NDA 211970

ACCELERATED APPROVAL

Sarepta Therapeutics, Inc.
Attention: Patrick O'Malley
Executive Director, Regulatory Affairs
215 First Street, Suite 415
Cambridge, MA 02142

Dear Mr. O'Malley:

Please refer to your new drug application (NDA) dated December 19, 2018, received December 19, 2018, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Vyondys 53 (golodirsen) injection, 50 mg per mL.

We acknowledge receipt of your amendment dated November 27, 2019, which constituted a complete response to our August 19, 2019, action letter.

This new drug application provides for the use of Vyondys 53 (golodirsen) injection for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping.

APPROVAL AND LABELING

We have completed our review of this application, as amended. It is approved under the provisions of accelerated approval regulations (21 CFR 314.500), effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval regulations.

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). Information on submitting SPL files using eLIST may be found

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

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.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the carton and container labeling submitted on April 15, 2019, 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 titled *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (April 2018, Revision 5)*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 211970**." Approval of this submission by FDA is not required before the labeling is used.

EXPIRY DATING PERIOD

An expiration dating period of 24 months is established for the drug product when stored refrigerated (5°C ± 3°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 211970. 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

[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.

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 Vyondys 53 was not referred to an FDA advisory committee because the safety profile of golodirsen is acceptable, the clinical trial design is acceptable, and the findings on the surrogate marker are clear.

[3] https://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/RarePediatricDiseasePriorityVoucherProgram/default.htm

ACCELERATED APPROVAL REQUIREMENTS

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled clinical trials to verify and describe clinical benefit. You are required to conduct such clinical trials with due diligence. If postmarketing clinical trials fail to verify clinical benefit or are not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 314.530, withdraw this approval. We remind you of your postmarketing requirement specified in your submission dated November 27, 2019. This requirement, along with required completion dates, is listed below.

3690-1 In order to verify the clinical benefit of golodirsen, complete Study 4045-301, A Double-Blind, Placebo-Controlled, Multicenter Study With an Open-Label Extension to Evaluate the Efficacy and Safety of SRP-4045 and SRP-4053 in Patients With Duchenne Muscular Dystrophy. The study includes a randomized, double-blind, placebo-controlled period of 96 weeks, and concludes after an open-label extension period to 144 weeks. The primary endpoint will be the 6-minute walk test.

Draft Protocol Submission: 11/2015 (submitted)
Final Protocol Submission: 03/2019 (submitted)
Trial Completion: 04/2024
Final Report Submission: 10/2024

Submit clinical protocols to your IND 119982 for this product. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each requirement in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial.

Submit final reports to this NDA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated "**Subpart H Postmarketing Requirement(s)**."

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.

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 carcinogenicity, unexpected serious risk of immunogenicity, or an unexpected serious risk of QT prolongation on the ECG.

Furthermore, the new pharmacovigilance system that FDA is required to establish 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:

3690-2 A two-year carcinogenicity study of intravenously administered golodirsen in rat.

The timetable you submitted on December 4, 2019, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	12/2019
Final Protocol Submission:	01/2020
Study Completion:	01/2022
Final Report Submission:	08/2022

3690-3 A 26-week carcinogenicity study of golodirsen, administered by a clinically relevant route, in an appropriate transgenic mouse model.

The timetable you submitted on December 4, 2019, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	12/2019
Final Protocol Submission:	01/2020
Study Completion:	07/2020
Final Report Submission:	02/2021

3690-4 Evaluate patient immune responses, including IgM and IgG isotypes to dystrophin, among patients treated with golodirsen in Study 4053-101 of the clinical development program. Test the samples, collected to detect early, peak, and late antibody responses, using fully validated anti-dystrophin assays that detect IgG and IgM antibodies. Test samples that are positive for antibodies to dystrophin for titer. Determine the impact of immune responses on product pharmacokinetics and clinical efficacy and safety.

The timetable you submitted on December 4, 2019, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	05/2017 (submitted)
Study Completion:	10/2019
Final Report Submission:	12/2019

3690-5 Evaluate patient immune responses to golodirsen among patients treated with golodirsen in Study 4053-101 of the clinical development program. Test the samples, collected to detect antibody responses, using a fully validated assay that detects IgG and IgM antibody isotypes. Test samples that are positive for antibodies to golodirsen for titer and neutralizing activity using fully validated assays. Until these assays have been fully validated and reviewed by FDA, sufficient samples should be banked and stored under appropriate conditions. Determine the impact of immune responses on product pharmacokinetics and clinical efficacy and safety.

The timetable you submitted on December 4, 2019, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	05/2017 (submitted)
Study Completion:	10/2019
Bridge Assay Validation Final Report:	12/2019
Neutralizing Antibody Validation Assay Final Report:	07/2020
Final Report Submission:	12/2020

3690-6 Evaluate the immunogenicity of golodirsen-induced truncated dystrophin protein. Assess the immunogenicity risk of any novel epitopes that will be present in the golodirsen-induced truncated dystrophin protein. This can be done in silico or in vitro. If there are novel epitopes that could increase the immunogenicity risk, evaluate the immunogenicity of golodirsen-induced truncated dystrophin protein in the corresponding subjects.

The timetable you submitted on December 4, 2019, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 12/2019
Final Protocol Submission: 02/2020
Epitope Analysis Report Submission: 04/2020
Study Completion: 04/2020
Final Report Submission: 08/2020

3690-7 Submit ECG data from Study 4045-301 to support your request to waive a thorough QT study. If these data do not support a TQT study waiver, you will need to evaluate the effect of golodirsen on the QTc interval in a dedicated study as per the ICH E14 guideline.

The timetable you submitted on December 4, 2019, states that you will conduct this study according to the following schedule:

Study Completion: 04/2024
Final Report Submission: 10/2024

Submit clinical protocol(s) to your IND 119982 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.

ENHANCED PHARMACOVIGILANCE

We request that you perform postmarketing surveillance for serious renal toxicity events and for rhabdomyolysis. Provide expedited reporting of serious renal toxicity events and of rhabdomyolysis, and provide comprehensive summaries and analyses of these events as part of your required postmarketing safety reports [e.g., periodic safety update reports (PSURs)]. In the analysis of each case, provide an assessment of causality, with documentation of risk factors and results of all assessments that support the diagnosis or the causality, along with duration of Vyondys 53 therapy, the time from first Vyondys 53 dose to adverse event onset, the time from last Vyondys 53 dose prior to the event onset, concomitant therapies, treatment given for the event, and outcome. Include a comparison of the rates of renal failure, glomerulonephritis, and rhabdomyolysis to background rates of those events in the general population (overall and stratified by age), as well as background rates (if available) for patients with Duchenne muscular dystrophy (DMD) (overall and stratified by age).

PROMOTIONAL MATERIALS

Under 21 CFR 314.550, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 314.550, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved Prescribing Information (PI)/Medication Guide/Patient Package Insert (as applicable).

Send each submission directly to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotions (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit promotional materials for accelerated approval products electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[4]

REPORTING REQUIREMENTS

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

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at FDA.gov.[5]

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics 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.

[4] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[5] http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm

If you have any questions, contact Fannie Choy, Regulatory Project Manager, by phone or email at (301) 796-2899 or fannie.choy@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Billy Dunn, M.D.
Director (Acting)
Office of Neuroscience
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information

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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