NDA 216660

NDA APPROVAL

Amylyx Pharmaceuticals, Inc.
Attention: Ms. Tammy Sarnelli
Global Head, Regulatory Affairs
43 Thorndike Street
Cambridge, MA 02141

Dear Ms. Sarnelli:

Please refer to your new drug application (NDA) dated October 29, 2021, received October 29, 2021, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Relyvrio (sodium phenylbutyrate and taurursodiol) for oral suspension.

We acknowledge receipt of your submissions dated May 18, 2022, May 24, 2022, and May 27, 2022, which constituted a major amendment to this application, and extended the goal date by three months.

This NDA provides for the use of Relyvrio (sodium phenylbutyrate and taurursodiol) for oral suspension for the treatment of amyotrophic lateral sclerosis (ALS) in adult patients.

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*

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

Technical Qs and As.[2]

The SPL will be accessible via publicly available labeling repositories.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the carton and container labeling submitted on September 27, 2022, and September 28, 2022, as soon as they are available, but no more than 30 days after they are printed. Please submit these 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 216660**." 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 Relyvrio (sodium phenylbutyrate and taurursodiol) for oral suspension shall be 12 months from the date of manufacture when stored at 20°C to 25°C.

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 Federal Food, Drug, and Cosmetic Act (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.

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

[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.

unexpected serious risk of carcinogenicity. 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 this serious risk.

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

4346-1 A carcinogenicity study of AMX0035 (sodium phenylbutyrate and taurursodiol) in rat.

The timetable you submitted on September 27, 2022, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 01/2023
Final Protocol Submission: 04/2023
Study Completion: 06/2025
Final Report Submission: 06/2026

4346-2 A carcinogenicity study of AMX0035 (sodium phenylbutyrate and taurursodiol) in mouse.

The timetable you submitted on September 27, 2022, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 01/2023
Final Protocol Submission: 04/2023
Study Completion: 06/2025
Final Report Submission: 06/2026

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.[3]

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 drug-drug interactions or to identify unexpected serious risks resulting from altered pharmacokinetics of Relyvrio due to hepatic impairment or renal impairment.

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

[3] 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.

4346-3 Conduct an in vivo pharmacokinetic drug interaction study to evaluate the effect of Relyvrio on inhibiting and/or inducing CYP2C8, CYP1A2, CYP2B6, and CYP3A4 enzymes using an appropriate probe substrate for each enzyme. We recommend you evaluate these drug interactions as a single cocktail Drug Drug Interaction (DDI) study. Please refer to the Guidance for Industry Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions (https://www.fda.gov/media/134581/download).

The timetable you submitted on September 26, 2022, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission: 02/2023
Final Protocol Submission: 08/2023
Trial Completion: 02/2024
Final Report Submission: 06/2024

4346-4 Conduct an in vivo drug interaction study to evaluate the effect of OATP1B3 transporter inhibitor on the pharmacokinetics of Relyvrio. Please refer to the Guidance for Industry Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions https://www.fda.gov/media/134581/download).

The timetable you submitted on September 26, 2022, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission: 03/2023
Final Protocol Submission: 08/2023
Trial Completion: 01/2024
Final Report Submission: 06/2024

4346-5 Conduct an in vivo pharmacokinetic drug interaction study to evaluate the effect of Relyvrio as an inhibitor of OAT1, BCRP, and P-gP. We recommend you consider evaluating these drug interactions as a single cocktail DDI study with an appropriate probe substrate of each transporter. Please refer to the Guidance for Industry Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions (https://www.fda.gov/media/134581/download).

The timetable you submitted on September 26, 2022, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission: 04/2023
Final Protocol Submission: 10/2023
Trial Completion: 03/2024
Final Report Submission: 07/2024

4346-6 Conduct a clinical trial to evaluate the effect of hepatic impairment on the exposure of sodium phenylbutyrate and taurursodiol after oral administration of Relyvrio (sodium phenylbutyrate and taurursodiolursodiol) relative to that in subjects with normal hepatic function. Please refer to the Guidance for Industry Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pharmacokinetics-patients-impaired-hepatic-function-study-design-data-analysis-and-impact-dosing-and).

The timetable you submitted on September 26, 2022, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission: 12/2022
Final Protocol Submission: 06/2023
Trial Completion: 03/2024
Final Report Submission: 12/2024

4346-7 Conduct a clinical trial to evaluate the effect of renal impairment on the exposure of sodium phenylbutyrate and taurursodiol after oral administration of Relyvrio (sodium phenylbutyrate and taurursodiol) relative to that in subjects with normal renal function. Please refer to the Guidance for Industry Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing and Labeling (https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM204959.pdf).

The timetable you submitted on September 26, 2022, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission: 11/2022
Final Protocol Submission: 06/2023
Trial Completion: 02/2024
Final Report Submission: 12/2024

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]

Submit clinical protocol(s) to your IND 129563 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).**

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 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.

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.*[5]

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, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[6] Information and Instructions for completing the form can be found at FDA.gov.[7]

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[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.

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

[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf

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

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 Michelle Mathers, Regulatory Project Manager, at michelle.mathers@fda.hhs.gov or at (240) 402-2645.

Sincerely,

{See appended electronic signature page}

Billy Dunn, MD
Director
Office of Neuroscience
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert

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/

WILLIAM H Dunn
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