5a. Does the Division agree that omaveloxolone does not meet the criteria for abuse potential and therefore, no abuse potential or liability study is required to support the filing of the NDA?

FDA Response to Question 5a:

No, we do not agree. The in vitro binding study (Study # RTA-P-18007) indicates that RTA 408 binds to the benzodiazepine and 5-HT2A receptors. Because activity at these receptors is associated with abuse potential, you will need to characterize the activity of RTA 408 at these receptors. Once these data are obtained, and submitted to the

Agency, a determination can be made as to whether further abuse liability studies are warranted.

Meeting Discussion:

The Agency agrees with the discussion provided by the sponsor, and requested that the sponsor include this discussion in the proposal and rationale for drug scheduling. The location of this proposal in the NDA submission is outlined in the response to question 5b.

5b. Does the Division agree that the proposal to discuss the assessment of abuse potential in the ISS is appropriate?

FDA Response to Question 5b:

The proposal and rationale related to drug scheduling should be placed in Module 1, tab 1.11.4. We recommend that your summary and discussion of all data related to abuse potential and dependence assessment of omaveloxolone be included as a subsection of the Summary of Clinical Safety in Module 2, under tab 2.7.4. This section should have appropriate cross-linkage to relevant study reports and other information in Modules 3, 4, and 5.

Meeting Discussion:

The sponsor agreed and no further discussion was necessary.

Question 6: Proposed Study Data Standardization Plan (SDSP)

Does the Division agree with the Sponsor's specified in the SDSP?

FDA Response to Question 6:

We agree with your plan for electronic data submission formats as specified in the SDSP.

Meeting Discussion: No discussion occurred.

Question 7: Proposed BIMO Datasets

Does the Division agree that datasets from Study 1402 (Part 1, 2 and Extension) will be included in the BIMO datasets and Reviewer's Guide?

FDA Response to Question 7:

Yes, we agree.

Please refer to the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018)[1] and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications (July 2020)[2].

Meeting Discussion: No discussion occurred.

Question 8: Proposed NDA 120-Day Safety Update

Does the Division agree with the proposed 120-day safety update submission during the NDA review?

FDA Response to Question 8:

The proposal appears adequate, given the small amount of additional data expected during this time-frame. Please ensure that any requisite narratives are included as part of the 120-day safety update.

Meeting Discussion: No discussion occurred.

2.2. Clinical Pharmacology

Question 9: Adequacy of Clinical Pharmacology Program
Does the Division have comment on the clinical pharmacology program to support the NDA filing?

FDA Response to Question 9:

On face, the clinical pharmacology program seems adequate for filing. However, we have the following comments for you to consider:

- Please clarify whether the final to-be-marketed formulation (50 mg oral capsules) was used in the completed Phase 2 study (408-C-1402, parts 1 and 2). If not, a PK bridging study may be needed before filing the NDA.

- The risk of QT prolongation associated with oral administration of omaveloxolone was not adequately characterized in previous studies (Study # 408-C-1703 and Study # 408-C-1806). These studies did not include – 1) a dedicated positive

[1] https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332466.pdf
[2] https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf

control (i.e., moxifloxacin) or 2) the dose levels to characterize the QTc at sufficiently high multiples of the clinically relevant exposure (e.g., twice the supratherapeutic dose) to waive the need for a separate positive control (ICH E14 Q&A (R3)). You will need to conduct a thorough QT study. Given the seriousness of the indication, this study may be conducted post-approval if the available data support such a strategy.

- You should submit a clinical pharmacology review aid document with your NDA. Please refer to the attachment at the end of this document, entitled "Clinical Pharmacology Summary Aid".

- We acknowledge your plan to use a PBPK analysis to address the drug-drug interaction effect of CYP3A modulators on omaveloxolone exposure. The adequacy of the PBPK analysis for the intended uses (i.e., in lieu of clinical DDI studies and inform labeling) will be a review issue and depend on overall clinical pharmacology considerations.

- In vitro and clinical data suggested that omaveloxolone is a sensitive CYP3A4 substrate with nonlinear PK. A significant decrease in exposure with CYP3A4 inducers was predicted by your PBPK simulations. Depending on the model adequacy, proposed dosing recommendation with CYP3A4 inducers and available clinical data to support dose adjustment recommendations, you may need to conduct a clinical DDI study with a moderate CYP3A4 inducer.

Regarding your PBPK analysis, we have the following additional comments for your consideration:

- The PBPK model of omaveloxolone should be able to recover the single and multiple-dose PK profiles under different dose levels (including the PK linearity), and steady-state exposure at the therapeutic dose level, in both healthy and patient populations in various exposure conditions.
- The mechanisms involved in the reported nonlinear Cmax should be identified and accounted for in the model, as appropriate.
- The underlying mechanism of the decreased exposure of midazolam (a sensitive CYP3A substrate) and repaglinide (CYP2C8 and CYP3A substrate) reported in the clinical DDI study with omaveloxolone should be identified to support the validity of your PBPK application.
- Fully utilize available in vitro and in vivo PK and DDI data for model development and validation
- Provide risk analysis of model uncertainties in relation to the impact on intended PBPK applications (e.g., items 2-3).
- Provide PBPK model files needed to verify and reproduce results, including workspaces and simulation output files. Provide a summary table to link model files to corresponding results in the PBPK report. Refer to the Guidance for

Industry: Physiologically Based Pharmacokinetic Analyses – Format and Content[3] for the PBPK information to be submitted with your NDA.

We recommend that you include allometry aspects in your population pharmacokinetic analyses. In addition to primary efficacy endpoints, we recommend assessing exposure-response relationships with relevant secondary efficacy endpoints. If the data permit, we recommend inclusion of the placebo data. For population PK and exposure-response analyses, in your NDA submission, please refer to our general expectations for submission of pharmacometric datasets and models[4].

Meeting Discussion:

The sponsor confirmed that the final to-be-marketed formulation was used in the Phase 2 study (408-C-1402, parts 1 and 2). Also, the sponsor acknowledged the need for, and committed to conduct, a dedicated thorough QT study with omaveloxolone, which can be completed post-approval. The sponsor also committed to submit the "Clinical Pharmacology Summary Aid" at the time of NDA submission.

The sponsor acknowledged that the adequacy of the PBPK analysis will be a matter of review, and a dedicated drug-drug interaction study with a moderate CYP3A inducer may be needed post-approval based on the submitted information. The sponsor also acknowledged the non-linear C_{max} of omaveloxolone in the Phase 1 study, which should be accounted for in the PBPK model.

The OCP pharmacometrics reviewer acknowledged the sponsor's responses regarding the population PK analyses and the exposure-response analyses. The reviewer indicated that there are no additional concerns or comments at this time.

2.3. Nonclinical

Question 10: Adequacy of the Nonclinical Program

Does the Division have comment on the adequacy of the completed nonclinical development program to support the NDA?

FDA Response to Question 10:

The nonclinical studies, as described in your briefing package, appear adequate to support an NDA.

Meeting Discussion: No discussion occurred.

[3] https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM531207.pdf
[4] https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/modeldata-format

Question 11: Inclusion and Exclusion of Nonclinical Study Reports

Does the Division agree with the proposed inclusion and exclusion of nonclinical study reports in the NDA?

FDA Response to Question 11:

All nonclinical study reports conducted for omaveloxolone should be submitted to the NDA.

Meeting Discussion:

The Division agreed with the sponsor's proposal to submit reports for all nonclinical studies of omaveloxolone to the NDA but only to provide summaries of those studies relevant to the Friedreich's ataxia indication.

Question 12: Metabolite Profile and Disproportionate Metabolite Proposed Resolution

Does the Division agree with the proposed strategy and rationale for addressing the safety of the disproportionate metabolite observed in human plasma?

FDA Response to Question 12:

Based on the information provided, it appears that metabolite M22 is not formed at sufficient levels in monkey or male rat (information was not provided for female rat). However, they do suggest M22 is formed in the CD-1 mouse at levels similar to those in humans. Therefore, we recommend that you explore the use of CD-1 mouse to qualify metabolite M22 in the appropriate nonclinical studies (ICH M3(R2), January 2010; ICH M3(R2), February 2013). Structural similarity between M22 and other metabolites would not be sufficient to address concerns regarding the potential toxicity of M22.

Because of the seriousness of the indication, nonclinical studies to qualify M22 may be conducted post-approval if the available data support such a strategy.

Meeting Discussion:

The sponsor stated that consideration will be given to conducting additional nonclinical studies to investigate the use of the CD1 mouse to qualify metabolite M22; however, the sponsor requested clarification on the types of studies that would be needed. The Division indicated that studies to qualify a metabolite generally include a chronic (e.g., 26-week) general toxicity study, an embryofetal development study, and a carcinogenicity study. The Division noted that the ongoing 26-week study in TgRas.H2 mice would likely not be adequate to assess the general toxicity of M22, but additional discussion may be warranted.

Question 13: Carcinogenicity Testing

Does the Division agree with the carcinogenicity testing strategy to waive a 2-year carcinogenicity study in rats and conduct the 6-month rasH2 transgenic mouse study, according to the approved protocol, as a post-submission commitment for completion and reporting?

FDA Response to Question 13:

The lack of carcinogenicity studies would not preclude filing of an NDA. However, if the 6-month Tg.rasH2 mouse study is submitted during the review cycle, we cannot commit to completing our review of the study prior to the action date. We have considered the 26-week toxicity study in rat and believe those data indicate a meaningful 2-year carcinogenicity study in rat can be conducted; therefore, the study will be needed for omaveloxolone. However, because of the seriousness of the indication, the 6-month and 2-year carcinogenicity studies may be submitted post-approval if the available data support such a strategy.

Meeting Discussion:

The sponsor requested clarification regarding the need for a 2-year carcinogenicity study in rat considering that the maximum tolerated dose (MTD, 1 mg/kg) would likely results in plasma exposure 20% less than those anticipated at the maximum recommended human dose (MRHD) and that exposures up to approximately 50 times that in humans at the MRHD are anticipated in the 26-week Tg.rasH2 mouse study. The sponsor also noted that there is concern that the MTD may lower with a dosing duration greater than 6 months.

The Division stated that being able to achieve plasma exposures only 20% lower than that expected in humans would still provide a meaningful carcinogenicity study in rat. In addition, an assessment of carcinogenic potential is to be assessed in two species if a meaningful study is feasible in each, which appears to be the case for omaveloxolone. The Division noted that there are no data to address the possibility of a lowering of the MTD with duration of dosing greater than 6 months.
The sponsor stated that a 2-year carcinogenicity study in rat will be conducted as a PMR.

Question 14: Fulfillment of Juvenile Toxicology Program Requirements

Does the Division agree with the adequacy of available data to fulfill the safety juvenile toxicity requirements (b) (4)

FDA Response to Question 14:

No additional nonclinical studies are required (b) (4)

Meeting Discussion: No discussion occurred.

2.4. CMC

Questions 15 and 16: Overall CMC Program and Drug Substance (b) (4)

Question 15: Does the Division have comments on the overall CMC program?

FDA Response to Question 15:

Since the manufacture of omaveloxolone remains the same as presented in the previous meeting package, and only the (b) (4) manufacturing site will be used from now on, the Agency has no additional comments.

Meeting Discussion: No discussion occurred.

Question 16: Does the Division agree with the proposed Drug Substance (b) (4) **approach?**

FDA Response to Question 16:

The proposed Drug Substance (b) (4) approach appears acceptable. A final decision will be made during the NDA review.

Meeting Discussion: No discussion occurred.

Question 17: Omaveloxolone Registration Batches

Does the Division agree with the proposal of which 24 months stability data from three registration batches are sufficient to support 36 months of shelf life for commercial omaveloxolone capsules?

FDA Response to Question 17:

It is acceptable to submit 24 months long-term stability data for three registration batches of the proposed omaveloxolone capsules. We expect the initial NDA to also contain 6-month accelerated stability data for the three registration batches.

Note that the registration batches should be representative of the commercial drug product batches (e.g., formulation, manufacturing process, container closure system).

The drug product expiry is determined at the time of NDA review when the data is evaluated in its totality.

For detailed recommendations regarding the batch selection, testing conditions, etc., refer to ICH Q1A (R2) Guidance "Stability Testing of New Drug Substances and Products."

Meeting Discussion: No discussion occurred.

2.5. Labeling

Question 18: Indication Statement

Does the Division have any preliminary comments on the proposed indication statement for the use of omaveloxolone in Friedreich's ataxia?

FDA Response to Question 18:

The indication statement is a matter of review of your NDA submission.

Meeting Discussion: No discussion occurred.

Question 19: Proposed Risk Management Approach

Does the Division have any preliminary comments on the proposed risk management approach?

FDA Response to Question 19:

At this time, the Agency has insufficient information to provide comments on whether the proposed risk management plan is sufficient. We will determine the need for enhanced risk management activities or a risk evaluation and mitigation strategy (REMS) during the review of your application.

Meeting Discussion: No discussion occurred.

2.6. Administrative

Question 20: Proposed NDA eCTD Content Plan

Does the Division have any comment on the dossier table of contents and proposed location of reports?

FDA Response to Question 20:

Forms 356h and 3397 should be placed in Section 1.1 (Forms). The Proposed eCTD Table of Contents (TOC) found in Appendix 7 contains Form 356h in Section 1.1.2 and Form 3397 in Section 1.1.3. Please refer to the Comprehensive Table of Contents Headings and Hierarchy Section 1.1 Forms for more details.

The FDA agrees with all of the other sections provided in the TOC.

Meeting Discussion: No discussion occurred.

Question 21: Proposed Ancillary Report Location, Datasets, and Format

Does the Division agree with the proposed ancillary reports, datasets, and location in the eCTD structure?

FDA Response to Question 21:

The FDA agrees with the proposed ancillary report and location to be placed in Section 5.3.5.3.

Providing datasets in ADaM standards is acceptable. Please make sure that an FDA-supported ADaMIG version is used. FDA supported ADaMIG versions can be found in the FDA Data Standards Catalog[5].

Meeting Discussion: No discussion occurred.

Question 22: NDA Priority Review Eligibility

Does the Division have preliminary comments on the eligibility of the omaveloxolone NDA for Priority Review?
FDA Response to Question 22:

Priority review designation requests may be submitted with the original NDA. Please refer to the *Guidance for Industry: Expedited Programs for Serious Conditions--Drugs and Biologics*[6].

The final decision regarding priority review designation is a matter of review. Applicants will be informed in writing by Day 60 of the review if the application will receive priority

[5] https://www.fda.gov/media/85137/download
[6] https://www.fda.gov/media/86377/download

review; or by Day 74 of the review for standard review designation. Applications that are not filed do not receive a review designation.

Meeting Discussion: No discussion occurred.

Question 23: Rare Pediatric Disease Designation Eligibility

Does the Division have preliminary comments on the Sponsor's proposal to submit a rare pediatric designation request for omaveloxolone for the treatment of Friedreich's ataxia?

FDA Response to Question 23:

We refer you to "Rare Pediatric Disease: Priority Review Vouchers Guidance for Industry" Section III (beginning on page 3)[7] for information regarding the application process. The Office of Orphan Products Development and the Office of Pediatric Therapeutics review the applications for Rare Pediatric Disease Designation and make the determination to grant or deny the request.

Please note the sequence and timing of the designation process relative to submission of a marketing application required to ensure voucher eligibility.

Meeting Discussion: No discussion occurred.

Question 24: Proposed Covered Studies Regarding Financial Disclosure

Does the Division agree with the proposal to include Financial Disclosures information for Study 1402 (Part 1, Part 2 and Extension) for the NDA submission?

FDA Response to Question 24:

We agree with the proposal to include Financial Disclosures information for Study 1402 (Part 1, Part 2, and Extension) for the NDA submission.

Meeting Discussion: No discussion occurred.

Question 25: Advisory Committee

Does the Division have any preliminary comments on the likelihood of having an Advisory Committee meeting to support omaveloxolone licensure in Friedreich's ataxia?

[7] https://www.fda.gov/media/90014/download

FDA Response to Question 25:

An Agency determination regarding the need for an Advisory Committee meeting will be made after submission and during review of your complete marketing application.

Meeting Discussion: No discussion occurred.

Question 26: Clinical Study Report Inclusion

Does the Division agree with the proposed CSR submission plan?

FDA Response to Question 26:

We agree with the proposed CSR submission plan.

Meeting Discussion: No discussion occurred.

3.0 ADDITIONAL INFORMATION

PROSPECTIVE ASSESSMENTS OF SUICIDAL IDEATION AND BEHAVIOR IN CLINICAL PROTOCOLS

Treatment-emergent suicidal ideation and behavior have been identified as a concern for a number of drugs and drug classes. For example, meta-analyses of clinical trial data for both antiepileptic drugs and antidepressants have demonstrated that these drugs increase the risk of suicidal ideation and behavior. Spontaneous reports have led to similar concerns with other drugs as well, e.g., isotretinoin and other tretinoins, beta blockers, reserpine, smoking cessation drugs, and drugs for weight loss. Because of these concerns, a prospective assessment for suicidal ideation and behavior should be included, when appropriate and feasible, in clinical trials involving all drugs and biological products for neurological indications. These assessments should generally be included in every clinical protocol, at every visit, and in every phase of development, with the exception of single-dose trials in healthy volunteers. These assessments should be conducted whether or not a particular product is known or suspected to be associated with treatment-emergent suicidal ideation and behavior. A sponsor considering the omission of the assessment of suicidal ideation and behavior from a particular clinical protocol should prospectively discuss this omission with the Division of Neurology 1.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. Fast Track Designation will be requested by the sponsor.

- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- We did not have a preliminary discussion on the need for a REMS, other risk management actions or the development of a Formal Communication Plan; however, at this time it is not anticipated that there will be a REMS for this application.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. There are no agreements for late submission of application components.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[8] and Pregnancy and Lactation Labeling Final Rule[9] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.

[8] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[9] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.

- Regulations and related guidance documents.

- A sample tool illustrating the format for Highlights and Contents, and

- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.[10]

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of

[10] http://www.fda.gov/ectd

regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.[11]

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				

[11] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway

(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[12] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[13]. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions,* and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications,* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[14]

[12] https://www.fda.gov/media/84223/download
[13] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and
[14] https://www.fda.gov/media/85061/download

4.0 ISSUES REQUIRING FURTHER DISCUSSION

No issues requiring further discussion were identified.

5.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Fast Track Designation Request	Reata	September 2021

6.0 ATTACHMENTS AND HANDOUTS

Included are attachments 1 and 2, provided by FDA to Reata with FDA's preliminary meeting comments. Also attached are meeting slides provided by Reata that were displayed during the meeting discussion.

44 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

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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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