NDA 216718

NDA APPROVAL

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

Dear Ms. Loewen:

Please refer to your new drug application (NDA) received March 30, 2022, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Skyclarys (omaveloxolone) capsules.

We acknowledge receipt of your major amendments dated July 21, 2022, July 25, 2022, and August 3, 2022, which extended the goal date by three months.

This NDA provides for the use of Skyclarys (omaveloxolone) capsules for the treatment of Friedreich's ataxia in adults and adolescents aged 16 years and older.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Patient Package Insert) as well as annual reportable changes not included in the enclosed labeling. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As.*[2]

The SPL will be accessible via publicly available labeling repositories.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

CARTON AND CONTAINER LABELING

Submit final printed container labeling that is identical to the container labeling submitted on February 17, 2023, as soon as it is available, but no more than 30 days after it is printed. Please submit this labeling electronically according to the guidance for industry *SPL Standard for Content of Labeling Technical Qs & As.* For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 216718**." Approval of this submission by FDA is not required before the labeling is used.

DATING PERIOD

Based on the stability data submitted to date, the expiry dating period for Skyclarys (omaveloxolone) capsules shall be 36 months from the date of manufacture when stored at 20°C to 25°C.

RARE PEDIATRIC DISEASE PRIORITY REVIEW VOUCHER

We also inform you that you have been granted a rare pediatric disease priority review voucher, as provided under section 529 of the FDCA. This priority review voucher (PRV) has been assigned a tracking number, PRV NDA 216718. All correspondences related to this voucher should refer to this tracking number.

This voucher entitles you to designate a single human drug application submitted under section 505(b)(l) of the FDCA or a single biologic application submitted under section 351 of the Public Health Service Act as qualifying for a priority review. Such an application would not have to meet any other requirements for a priority review. The list below describes the sponsor responsibilities and the parameters for using and transferring a rare pediatric disease priority review voucher.

- The sponsor who redeems the priority review voucher must notify FDA of its intent to submit an application with a priority review voucher at least 90 days before submission of the application, and must include the date the sponsor intends to submit the application. This notification should be prominently marked, "Notification of Intent to Submit an Application with a Rare Pediatric Disease Priority Review Voucher."

- This priority review voucher may be transferred, including by sale, by you to another sponsor of a human drug or biologic application. There is no limit on the number of times that the priority review voucher may be transferred, but each person to whom the priority review voucher is transferred must notify FDA of the change in ownership of the voucher not later than 30 days after the transfer. If you retain and redeem this priority review voucher, you should refer to this letter as an official record of the voucher. If the priority review voucher is transferred, the sponsor to whom the priority review voucher has been transferred should

include a copy of this letter (which will be posted on our Web site as are all approval letters) and proof that the priority review voucher was transferred.

- FDA may revoke the priority review voucher if the rare pediatric disease product for which the priority review voucher was awarded is not marketed in the U.S. within 1 year following the date of approval.

- The sponsor of an approved rare pediatric disease product application who is awarded a priority review voucher must submit a report to FDA no later than 5 years after approval that addresses, for each of the first 4 post-approval years:

  - the estimated population in the U.S. suffering from the rare pediatric disease for which the product was approved (both the entire population and the population aged 0 through 18 years),

  - the estimated demand in the U.S. for the product, and

  - the actual amount of product distributed in the U.S.

- You may also review the requirements related to this program by visiting FDA's Rare Pediatric Disease Priority Review Voucher Program web page.[3]

ADVISORY COMMITTEE

Your application for Skyclarys was not referred to an FDA advisory committee because the application did not raise significant safety or efficacy issues that were unexpected in the intended population.

REQUIRED PEDIATRIC ASSESSMENTS

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 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 this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

[3] https://www.fda.gov/industry/developing-products-rare-diseases-conditions/rare-pediatric-disease-rpd-designation-and-voucher-programs

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of adverse maternal, fetal, and infant outcomes resulting from the use of Skyclarys (omaveloxolone) during pregnancy, an unexpected serious risk of the potential presence of Skyclarys (omaveloxolone) in human breast milk resulting in effects on the breastfed infant, an unexpected serious risk of carcinogenicity after exposure to omaveloxolone, and unexpected serious risks of toxicity, including adverse effects on embryofetal development, from metabolite M22.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following studies:

4410-1 Conduct a worldwide descriptive study that collects prospective and retrospective data in women exposed to omaveloxolone during pregnancy and/or lactation to assess risk of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant. Infant outcomes will be assessed through at least the first year of life. The minimum number of patients will be specified in the protocol.

The timetable you submitted on February 10, 2023, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	08/2023
Final Protocol Submission:	06/2024
Interim Report Submission:	04/2025
	04/2026
	04/2027
	04/2028
	04/2029
	04/2030
	04/2031
	04/2032
	04/2033
	04/2034
Study Completion:	04/2035
Final Report Submission:	04/2036

4410-2 Perform a lactation study (milk only) in lactating women who have received therapeutic doses of omaveloxolone using a validated assay to

assess concentrations of omaveloxolone in breast milk and the effects on the breastfed infant as applicable.

The timetable you submitted on February 10, 2023, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 12/2023
Final Protocol Submission: 07/2024
Study Completion: 12/2025
Final Report Submission: 05/2026

4410-3 Conduct a 26-week carcinogenicity study of omaveloxolone in Tg.rasH2 mouse.

The timetable you submitted on February 27, 2023, states that you will conduct this study according to the following schedule:

Study Completion: 07/2022
Final Report Submission: 03/2023

4410-4 Conduct a 2-year carcinogenicity study of omaveloxolone in rat.

The timetable you submitted on February 27, 2023, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 12/2022 (submitted)
Study Completion: 09/2024
Final Report Submission: 09/2025

4410-5 Conduct an embryofetal development study of metabolite M22 in one species.

The timetable you submitted on February 27, 2023, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 04/2023
Final Protocol Submission: 06/2023
Study Completion: 09/2023
Final Report Submission: 12/2023

4410-6 Conduct a 26-week toxicity study of metabolite M22 in rat.

The timetable you submitted on February 27, 2023, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 04/2023
Final Protocol Submission: 06/2023
Study Completion: 05/2024
Final Report Submission: 07/2024

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[4]

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify an unexpected serious risk of QT prolongation or an unexpected serious risk of a drug interaction between a CYP3A4 inducer and omaveloxolone.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following trials:

4410-7 Conduct a clinical trial to assess the risk of QT prolongation with omaveloxolone to exclude mean QTc effects greater than 10 ms.

The timetable you submitted on February 10, 2023, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission: 12/2022 (submitted)
Final Protocol Submission: 05/2023
Trial Completion: 11/2023
Final Report Submission: 06/2024

4410-8 Conduct a clinical drug interaction study to determine the effect of concomitant administration of a moderate CYP3A4 inducer on pharmacokinetics of omaveloxolone in healthy volunteers. Design and conduct the trial in accordance with the 2020 FDA Guidance for Industry entitled “Clinical Drug Interaction Studies - Cytochrome P450 Enzyme-

[4] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

and Transporter-Mediated Drug Interactions"
(https://www.fda.gov/media/134581/download).

The timetable you submitted on February 10, 2023, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission: 02/2023
Final Protocol Submission: 05/2023
Trial Completion: 10/2023
Final Report Submission: 03/2024

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[5]

Submit clinical protocol(s) to your IND 122349 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).

Submission of the protocol(s) for required postmarketing observational studies to your IND is for purposes of administrative tracking only. These studies do not constitute clinical investigations pursuant to 21 CFR 312.3(b) and therefore are not subject to the IND requirements under 21 CFR part 312.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies

[5] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

REQUESTED PHARMACOVIGILANCE

We request that you perform postmarketing pharmacovigilance to better characterize the risks of Skyclarys on cardiac function. Please provide biannual reports of events of worsening cardiac function and/or heart failure in patients taking Skyclarys. Provide narratives of individual cases as well as a synthesized summary and analysis, including incidence in clinical trial cases, postmarketing cases, and total cases. The narratives should include a description of baseline cardiac function and BNP levels, the signs and symptoms that prompted the cardiac evaluation, the management of the event, and patient outcome. Include information about whether Skyclarys was discontinued, either temporarily or permanently, and also provide information on concomitant medications and other potentially confounding factors, time from the first dose of Skyclarys, time from the last dose of Skyclarys, as well as demographics.

We request that you perform postmarketing pharmacovigilance to characterize elevations in liver function tests (ALT, AST, and total bilirubin) and adverse effects on liver function in patients taking Skyclarys. Please provide biannual reports that include baseline and subsequent elevations of ALT or AST greater than 3 times the upper limit of normal (ULN) with evidence of liver dysfunction, and reports of levels greater than 5 times the ULN. Provide narratives of individual cases as well as a synthesized summary and analysis, including incidence in clinical trial cases, postmarketing cases, and total cases. Include information about whether Skyclarys was discontinued either temporarily or permanently, and patient outcome including resolution and time to resolution. Also provide information on concomitant medications and other potentially confounding factors, time from the first dose of Skyclarys, time from the last dose of Skyclarys, as well as demographics.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[6]

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication,

[6] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.

accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[7] Information and Instructions for completing the form can be found at FDA.gov.[8]

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

POST APPROVAL FEEDBACK MEETING

New molecular entities qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

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
Director (Acting)
Office of Neuroscience
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert

[7] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[8] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

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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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