CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

206488Orig1s000

Trade Name:	Exondys 51 Injection, 50 mg per mL
Generic or Proper Name:	eteplirsen
Sponsor:	Sarepta Therapeutics, Inc.
Approval Date:	September 19, 2016
Indication:	For the use of Exondys 51 (eteplirsen) Injection, 50 mg per mL, for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping.

CENTER FOR DRUG EVALUATION AND RESEARCH

206488Orig1s000

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206488Orig1s000

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206488

ACCELERATED APPROVAL

Sarepta Therapeutics, Inc.
Attention: Shamim Ruff, MSc.
Sr. Vice President, Regulatory Affairs and Quality
215 First Street, Suite 415
Cambridge, MA 02142

Dear Ms. Ruff:

Please refer to your New Drug Application (NDA) dated June 26, 2015, received June 26, 2015, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Exondys 51 (eteplirsen) Injection, 50 mg per mL.

We acknowledge receipt of your major amendment dated January 8, 2016, which extended the goal date by three months.

This new drug application provides for the use of Exondys 51 (eteplirsen) Injection, 50 mg per mL, for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping.

APPROVAL & 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 text. 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 http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the carton and immediate container labels submitted on March 28, 2016, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)." Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 206488**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

In addition, we refer to your June 10, 2016, submission in which you commit to implement the carton container label revisions requested in our June 6, 2016, correspondence. Specifically, you agree to remove the reference to the compendial grades from the carton labels at the time of next printing, but no later than 120 days post-approval, and to notify us of this change via submission of a "Changes Being Effected" supplemental application.

PRODUCT QUALITY

Based on evaluation of the stability data provided, an expiration dating period of 18 months is established for eteplirsen injection when stored refrigerated (5°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 206488. 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 at http://www.gpo.gov/fdsys/pkg/PLAW-112publ144/pdf/PLAW-112publ144.pdf1 (see Section 908 of FDASIA on pages 1094-1098 which amends the FD&C Act by adding Section 529). Formal guidance about this program will be published in the future.

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 August 4, 2016. This requirement, along with required completion dates as agreed upon on September 16, 2016, is listed below.

3095-1 In order to verify the clinical benefit of eteplirsen, conduct a 2-year randomized, double-blind, controlled trial of eteplirsen in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping. Patients should be randomized to the approved dosage of eteplirsen (30 mg/kg weekly) or to a dosage that provides significantly higher exposure, e.g., 30 mg/kg daily. The primary endpoint will be the North Star Ambulatory Assessment.

Draft Protocol Submission:	10/2016
Final Protocol Submission:	04/2017
Trial Completion:	11/2020
Final Report Submission:	05/2021

You should allow sufficient time for the Agency to review, provide feedback, and come to concurrence on the protocol prior to initiation of the trial.

Submit clinical protocol to your IND 077429 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, 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 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 or an unexpected serious risk of immunogenicity.

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 this serious risk.

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

3095-2 A two-year carcinogenicity study of intravenously administered eteplirsen in rat.

The timetable you submitted on September 16, 2016, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	12/2016
Final Protocol Submission:	03/2017
Study Completion:	04/2020
Final Report Submission:	06/2020

3095-3 A 26-week carcinogenicity study of eteplirsen, administered by a clinically relevant route, in an appropriate transgenic mouse model.

The timetable you submitted on September 16, 2016, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	10/2016
Final Protocol Submission:	01/2017
Study Completion:	05/2018
Final Report Submission:	06/2018

You should allow sufficient time for the Agency to review, provide feedback, and come to concurrence on these protocols prior to beginning the studies.

3095-4 A study to evaluate:

1. patient immune responses, including IgM and IgG isotypes, to eteplirsen, its induced dystrophin protein, and full length dystrophin;
2. the impact of immune responses on product PK and clinical efficacy and safety.

The assays for antibodies to eteplirsen, the induced dystrophin, and full length dystrophin should be performed with sampling times optimized to detect early, peak, and late antibody responses, and should be fully validated.

3. for subjects whose serum screens positive for antibodies, the samples should be tested for neutralizing activity, to product activity, and/or product uptake. Antibody titer and persistence should be monitored throughout the duration of the study.
4. in patients who seroconvert, antibody levels should be monitored until they return to baseline.
5. for patients developing hypersensitivity responses, assays to evaluate IgE responses including skin testing or RAST assays should be developed and employed.

Until these assays have been fully validated and reviewed by FDA, sufficient samples should be banked and stored under appropriate conditions so as to allow for re-testing if deemed necessary.

The timetable you submitted on September 16, 2016, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	01/2017
Final Protocol Submission:	08/2017
Study Completion:	12/2017
Final Report Submission:	02/2018

Additional guidance for immunogenicity assay development, though more specific for therapeutic protein products, may be found in the draft guidance: “Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Products

http://www.fda.gov/downloads/Drugs/.../Guidances/UCM192750.pdf. You should allow sufficient time for the Agency to review, provide feedback, and come to concurrence on the protocols prior to initiation of the studies.

Submit the protocols to your IND 077429, with a cross-reference letter to this NDA. Submit all final reports 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.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

3095-5 Conduct a 2-year controlled trial in patients who have a confirmed mutation of the DMD gene that is amenable to exon 45 or 53 skipping with a phosphorodiamidate morpholino oligomer (PMO) designed to bind to a regulatory site governing splicing of the corresponding exon. The trial should include at least two well-separated doses of each PMO, with the high dose designed to provide the greatest dystrophin response possible, based upon preliminary dose-finding, with an expectation of acceptable tolerability. The primary objective of this study will be to evaluate the effect of the two PMO doses (combined-active group) compared to control on the North Star Ambulatory Assessment. The secondary objective will be to evaluate dystrophin levels as percent of normal by Western blot, with tissue to be obtained by needle biopsy.

The timetable you submitted on September 16, 2016, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 12/2016
Final Protocol Submission: 04/2017
Trial Completion: 04/2021
Final Report Submission: 10/2021

A double-blind, placebo-controlled trial design should be used, if feasible, as this would be most informative. If it is not feasible to include a placebo group, an untreated concurrent control group may be considered, with appropriate care to reduce bias in outcome assessments given the lack of randomization and blinding. You should allow sufficient time for the Agency to review, provide feedback, and come to concurrence on the protocol prior to initiation of the trial.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

3095-6 Evaluate possible reasons for the upward trend in assay results from drug product stability studies. Initial investigations are expected to focus on any potential degradants that could co-elute with the main peak, re-authentication of the concentration of the reference standard solution, and quality attributes of the IP-HPLC reagents. Identify any other potential causes for the upward trend observed in the drug product stability.

The timetable you submitted on September 16, 2016, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 11/2016
Study Completion: 06/2017
Final Report Submission: 08/2017

If you believe proposed changes to your manufacturing and control procedures are warranted based on the data derived from this study, we request that you submit the final report for this study as a supplement to your approved NDA.

3095-7 Revalidate the suitability in-process (b) (4) used during drug product manufacture with respect to the accuracy of the method and the robustness of the method in terms of (b) (4). Explore additional possible root causes for the bias in the in-process (b) (4) results and the release (b) (4) results that were observed at lot release.

The timetable you submitted on September 16, 2016, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 11/2016
Study Completion: 06/2017
Final Report Submission: 08/2017

If you believe proposed changes to your manufacturing and control procedures are warranted based on the data derived from this study, we request that you submit the final report for this study as a supplement to your approved NDA.

Submit clinical protocols to your IND 077429 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment 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. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled **"Postmarketing Commitment Protocol," "Postmarketing Commitment Final Report," or "Postmarketing Commitment Correspondence."**

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 (301) 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 package insert (PI)/Medication Guide/patient PI (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 (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

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

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.

PDUFA V APPLICANT INTERVIEW

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs under PDUFA V ('the Program'). The PDUFA V Commitment Letter states that these assessments will include interviews with applicants following FDA action on applications reviewed in the Program. For this purpose, first-cycle actions include approvals, complete responses, and withdrawals after filing. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

ERG will contact you to schedule a PDUFA V applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

FDA BENEFIT-RISK FRAMEWORK APPLICANT INTERVIEW

FDA has also contracted with Eastern Research Group, Inc. (ERG) to conduct an assessment of FDA's initial phase implementation of the Benefit-Risk Framework (BRF) in human drug review. A key element of this evaluation includes interviews with applicants following FDA approval of New Molecular Entity (NME) New Drug Applications (NDAs) and original Biologic

License Applications (BLAs). The purpose of the interview is to assess the extent to which the BRF provides applicants with a clear understanding of the reasoning behind FDA's regulatory decisions for NME NDAs and original BLAs.

ERG will contact you to schedule a BRF applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final reports. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to this evaluation.

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}

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JANET WOODCOCK
09/19/2016