

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206488Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # **206488**

SUPPL # N/A

HFD # 120

Trade Name EXONDYS 51

Generic Name Eteplirsen

Applicant Name Sarepta Therapeutics, Inc.

Approval Date September 19, 2016

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

N/A

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

N/A

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

N/A

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

N/A – not a combination product

YES

NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference

to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2

YES

NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND #

YES

!
!
! NO
! Explain:

Investigation #2

IND #

YES

!
!
! NO
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES

Explain:

!

!

! NO

! Explain:

Investigation #2

YES

Explain:

!

!

! NO

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES

NO

If yes, explain:

Name of person completing form: Fannie (Yuet) Choy
Title: Regulatory Project Manager, Division of Neurology Products
Date: September 19, 2016

Name of Office/Division Director signing form: Eric Bastings, M.D.
Title: Deputy Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

YUET L CHOY
09/19/2016

ERIC P BASTINGS
09/19/2016

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 206488 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: EXONDYS 51 Established/Proper Name: eteplirsen Dosage Form: Injection		Applicant: Sarepta Therapeutics, Inc. Agent for Applicant (if applicable):
RPM: Fannie (Yuet) Choy		Division: Division of Neurology Products
NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)	<p><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></p> <ul style="list-style-type: none"> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <p><input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check:</p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>	
❖ Actions		
<ul style="list-style-type: none"> Proposed action User Fee Goal Date is <u>May 26, 2016 (Major Extension)</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> Previous actions <i>(specify type and date for each action taken)</i> 		<input checked="" type="checkbox"/> None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		<input checked="" type="checkbox"/> Received
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: Standard Priority
 Chemical classification (new NDAs only): New Molecular Entity
(confirm chemical classification at time of approval)

- | | |
|---|---|
| <input checked="" type="checkbox"/> Fast Track | <input type="checkbox"/> Rx-to-OTC full switch |
| <input checked="" type="checkbox"/> Rolling Review | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input checked="" type="checkbox"/> Orphan drug designation | <input type="checkbox"/> Direct-to-OTC |
| <input type="checkbox"/> Breakthrough Therapy designation | |

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: [CST SharePoint](#))

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
 Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR
 Submitted in response to a PMC
 Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS: MedGuide
 Communication Plan
 ETASU
 MedGuide w/o REMS
 REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 <i>(approvals only)</i>	<input type="checkbox"/> Yes <input type="checkbox"/> No N/A
❖ Public communications <i>(approvals only)</i>	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input type="checkbox"/> None <input checked="" type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list <i>(approvals only)</i>	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	1 st Cycle Approval: Sept 19, 2016
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) 	<input type="checkbox"/> Included N/A
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input type="checkbox"/> Included N/A
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
<ul style="list-style-type: none"> • Most-recent draft labeling 	<input checked="" type="checkbox"/> Included
❖ Proprietary Name	Acceptable: 10/3/15 Review Memo: 9/30/15
<ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) 	
❖ Labeling reviews (<i>indicate dates of reviews</i>)	RPM: 9/4/15 DMEPA: #1: 10/23/15 #2: 1/11/16 #3: 4/28/16 DMPP/PLT (DRISK): <input checked="" type="checkbox"/> None OPDP: 7/14/16 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Product Quality: 1/21/16 (included in Product Quality Review) Other: <input checked="" type="checkbox"/> None
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting (<i>indicate date of each review</i>)	Filing memo: 9/4/15
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>N/A</u> If PeRC review not necessary, explain: <u>Orphan Designation, Exempt from PREA requirements</u> 	
<ul style="list-style-type: none"> ❖ Breakthrough Therapy Designation 	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> • Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded) 	
<ul style="list-style-type: none"> • CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) 	
<ul style="list-style-type: none"> • CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) (<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site</i>) 	
<ul style="list-style-type: none"> ❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) (<i>do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package</i>) 	
<ul style="list-style-type: none"> ❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes) 	Administrative Reviews
<ul style="list-style-type: none"> ❖ Minutes of Meetings 	
<ul style="list-style-type: none"> • If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> No mtg Meeting #1: 9/18/14 Meeting #2: 5/19/15
<ul style="list-style-type: none"> • EOP2 meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> No mtg Meeting #1: 3/13/13 Meeting #2: 7/23/13
<ul style="list-style-type: none"> • Mid-cycle Communication (<i>indicate date of mtg</i>) 	<input type="checkbox"/> N/A 10/22/15
<ul style="list-style-type: none"> • Late-cycle Meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> N/A 1/11/16
<ul style="list-style-type: none"> • Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>) 	Guidance Mtg: 11/8/13; 11/15/13; 12/19/13; 3/19/14 CMC-EOP2: 10/17/13 CMC-preNDA: 9/3/14

❖ Advisory Committee Meeting(s)	<input type="checkbox"/> No AC meeting
• Date(s) of Meeting(s): April 25, 2016	4/25/16
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input type="checkbox"/> None CDER Director: 7/14/16 ODE1 Director: 7/16/16
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 7/15/16
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 5/17/16 Addendum: 7/15/16
PMR/PMC Development Templates (<i>indicate total number</i>)	7 templates: 9/16/16
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
• Clinical review(s) (<i>indicate date for each review</i>)	Filing Review: 8/25/16 Final Review: 5/9/16, Errata 7/20/16
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	Clinical Addendum: 5/11/26
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>) ⁵	Dystrophin bioassays review (OPQ/OBP) 7/15/16
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input type="checkbox"/> N/A Review memo: 11/23/15
❖ Risk Management <ul style="list-style-type: none"> REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	<input type="checkbox"/> None Review: 5/5/16
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	5/24/16; Amended 9/8/16 OSIS Review: 7/13/16
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None Filing Review: 8/19/15 Final Review: 5/3/16

⁵ For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see "Section 508 Compliant Documents: Process for Regulatory Project Managers" located in the CST electronic repository).

Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None Final Review: 5/6/16
❖ OSI Clinical Pharmacology Inspection Review Summary <i>(include copies of OSI letters)</i>	<input checked="" type="checkbox"/> None Requested
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) <i>(indicate date for each review)</i>	7/5/16
• Supervisory Review(s) <i>(indicate date for each review)</i>	5/25/16
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	Filing Review: 8/4/15 Final Review: 1/22/16
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary <i>(include copies of OSI letters)</i>	<input type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews ⁶	
• Tertiary review <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Secondary review (e.g., Branch Chief) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) <i>(indicate date for each review)</i>	<input type="checkbox"/> None Filing Checklist 8/28/15 Overall Assessment 5/6/16
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team <i>(indicate date of each review)</i>	<input type="checkbox"/> None Stat Review Stability: 1/7/16
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	4/7/16
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ Facilities Review/Inspection	
<input type="checkbox"/> Facilities inspections <i>(action must be taken prior to the re-evaluation date) (only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i>	<input checked="" type="checkbox"/> Acceptable Re-evaluation date: <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable

⁶ Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

Day of Approval Activities	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) 	<input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>) N/A
<ul style="list-style-type: none"> • Finalize 505(b)(2) assessment 	<input type="checkbox"/> Done N/A
❖ For Breakthrough Therapy (BT) Designated drugs: <ul style="list-style-type: none"> • Notify the CDER BT Program Manager 	<input type="checkbox"/> Done N/A (<i>Send email to CDER OND IO</i>)
❖ For products that need to be added to the flush list (generally opioids): Flush List <ul style="list-style-type: none"> • Notify the Division of Online Communications, Office of Communications 	<input type="checkbox"/> Done N/A
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input checked="" type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input checked="" type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input checked="" type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

From: Borio, Luciana
Sent: Wednesday, September 14, 2016 5:30 PM
To: Califf, Robert; Woodcock, Janet; Jenkins, John K; Unger, Ellis
Subject: RE: memo

Dear Dr. Califf,

Thank you for the opportunity to review a draft of your decisional memo on Dr. Unger's appeal related to eteplirsen. Attached is a red-line version with some minor edits (to ensure accuracy) and two embedded comments. I have a few overarching comments that I include here:

- At several points your draft decisional memo erroneously attributes statements, views and conclusions of the SDR Board to me. Consistent with the SMG, the SDR Board recommendation memo reflects the consensus views of the SDR Board, which I communicated to you in my capacity as Chair. In accordance with the SMG, the recommendation memo would have documented any "minority views" expressed by members of the SDR Board. In this instance, there were no dissenting views. As such, contents of the SDR Board memo should be attributed to the SDR Board. The one exception is the section entitled "Considerations from the Acting Chief Scientist" on pages 25-26 of the SDR Board memo, where I speak in my capacity as Acting Chief Scientist.
- Your draft decisional memo erroneously suggests that the SDR Board expressed concerns or views about Dr. Woodcock's scientific conclusions. The SDR Board did not do so; it restricted its review to procedural issues.
- In footnote 23, you indicate that you were troubled by "Dr. Borio's suggestion" (see first bullet point) that Dr. Woodcock might have been motivated by financial considerations in rendering her decision. The "Procedural History" section of the SDR Board memo (pages 9-16) is not intended to set forth suggestions or conclusions by the SDR Board. Rather, it factually recites information gathered by the SDR Board during the course of its investigation of the procedural history of the scientific dispute within CDER. The paragraph you are referencing describes statements made by Dr. Woodcock during the SDR Board's interview of her. Likewise, the other parts of the procedural history simply summarize the administrative record and the views and recollections provided during interviews conducted by the SDR Board with Dr. Unger, the CDER Ombudsman, the review team member (who requested anonymity), and Dr. Woodcock.
- Lastly, your draft decisional memo seems to downplay the significance of the very small amount of dystrophin reported in the eteplirsen NDA (see, e.g., pages 4-5 of your draft decisional memo). In fact, your draft decisional memo never once cites the 0.3% increase in dystrophin production shown by Study 301 (or the 0.93% detected in Studies 201/202). Instead, your draft decisional memo attributes the scientific disagreement to: (1) a lack of consensus on the appropriate threshold for clinical benefit both within CDER and in the scientific literature, and (2) concerns regarding the correlation between dystrophin production and clinical outcomes in Study 201/202. To me, the crux of the disagreement is not whether there is an appropriate threshold, but whether such a

miniscule amount of dystrophin is reasonably likely to predict clinical benefit. Your draft decisional memo does not address that issue. In my view, it is not sufficient to say that no threshold has been established and that, therefore, any increase in dystrophin production is reasonably likely to predict clinical benefit.

I would be glad to discuss any concerns or questions you might have about my comments or suggested edits.

Sincerely,

Luciana Borio, M.D.
Acting Chief Scientist
Food and Drug Administration
White Oak Building 1, Room 3317
10903 New Hampshire Ave.
Silver Spring, MD 20993
Tel. (301)796-4637

From: Califf, Robert
Sent: Tuesday, September 13, 2016 6:40 PM
To: Woodcock, Janet; Jenkins, John K; Unger, Ellis; Borio, Luciana
Subject: memo

Dear Colleagues,

Today I am providing to you a copy of the penultimate draft of my decisional memorandum. Although I believe the contents are self-explanatory, there are a few points that I wish to emphasize.

First, I deeply appreciate the dedication to our shared mission displayed by everyone involved in this process.

Second, I am heartened that our processes and policies worked as they should, and that we have resolved a matter of great complexity in an orderly and transparent manner.

Third, I believe this appeal highlights a critical point: it is precisely in circumstances where the evidentiary basis for our decisions is less strong that judgment and opinion necessarily assume greater prominence. We must redouble our efforts to ensure that our system for evidence generation is as robust as possible.

Finally, it is precisely because of the complexity of the subject matter and the subtle regulatory judgment required that I have come to the following major conclusions:

- All applicable processes and procedures were followed;
- The appealing parties had ample opportunity to present their views; and

- The decision to grant accelerated approval was made following consideration of all relevant scientific evidence.

I elected to review the scientific basis for this regulatory action to ensure that I fully understood the positions of both parties and to evaluate whether an additional expert panel, as recommended in the Scientific Dispute Process Review Board's memorandum, would be needed. I have concluded that although I believe that both views are rational and reflect extraordinary dedication to the topic, there is no basis upon which I should overrule Dr. Woodcock's decision, and that additional external review is not indicated. Furthermore, I have evaluated and am satisfied with the post-marketing requirements that have been developed and understand that the Center for Drug Evaluation and Research will closely monitor the sponsor's compliance with these requirements.

I look forward to continued vigorous discussion and debate as we continue to move this field forward. Thank you for your determination, dedication, and perseverance in serving the patient and healthcare communities.

I would request that you maintain this memorandum in confidence and do not further distribute it until such time as my decision has been made available in final form. If you identify any significant factual errors in this document, please advise me by COB Wednesday, September 14.

Robert M. Califf, MD

Commissioner, Food and Drugs

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

/s/

COLLEEN L LOCICERO

09/20/2016

Filed by Colleen LoCicero in CDER's electronic archive on 9/20/16 on behalf of Luciana Borio, M.D., Acting Chief Scientist, Office of the Commissioner

From: Unger, Ellis
To: [Califf, Robert](#)
Cc: [Woodcock, Janet](#); [Jenkins, John K](#); [Borio, Luciana](#)
Subject: RE: memo
Date: Wednesday, September 14, 2016 6:51:00 PM
Attachments: [2016 Sept 012 R2 Eteplirsen CLEAN unger.doc](#)

Rob,

I have concerns with respect to two areas of your memo, first, whether proper procedures were followed such that all evidence and analyses were reviewed by the Center Director before a decision was rendered, and second, whether this decision will set a general precedent – where accelerated approval could be provided for a rare disease based solely only on the medical and scientific judgment/opinion of the Center Director, as was clearly the case here. I’ve also returned your memo with just a few tracked comments and text.

1. Whether proper procedures were followed; whether all evidence was considered

Having read your draft memo and the August 8, 2016, memorandum of the Scientific Dispute Process Review Board (SDR Board), I do not agree with your conclusions that:

- all applicable processes and procedures were followed;
- the appealing parties had ample opportunity to present their views; and
- the decision to grant accelerated approval was made following consideration of all relevant scientific evidence.

As Director of Office of Drug Evaluation-I, I provide a final level of review and sign-off for various New Drug Applications. Not infrequently, as I write these memoranda, I recognize areas where there is lack of clarity, or I may have concerns about the data or the reviews. In these situations, I find myself doing some last minute “digging” on my own.

Such was the case here. As I was writing my Complete Response memorandum for eteplirsen, I began to recognize the very confusing nature of the immunohistochemistry results from Study 201/202. As stated in the SDR Board’s memo (page 12), Dr. Woodcock “...thought that the review team’s presentation of the IHC data, in particular, was confusing.”

In trying to understand the ambiguities and discrepancies myself, I realized that the original analysis for Study 201/202 showed 13% positive muscle fibers at baseline, whereas a subsequent analysis found only 1.1% positive fibers. (All slides had been analyzed by the same panel of pathologists.) As noted in Figure 2 of my appeal, for the 3 patients whose baseline tissue blocks were analyzed on two occasions, the immunohistochemistry results differed by an order of magnitude. Unfortunately, this disparity had not been addressed adequately by the review team, and had not been described at the April 25, 2016, Advisory Committee meeting.

Because of this lack of reliability, there is simply no way to relate or compare the applicant’s immunohistochemistry results to results from other laboratories reported in the literature.

Importantly, this discrepancy, raising important doubts about all of the immunohistochemistry data, was not known to Dr. Woodcock at the time she filed her approval memo on 7/14/16. (I had not performed these analyses until the evening of 7/15/16.) Her issuance of a decisional memorandum prior to careful consideration of my final review represents a critical deviation from protocol. As pointed out in the SDR memo (page 10): “Dr. Woodcock conceded to the SDR Board that she was leaning toward granting approval in light of the available data as early as 2014,” and page 20: “...at the conclusion of the review, Dr. Unger will not have received a substantive review of his scientific concerns under any formal process at any level.”

It follows, therefore, that:

- All applicable processes and procedures were not followed;
- I did not have the opportunity to present this highly relevant scientific evidence to Dr. Woodcock; and
- Dr. Woodcock’s decision to grant accelerated approval was made prior to consideration of all relevant scientific evidence.

The information showing the applicant’s lack of ability to reproduce its own dystrophin results is critically important because any attempt to identify a quantity of truncated dystrophin that is “reasonably likely to predict clinical benefit” would hinge on the demonstration of a relationship between skeletal muscle dystrophin content and physical function, presumably as accepted by the scientific/medical community. With respect to the immunohistochemistry analyses in Study 201/202, the applicant’s inability to reproduce its own findings raises considerable doubt about any ability to relate and compare the dystrophin values obtained by the applicant to those reported in the literature.

With respect to the Western blot analyses, the applicant stated at the Advisory Committee meeting that their data should not be compared to data from other laboratories (page 14 of my appeal):

“Our validated Western blot method, optimized to detect low levels of dystrophin, is arguably the first dystrophin Western blot to be truly quantitative. This was achieved by use of a 5 point calibration curve on each gel and prespecified loading and exposure limits to avoid signal saturation....Given these significant methodological differences, it is inappropriate to compare our data to literature approximations.” (Source: Official transcript of the meeting; underlining for emphasis.)

In conclusion therefore, there is no way to reach a rational conclusion that the dystrophin detected by the applicant, by either immunohistochemistry or Western blot, is “reasonably likely to predict clinical benefit.” There is no way to correlate a mean increase of 0.3% (median increase = 0.1%) to an effect on physical function, based on clinical experience external to the development program.

Unaware of my final conclusions on this matter, Dr. Woodcock did not rebut the above reasoning. As I noted (and the SDR Board appeared to agree), she provided no cogent rationale for her decision that the barely detectable amount of dystrophin produced is “reasonably likely to predict clinical benefit.” Dr. Woodcock told the SDR Board that her decision was based on her 30 years of experience at FDA and her own “medical/scientific judgment.” (SDR Board Memo, page 16).

I think it will be important for the regulatory record to reflect that there was no scientific basis underlying the conclusion of “reasonably likely” in this case. This was simply a judgment call by Dr. Woodcock. (Dr. Woodcock might have also taken the position that, in this desperate patient population, *any* dystrophin production would suffice as a basis for accelerated approval, but she didn’t state this.)

2. Whether this decision will set a general precedent and degrade the evidence standard for accelerated approval

In your draft Commissioner’s Decisional Memorandum, I fail to see any explicit basis for considering how DMD differs from many other rare diseases, i.e., why DMD/eteplirsen represents a “unique situation that will not set a general precedent for the standard of evidence supporting drug approvals under the accelerated approval pathway.” You note that “...the statute and regulations are clear that each situation must be evaluated on its own merits based on the totality of data and information.”

We all agree that each situation must be evaluated on its own merits; however, I fail to see how DMD differs intrinsically from other rare neurological diseases, e.g., Alexander disease, Canavan disease, Early infantile GM1 gangliosidosis, Krabbe disease, Metachromatic leukodystrophy, Niemann–Pick disease, Pelizaeus–Merzbacher disease, Pompe disease, Sandhoff disease, and X-linked adrenoleukodystrophy. Based on what you have written in your draft memo, it is not clear to me why a standard of any increase in the surrogate endpoint wouldn’t apply for these diseases.

Perhaps granting accelerated approval to drugs that show a mere scintilla of an effect on a surrogate endpoint represents a stroke of brilliance – one that will stimulate investment in the development of drugs for these disorders. But in my opinion, this approach should receive broader public (and FDA) input before being implemented.

Your decision seems to say that the “reasonably likely” standard for accelerated approval need have no quantitative component at all. We all agree that making a reasonable amount of dystrophin would provide a sound basis for accelerated approval. But the amount here – a median value of one part in a thousand that is not perceptibly greater than none – fails to meet the “reasonably likely” test.

I thank you for your consideration in all of this.

Ellis

From: Califf, Robert
Sent: Tuesday, September 13, 2016 6:40 PM
To: Woodcock, Janet; Jenkins, John K; Unger, Ellis; Borio, Luciana
Subject: memo

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/s/

ELLIS F UNGER
09/19/2016

From: [Shamim Ruff](#)
To: [Choy, Fannie \(Yuet\)](#)
Cc: [Matthew Rael](#)
Subject: RE: FDA Proposed PMRs/PMCs: re: NDA 206488 / eteplirsen
Date: Friday, September 16, 2016 11:24:59 AM

Dear Fannie,

We accept FDA's proposal to adjust the PMR/PMC milestones.

Please confirm receipt.

Regards,
Shamim

Shamim Ruff

SVP Regulatory Affairs and Quality

p 617-274-4009 (b) (6)

e sruff@sarepta.com



215 First Street, Cambridge, MA 02142

From: Choy, Fannie (Yuet) [mailto:Fannie.Choy@fda.hhs.gov]
Sent: Friday, September 16, 2016 10:56 AM
To: Shamim Ruff <SRuff@Sarepta.com>
Cc: Matthew Rael <MRael@Sarepta.com>; Choy, Fannie (Yuet) <Fannie.Choy@fda.hhs.gov>
Subject: FDA Proposed PMRs/PMCs: re: NDA 206488 / eteplirsen
Importance: High

Dear Shamim,

Reference is made to your pending NDA 206488 for eteplirsen submitted on June 26, 2015. Attached please find the list of PMRs/PMCs that we have previously communicated to you with the dates moved forward by 2 months. We are proposing to adjust these milestones dates because the Agency has not taken action on your application. Please review and respond by 12 noon today, September 16, 2016, with your agreement to these adjusted dates.

Kindly confirm receipt of email.

Regards,
Fannie

Fannie Choy, RPh.

Regulatory Project Manager
Division of Neurology Products
ODE I/OND/CDER
Food and Drug Administration
10903 New Hampshire Avenue, WO22 Rm. 4215
Silver Spring, MD 20993-0002
301-796-2899 phone
fannie.choy@fda.hhs.gov

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Clinical PMR #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.

Clinical PMR#2

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.

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.

Clinical PMC

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.

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.

Nonclinical PMR #1

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

Draft Protocol Submission: 12/2016

Final Protocol Submission: 03/2017

Study Completion: 04/2020

Final Report Submission: 06/2020

Nonclinical PMR#2

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

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.

CMC PMC#1

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.

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.

CMC PMC #2

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) assay results that were observed at lot release.

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.

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/s/

YUET L CHOY
09/16/2016

From: [Choy, Fannie \(Yuet\)](#)
To: [Shamim Ruff](#)
Cc: [Choy, Fannie \(Yuet\)](#)
Subject: RE: FDA Proposed Labeling Text: NDA 206488 / eteplirsen
Date: Friday, August 05, 2016 11:13:08 AM
Attachments: [FDAEdits-COMLETE_Round6_03Aug16-Eteplirsen_PI_to_Sarepta.docx](#)

Dear Shamim,

Attached please find a clean version of the current eteplirsen PI, dated August 3, 2016. Please note that we always reserve the right to change labeling until we take an action, as we strive to make labeling accurate and informative.

Kindly confirm receipt of email and attachment.

-
Regards,
Fannie

Fannie Choy, RPh.
Regulatory Project Manager
Division of Neurology Products

From: Shamim Ruff [<mailto:SRuff@Sarepta.com>]
Sent: Tuesday, August 02, 2016 1:53 PM
To: Choy, Fannie (Yuet)
Subject: RE: FDA Proposed Labeling Text: NDA 206488 / eteplirsen

Dear Fannie,

We accept your latest edits to include the median value. Can you please confirm that the USPI is now final and provide us with a "clean" version at your earliest convenience.

Please confirm receipt.

Regards,
Shamim

Shamim Ruff
SVP Regulatory Affairs and Quality
p 617-274-4009 (b) (6)
e sruff@sarepta.com



215 First Street, Cambridge, MA 02142

From: Choy, Fannie (Yuet) [<mailto:Fannie.Choy@fda.hhs.gov>]
Sent: Tuesday, August 02, 2016 11:15 AM
To: Shamim Ruff <SRuff@Sarepta.com>
Cc: Choy, Fannie (Yuet) <Fannie.Choy@fda.hhs.gov>
Subject: RE: FDA Proposed Labeling Text: NDA 206488 / eteplirsen

Dear Shamim,

Reference is made to your pending NDA 206488 for eteplirsen submitted on June 26, 2015, and to your email dated July 29, 2016 (attached below).

In response to your July 29, 2016 email regarding eteplirsen labeling, please note that we always reserve the right to change labeling until we take an action, as we strive to make labeling accurate and informative.

With respect to the specific issue at hand (inclusion of the median value for dystrophin), please note that the dystrophin data are not normally distributed; they are skewed. Thus, the median provides a better representation than the mean in helping to predict what patients might expect, and we believe this is critical information for prescribers and patients.

Regards,
Fannie

Fannie Choy, RPh.
Regulatory Project Manager
Division of Neurology Products

From: Shamim Ruff [<mailto:SRuff@Sarepta.com>]
Sent: Friday, July 29, 2016 3:34 PM
To: Choy, Fannie (Yuet)
Cc: Shamim Ruff
Subject: RE: FDA Proposed Labeling Text: NDA 206488 / eteplirsen

Dear Fannie

We were somewhat surprised to receive this latest set of comments from the Division given that we already had quite a number of requests on the label, all of which were accepted by us. We have reviewed the latest set of comments and accept all of them except the following two:

- Section 12.2: We believe it is redundant to include the median value for dystrophin as Table 2 in section 14 includes the dystrophin values from all 12 patients.
- Section 14: As above, we also believe it is redundant to include the median value for dystrophin as Table 2 includes the dystrophin values from all 12 patients.

Please note that we are happy to have a telephone call early next week (Monday or Tuesday) if we need to discuss otherwise please confirm that this is now the final version of the USPI.

Regards,
Shamim

Shamim Ruff

SVP Regulatory Affairs and Quality

p 617-274-4009 (b) (6)

e sruff@sarepta.com



215 First Street, Cambridge, MA 02142

From: Choy, Fannie (Yuet) [<mailto:Fannie.Choy@fda.hhs.gov>]

Sent: Thursday, July 28, 2016 5:27 PM

To: Shamim Ruff <SRuff@Sarepta.com>

Cc: Choy, Fannie (Yuet) <Fannie.Choy@fda.hhs.gov>

Subject: FDA Proposed Labeling Text: NDA 206488 / eteplirsen

Dear Shamim,

Attached please find the FDA proposed labeling text for package insert (PI) for your pending application: NDA 206488 / eteplirsen submitted on June 26, 2015. The base document is the firm's version dated July 12, 2016 with FDA proposed changes identified via track changes.

We have incorporated the proposed edits after additional review of the PI. Please review and provide any edits as tracked changes using our proposed text as the base.

-

Kindly confirm receipt of email.

Regards,
Fannie

Fannie Choy, RPh.

Regulatory Project Manager

Division of Neurology Products

ODE I/OND/CDER

Food and Drug Administration

10903 New Hampshire Avenue, WO22 Rm. 4215

Silver Spring, MD 20993-0002

301-796-2899 phone

fannie.choy@fda.hhs.gov

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11 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

YUET L CHOY
09/16/2016

From: [Shamim Ruff](#)
To: [Choy, Fannie \(Yuet\)](#)
Subject: Re: FDA Proposed PMR/PMC: re: NDA 206488 / eteplirsen - Revised Dates
Date: Friday, July 15, 2016 9:24:50 PM

Dear Fannie

We accept the revised dates.

Regards
Shamim

On Jul 15, 2016, at 6:53 PM, Choy, Fannie (Yuet) <Fannie.Choy@fda.hhs.gov> wrote:

Dear Shamim,

In order to allow sufficient time for FDA feedback/discussions, we suggest allowing 6 months to come to agreement with the Agency. Below are the FDA proposed dates. Please review and let us know the dates are acceptable.

PMR:

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

Draft Protocol Submission:	08/2016
Final Protocol Submission:	12/2016 02/2017 (allowing 4 6 months for FDA feedback/discussions)
Trial Completion:	07/2020 09/2020
Final Report Submission:	01/2021 03/2021

Regards,
Fannie

Fannie Choy, RPh.
Regulatory Project Manager
Division of Neurology Products

From: Shamim Ruff [<mailto:SRuff@Sarepta.com>]
Sent: Friday, July 15, 2016 12:12 AM

To: Choy, Fannie (Yuet)
Subject: RE: FDA Proposed PMR/PMC: re: NDA 206488 / eteplirsen - Revised Dates

Dear Fannie,

As per FDA's request, below are revised dates to allow time for Agency review. Please confirm if these updated dates are acceptable to FDA.

Draft Protocol Submission: **08/2016**
Final Protocol Submission: **12/2016 (allowing 4 months for FDA feedback/discussions)**
Trial Completion: **07/2020**
Final Report Submission: **01/2021**

Regards,
Shamim

From: Choy, Fannie (Yuet) [<mailto:Fannie.Choy@fda.hhs.gov>]
Sent: Thursday, July 14, 2016 6:11 PM
To: Shamim Ruff <SRuff@Sarepta.com>
Cc: Choy, Fannie (Yuet) <Fannie.Choy@fda.hhs.gov>
Subject: RE: FDA Proposed PMR/PMC: re: NDA 206488 / eteplirsen - Dates included
Importance: High

Dear Shamim,

Please see the updated clinical PMR below (text added is underlined). That may affect your proposed dates. We ask that you review the dates and adjust accordingly. Please let me know if you have any questions.

PMR:

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

Draft Protocol Submission: **08/2016**
Final Protocol Submission: **11/2016**
Trial Completion: **06/2020**

Final Report Submission:

12/2020

Regards,
Fannie

Fannie Choy, RPh.
Regulatory Project Manager
Division of Neurology Products

From: Shamim Ruff [<mailto:SRuff@Sarepta.com>]
Sent: Thursday, July 14, 2016 1:04 PM
To: Choy, Fannie (Yuet)
Cc: Shamim Ruff
Subject: FW: FDA Proposed PMR/PMC: re: NDA 206488 / eteplirsen - Dates included

Dear Fannie,

Please find below, in red, the dates requested for the PMR and PMC. Let me know if you have any questions.

Please confirm receipt.

Regards,
Shamim

Shamim Ruff
SVP Regulatory Affairs and Quality
p 617-274-4009 (b) (6)
e sruff@sarepta.com

[<image001.jpg>](#)
215 First Street, Cambridge, MA 02142

From: Choy, Fannie (Yuet) [<mailto:Fannie.Choy@fda.hhs.gov>]
Sent: Wednesday, July 13, 2016 5:32 PM
To: Shamim Ruff <SRuff@Sarepta.com>
Cc: Choy, Fannie (Yuet) <Fannie.Choy@fda.hhs.gov>
Subject: FDA Proposed PMR/PMC: re: NDA 206488 / eteplirsen

Dear Shamim,

Please see below for the FDA proposed clinical postmarketing requirement (PMR) and postmarketing commitment (PMC) for your pending NDA 206488 / eteplirsen. We request that you propose dates for draft protocol submission, final protocol submission, trial completion, and final report submission.

PMR:

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: **08/2016**
Final Protocol Submission: **11/2016**
Trial Completion: **06/2020**
Final Report Submission: **12/2020**

PMC:

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 study 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. 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 study.

Draft Protocol Submission: **10/2016**
Final Protocol Submission: **02/2017 (allowing 4 months for FDA feedback/discussions)**
Trial Completion: **02/2021**
Final Report Submission: **08/2021**

-
Kindly confirm receipt of email.

Regards,
Fannie

Fannie Choy, RPh.
Regulatory Project Manager
Division of Neurology Products
ODE I/OND/CDER
Food and Drug Administration
10903 New Hampshire Avenue, WO22 Rm. 4215
Silver Spring, MD 20993-0002
301-796-2899 phone
fannie.choy@fda.hhs.gov

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From: [Shamim Ruff](#)
To: [Choy, Fannie \(Yuet\)](#)
Cc: [Shamim Ruff](#)
Subject: RE: Proposed date for draft protocol submission (nonclinical): re: NDA 206488 - Revised Dates To Allow For SPAs
Date: Friday, July 15, 2016 12:19:40 AM

Dear Fannie,

As requested, please find below revised dates allowing for the SPA process:

PMRs for eteplirsen NDA 206488

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

Draft Protocol Submission: 10/2016

Final Protocol Submission: 01/2017 – 3 months to allow for the SPA process

Study Completion: 02/2020

Final Report Submission: 04/2020

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

Draft Protocol Submission: 08/2016

Final Protocol Submission: 11/2016 - 3 months to allow for the SPA process

Study Completion: 03/2018

Final Report Submission: 04/2018

Please let me know if the revised dates are acceptable to FDA.

Regards,
Shamim

From: Choy, Fannie (Yuet) [mailto:Fannie.Choy@fda.hhs.gov]
Sent: Thursday, July 14, 2016 6:00 PM
To: Shamim Ruff <SRuff@Sarepta.com>
Cc: Choy, Fannie (Yuet) <Fannie.Choy@fda.hhs.gov>
Subject: RE: Proposed date for draft protocol submission (nonclinical): re: NDA 206488 - dates as requested
Importance: High

Dear Shamim,

The proposed goal dates for submission of the carcinogenicity study protocols do not allow sufficient time for us to review and provide feedback, which would be conducted under SPAs. If you intend to submit SPAs for the protocols, we ask that you adjust your milestone dates to allow for the 45-day

protocol review period.

Please let me know if you have any questions.

Regards,
Fannie

Fannie Choy, RPh.
Regulatory Project Manager
Division of Neurology Products

From: Shamim Ruff [<mailto:SRuff@Sarepta.com>]
Sent: Thursday, July 14, 2016 11:03 AM
To: Choy, Fannie (Yuet)
Cc: Shamim Ruff
Subject: RE: Proposed date for draft protocol submission (nonclinical): re: NDA 206488 - dates as requested

Dear Fannie,

The dates requested for the 2 studies are in **red** below.

Please confirm receipt.

Regards,
Shamim

From: Choy, Fannie (Yuet) [<mailto:Fannie.Choy@fda.hhs.gov>]
Sent: Wednesday, July 13, 2016 5:57 PM
To: Shamim Ruff <SRuff@Sarepta.com>
Cc: Choy, Fannie (Yuet) <Fannie.Choy@fda.hhs.gov>
Subject: Proposed date for draft protocol submission (nonclinical): re: NDA 206488

Dear Shamim,

Reference is made to your pending NDA 206488 for eteplirsen submitted on June 26, 2015. Below are the nonclinical PMRs that we have previously communicated to you and the timetable you submitted on June 27, 2016, states that you will conduct the studies according to the following schedule. We ask that you propose a Draft protocol submission milestone date for the nonclinical protocols. We strongly recommend that you wait for our feedback on the draft protocols before initiating the studies.

-

[PMRs for eteplirsen NDA 206488](#)

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

Draft Protocol Submission: 10/2016
Final Protocol Submission: 10/2016
Study Completion: 11/2019
Final Report Submission: 12/2019

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

Draft Protocol Submission: 08/2016
Final Protocol Submission: 08/2016
Study Completion: 12/2017
Final Report Submission: 01/2018

-
Kindly confirm receipt of email.

Regards,
Fannie

Fannie Choy, RPh.
Regulatory Project Manager
Division of Neurology Products
ODE I/OND/CDER
Food and Drug Administration
10903 New Hampshire Avenue, WO22 Rm. 4215
Silver Spring, MD 20993-0002
301-796-2899 phone
fannie.choy@fda.hhs.gov

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/s/

YUET L CHOY

07/19/2016

w/ concurrence:

Eric Bastings, MD, DNP Deputy Director

Lois Freed, PhD, DNP Supervisory Pharmacologist



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20903

Subject: Agreement to utilize FDA Staff Manual Guide 9010.1 for internal appeal related to NDA 206488, eteplirsen injection

Date: July 16, 2016

From: Virginia L. Behr
Ombudsman, FDA Center for Drug Evaluation and Research (CDER)

To: Matt Warren, Director, Office of Scientific Integrity, Office of the Commissioner
NDA 206488 administrative file

Summary: This memorandum requests that you hear an appeal under Staff Manual Guide (SMG) 9010.1 *Scientific Dispute Resolution at FDA*. In my role as the CDER Ombudsman, I serve as an advisor to CDER staff regarding dispute resolution processes. Review officials within CDER's Office of New Drugs (OND) sought my assistance in determining the most appropriate dispute resolution pathway to resolve differences of opinion concerning the official action to be taken on NDA 206488. After thorough analysis of the available dispute resolution processes, my conclusion is that SMG 9010.1 is the most appropriate process for resolving the dispute. The involved parties agree with my recommendation and have waived rights to alternate CDER dispute resolution processes.

Background: On June 26, 2015, Sarepta Therapeutics submitted NDA 206488, eteplirsen 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 51 skipping. In CDER, the appropriate Office of Drug Evaluation (ODE) Director – in this case, Ellis Unger, MD, ODE I Director – has the delegated authority for action on NDAs with a new molecular entity. Dr. Unger's final memo dated July 16, 2016, asserts his position that this NDA should receive a complete response letter (i.e., eteplirsen cannot be approved for marketing at this time) because the amount of dystrophin (surrogate endpoint) produced by eteplirsen administration is not reasonably likely to predict a clinical benefit. John Jenkins, MD, OND Director, agrees with Dr. Unger's final conclusions. Janet Woodcock, MD, CDER Director, disagrees with Dr. Unger's final conclusions and issued her final memo dated July 14, 2016, stating her intention to approve the NDA and overrule Dr. Unger's decision. Dr. Unger plans to formally appeal Dr. Woodcock's decision.

Applicable Policies and Procedures: CDER's Manual of Policies and Procedures (MAPP 4151.1) *Scientific / Regulatory Dispute Resolution for Individuals Within a Management Chain* details how a CDER employee whose position on an issue does not align with a higher official in their management chain may submit a formal appeal. The appeal is submitted up the supervisory chain of command, potentially up to the Center Director. In this case, the chain of command is ODE I Director → OND Director → CDER Director.

Because this dispute is between the ODE I Director and the CDER Director, the process outlined in MAPP 4151.1 does not apply. Therefore, one may refer to MAPP 4151.2 *Resolution of Differing Professional Opinions: Review by Ad Hoc Panel and CDER Director* to appeal. CDER MAPP

4151.2 describes a formal process by which individuals in this situation can ensure that their views are heard. These individuals are given an opportunity to request a review of the dispute by the Center Director and an Ad Hoc panel. CDER MAPP 4151.2 “should be used only if an individual expects that an Agency action, or inaction, will have a significantly negative public health impact and 1) the mechanisms detailed in CDER MAPP 4151.1 have been utilized to their full extent, i.e., up to the highest management official or 2) are unlikely to lead to a timely resolution.” The difference of opinion between Drs. Unger and Woodcock could be considered to meet the criteria for filing an appeal under MAPP 4151.2 because the drug indication sought is one for a serious and life-threatening disease that has limited treatment options.

I question the utility of using MAPP 4151.2 in this dispute for two reasons: 1) the CDER Director has already fully evaluated the issues and is one of the parties involved in the dispute, and 2) utilizing this MAPP could potentially extend this already lengthy NDA action another 50 business days. Further appeal beyond MAPP 4151.2 follows the Agency SMG 9010.1 *Scientific Dispute Resolution at FDA* which is handled by FDA’s Office of the Commissioner.

Agreement on Appeal Process: I asked Drs. Unger and Woodcock their opinion about waiving the use of MAPP 4151.2 and allowing the appeal to be heard under SMG 9010.1. I received written affirmation from Dr. Unger via email on July 8, 2016 and verbal agreement from Dr. Woodcock on that same date. Therefore, the disputing parties agree to have Dr. Unger’s appeal submitted to FDA’s Office of the Commissioner under SMG 9010.1 *Scientific Dispute Resolution at FDA*. Their agreement is indicated by their signatures below.

Ellis F.
X Unger -S

Digitally signed by Ellis F. Unger -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Ellis F. Unger -
S,
0.9.2342.19200300.100.1.1=1300127434
Date: 2016.07.16 15:00:05 -04'00'

Ellis Unger, MD
Office of Drug Evaluation 1 Director

Janet
X Woodcock -S

Digitally signed by Janet Woodcock -S
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
cn=Janet Woodcock -S,
0.9.2342.19200300.100.1.1=20000920
18
Date: 2016.07.18 08:56:26 -04'00'

Janet Woodcock, MD
Center for Drug Evaluation and Research Dire...

cc:

Matt Warren, Director, Office of Scientific Integrity, Office of the Commissioner
Elizabeth Dickinson, Director, Office of Chief Counsel
Janet Woodcock, CDER Director
John Jenkins, Director, Office of New Drugs
Ellis Unger, Director, Office of Drug Evaluation 1
Administrative file for NDA 206488

NDA 206488

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

/s/

VIRGINIA L BEHR
07/18/2016

From: [Woodcock, Janet](#)
To: [Choy, Fannie \(Yuet\)](#)
Subject: FW: URGENT: Follow Up From Telecon This Morning
Date: Friday, June 03, 2016 5:50:23 PM
Attachments: [PROMOVI Dystrophin Assay June 2016 SR.pptx](#)
Importance: High

This was the communication we got from the company. I had sent it around this AM. jw

From: Shamim Ruff [mailto:SRuff@Sarepta.com]
Sent: Thursday, June 02, 2016 6:17 PM
To: Woodcock, Janet; Moscicki, Richard
Cc: Ed Kaye
Subject: URGENT: Follow Up From Telecon This Morning
Importance: High

Dear Dr. Woodcock and Dr Moscicki

Thank you for the discussion this morning. Based on our conversation, if we reduce the dystrophin procedures down to the bare essentials, we could perform the analyses by the end of June; this is assuming the process goes perfectly the first time, without any delays or repeats. We have discussed with our team FDA's request to expedite the dystrophin analysis. In order to meet this request, we need FDA to agree to the following conditions:

1. **We must start the process by June 6, 2016.** There is no room for flexibility with this date due to our dire financial constraints as a result of the ongoing delays.
2. **Dr. Rao will be an observer/advisor throughout the whole process** (3-4 weeks during June in (b) (4) Oregon) since he is the only FDA representative with the requisite knowledge, expertise and familiarity with the eteplirsen dystrophin analyses/protocol.
3. Dystrophin assays will be conducted using an adapted, pre-defined protocol based on the Week 180 methodology, e.g. no blinding.
4. A different "normal" control to Week 180 will be used due to lack of availability of previous/Week 180 normal control tissue.
5. Non-GLP facility - the assays will be performed at the Sarepta Corvallis site in Oregon by trained Sarepta personnel. As discussed, our Corvallis site is in the process of being closed down so will not be

in an ideal state although the lab is still functional.

Deliverables:

- Success is defined as demonstration of an increase in dystrophin using Western Blot assay.
- FDA will confirm – by June 3, **in writing**, that **Accelerated Approval will be granted by the end of June when an increase in dystrophin is demonstrated based on the assumptions above.**
- Labeling discussions and post-marketing commitments to be conducted concurrently and completed by the end of June or sooner. Any delay, for any reason, past June will significantly impact our ability to continue the ongoing eteplirsen studies (202, 203, 204, PROMOVI).

Regards,

Shamim

From: Shamim Ruff <SRuff@Sarepta.com>

Date: June 1, 2016 at 9:08:37 PM PDT

To: "janet.woodcock@fda.hhs.gov" <janet.woodcock@fda.hhs.gov>, "Rich Moscicki (richard.moscicki@fda.hhs.gov)" <richard.moscicki@fda.hhs.gov>

Cc: Ed Kaye <EKaye@Sarepta.com>

Subject: FW: Request Below From DNP - URGENT Tcon Request

Dear Dr Woodcock and Dr Moscicki

Dr Kaye and I would like to request an urgent telephone call with you both to discuss the Division's request for additional dystrophin data.

Please see below a request for additional dystrophin data from the ongoing PROMOVI study. We want to emphasize that we cannot meet their request in a timely manner. Please note that even if a protocol amendment is not required, it would take us several months to analyze the PROMOVI samples.

Regards,
Shamim

Shamim Ruff

SVP Regulatory Affairs and Quality

p 617-274-4009 (b) (6)

e sruff@sarepta.com

[<image001.jpg>](#)

215 First Street, Cambridge, MA 02142

From: Choy, Fannie (Yuet) [<mailto:Fannie.Choy@fda.hhs.gov>]

Sent: Wednesday, June 01, 2016 10:54 AM

To: Shamim Ruff <SRuff@Sarepta.com>

Cc: Matthew Rael <MRael@Sarepta.com>; Choy, Fannie (Yuet) <Fannie.Choy@fda.hhs.gov>

Subject: FDA Information: re: NDA 206488 / eteplirsen

Importance: High

Dear Shamim:

We refer to NDA 206488 for eteplirsen submitted on June 26, 2015.

As you know, we were unable to complete our review by the PDUFA date of May 26, but we are committed to completing our review process in a timely manner. A critical component of our ongoing review is whether there is substantial evidence that eteplirsen increases the production of dystrophin, as such a finding could potentially support an accelerated approval. As you know, the dystrophin biomarker data from Study 201/202 include only two pre/post biopsy samples from boys originally randomized to Study 201, and these samples, and all but one of the samples from external control boys, were obtained from a different muscle group. On May 5, you responded to our request for information about completed biopsies from the ongoing Promovi trial. You reported that baseline biopsies have been obtained from 62 boys in the eteplirsen-treated arm and that 10 boys each have undergone a biopsy following 24 and 48 weeks of eteplirsen treatment. Analysis of the data for immunohistochemistry and Western blotting from these additional biopsies would substantially enhance our assessment of whether eteplirsen treatment leads to dystrophin production. You suggested that a protocol amendment would require 3-6 months, because of the time needed to amend the protocol, distribute it to the sites, and gain IRB approvals. We are eager to work with you to explore ways we can collaborate to expedite the timeline for making these data available for review and will do all we can to assist you in this effort. We would like to schedule a teleconference with you in the next day or two to explore the most efficient options to obtain these

analyses.

Please confirm receipt of email.

Regards,
Fannie

Fannie Choy, RPh.
Regulatory Project Manager
Division of Neurology Products
ODE I/OND/CDER
Food and Drug Administration
10903 New Hampshire Avenue, WO22 Rm. 4215
Silver Spring, MD 20993-0002
301-796-2899 phone
fannie.choy@fda.hhs.gov

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/s/

YUET L CHOY
06/30/2016

From: [Shamim Ruff](#)
To: [Choy, Fannie \(Yuet\)](#)
Cc: [Matthew Rael](#); [Shamim Ruff](#)
Subject: RE: FDA comments: re: NDA 206488
Date: Thursday, June 23, 2016 5:42:01 PM

Dear Fannie,

Sarepta accepts FDA's recommendation and will perform the "one sample permutation t test (Good, P. 2000. Permutation Tests) for the primary analysis".

Regards,
Shamim

Shamim Ruff

SVP Regulatory Affairs and Quality
p 617-274-4009 (b) (6)
e sruff@sarepta.com



215 First Street, Cambridge, MA 02142

From: Choy, Fannie (Yuet) [mailto:Fannie.Choy@fda.hhs.gov]
Sent: Thursday, June 23, 2016 4:26 PM
To: Shamim Ruff <SRuff@Sarepta.com>
Cc: Matthew Rael <MRael@Sarepta.com>; Choy, Fannie (Yuet) <Fannie.Choy@fda.hhs.gov>
Subject: FDA comments: re: NDA 206488
Importance: High

Dear Shamim,

We refer to NDA 206488 for eteplirsen submitted on June 26, 2015. We also refer to the final Western Blot Protocol for Study 4658-301 dated June 17, 2016. The Division has the following comment regarding the Statistical Analysis Plan.

We have concern with the proposed primary analysis that uses a normality test for choosing the primary test statistic, as the normality test is most likely underpowered with small sample size. That is, the normality test cannot determine whether change from baseline in dystrophin is normally distributed or not. We suggest that you consider one sample permutation t test (Good, P. 2000. Permutation Tests) for the primary analysis. The one sample permutation t test can be performed using a R function, `onetPermutation()`.

Kindly confirm receipt of email.

Regards,

Fannie

Fannie Choy, RPh.

Regulatory Project Manager

Division of Neurology Products

ODE I/OND/CDER

Food and Drug Administration

10903 New Hampshire Avenue, WO22 Rm. 4215

Silver Spring, MD 20993-0002

301-796-2899 phone

fannie.choy@fda.hhs.gov

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/s/

YUET L CHOY

06/24/2016

with concurrence: Billy Dunn, MD, DNP Division Director

Kelley, Laurie

From: Kelley, Laurie
Sent: Friday, June 10, 2016 8:08 PM
To: Shamim Ruff
Cc: Choy, Fannie (Yuet); Matthew Rael; Ware, Jacqueline H; Kelley, Laurie
Subject: RE: RE Urgent Request For Teleconference with Dr Ash Rao on 6 June

Shamim

We refer to NDA 206488 for eteplirsen. We also refer to the June 6, 2016, teleconference held between Sarepta and the FDA. Below is our record of that teleconference.

1. Sarepta agreed to provide the blinding procedure and updated western blot protocol as soon as possible for FDA review.
2. Sarepta will confirm the workflow and timeline when Sarepta will run the samples using Western blot and start preparing data tables. FDA requests confirmation that June 20-24 are the specific days when Sarepta will run the gels and perform quantitation.
3. Normal muscle tissue control: FDA agreed that the "NC2" control can be used in this study as the normal reference, but explained that it was important to compare the NC2 sample to several other randomly selected normal muscle samples to confirm that the dystrophin level in NC2 was generally similar. Sarepta is in the process of determining how many other normal muscle samples can be obtained, and will inform FDA shortly. Depending on the number of other normal muscle samples that it is possible for Sarepta to obtain, additional discussions may be needed.

POST-MEETING NOTE: Sarepta responded to FDA on June 8, 2016, that control biopsy blocks are available from Nationwide Children's Hospital (b) (4), and that Sarepta will screen between 5 to 7 biopsies from each center. This proposal is acceptable to FDA.

4. DMD-negative control tissue: FDA agrees that the DMD control sample used for dilution of calibration curves and for negative control lanes can be derived from screening up to 10 samples for dystrophin by Western blot, and selecting the samples with the lowest levels to combine as the negative control. It is not necessary for Sarepta to examine dystrophin in these DMD samples by immunofluorescence within the defined time frame; however, it is important to understand that trace dystrophin levels are present in many DMD muscle samples, and that if low-level dystrophin is observed by Western blot in the pooled negative control, such levels need to be considered when interpreting findings, e.g., particularly for any PROMOVI samples that may show low-level dystrophin expression similar to what might be seen in the negative control.
5. FDA agreed that Sarepta will define the system suitability criteria in the protocol entitled "Establishment of the Western Blot Analysis Method in the Sarepta Corvallis Facility for the Week 48 PROMOVI (4658 301) Sample Analysis."
6. RT-PCR to confirm the expected skip product is needed and can be performed on the biopsy tissue as a potential PMC if it is not feasible to conduct within the defined timeframe.
7. Sarepta explained that running each block (A and B) separately from the PROMOVI patient samples cannot be completed within the timeframe, and FDA agreed.
8. Sarepta is looking into appropriate statistical analyses for comparison of baseline and post-treatment dystrophin levels including, for example, a pre-specified plan for alternative analyses if normality assumptions are not met.

POST-MEETING NOTE: Per Appendix C, blinding procedure, we note that you will be creating a number of Microsoft Excel files, including the assignment of 4658-301 Patient IDs to individual de-identified Patient IDs, a list of 13 random

numbers, and a file that includes the randomized assignment of pre- and post-treatment samples to “Ford” and “Chevy.”

In addition to the blinding procedures you plan, please send encrypted versions of the Excel files to the Division. Please retain the passwords for future use, but DO NOT FORWARD THEM to FDA at this time.

From: Matthew Rael [mailto:MRael@Sarepta.com]
Sent: Wednesday, June 08, 2016 3:59 PM
To: Kelley, Laurie
Cc: Choy, Fannie (Yuet); Shamim Ruff; Ware, Jacqueline H
Subject: RE: RE Urgent Request For Teleconference with Dr Ash Rao on 6 June

Hi Laurie,

We ask that FDA provide any feedback on these protocols by Friday June 10.

Regards,

Matt

From: Kelley, Laurie [mailto:Laurie.Kelley@fda.hhs.gov]
Sent: Wednesday, June 08, 2016 3:36 PM
To: Matthew Rael <MRael@Sarepta.com>
Cc: Choy, Fannie (Yuet) <Fannie.Choy@fda.hhs.gov>; Shamim Ruff <SRuff@Sarepta.com>; Ware, Jacqueline H <Jacqueline.Ware@fda.hhs.gov>; Kelley, Laurie <Laurie.Kelley@fda.hhs.gov>
Subject: RE: RE Urgent Request For Teleconference with Dr Ash Rao on 6 June

Matt

Confirming receipt.

Regards, Laurie

From: Matthew Rael [mailto:MRael@Sarepta.com]
Sent: Wednesday, June 08, 2016 3:09 PM
To: Kelley, Laurie
Cc: Choy, Fannie (Yuet); Shamim Ruff; Ware, Jacqueline H
Subject: RE: RE Urgent Request For Teleconference with Dr Ash Rao on 6 June

Hi Laurie,

Please find attached new and updated draft protocols, including the blinding procedure requested yesterday (Appendix C):

- Study 4658-301 Interim Western Blot Protocol v8
 - Appendix A: Sarepta Western Blot Method v5
 - Appendix C: Blinding and Randomization Procedure v7
- System Suitability Protocol v5

The 4658-301 Western blot protocol and its Appendix A have undergone some minimal modifications from the versions sent to FDA on Sunday.

The content changes are summarized as follows:

Study 4658-301 Interim Western Blot Protocol v8

1. Section 8: Updated list of personnel, primarily personnel at Nationwide Children’s Hospital (b) (4) Clinic who will be performing cryosectioning of biopsy blocks (including patient and control tissues); Johannes Dworzak from Sarepta has also been added.
2. Section 11.3.1 has been updated to specify that the 30-minute gel exposure is the preferred exposure and the 20-minute exposure is the reserved exposure. This change reflects experience gained from the performance of the Western blot method in support of the 4th Biopsy, in which the exposure times were reversed.
3. Section 12: Updated Data Analysis description.
4. Section 13: Updated Statistical Plan, which now includes testing normal distribution assumption of the paired sample t-test and alternative Wilcoxon nonparametric test if the normal distribution assumption is not met.
5. Section 13: Data Management now describes blinding, randomization, and database creation, database lock and unblinding by (b) (4) was also added to Section 7 Facilities.
6. Section 11.2.5 has been updated to describe shipping of samples from (b) (4) to the Sarepta Corvallis laboratory site.

Appendix A: Sarepta Western Blot Method v7

(b) (4)

Regards,

Matt

Matthew Rael, MS
Senior Manager, Regulatory Affairs
p 617.274.4029 (b) (6) f 617.812.0509
e mrael@sarepta.com



215 First Street, Cambridge, MA 02142 USA

From: Kelley, Laurie [<mailto:Laurie.Kelley@fda.hhs.gov>]
Sent: Wednesday, June 08, 2016 1:08 PM
To: Matthew Rael <MRael@Sarepta.com>
Cc: Choy, Fannie (Yuet) <Fannie.Choy@fda.hhs.gov>; Shamim Ruff <SRuff@Sarepta.com>; Ware, Jacqueline H <Jacqueline.Ware@fda.hhs.gov>; Kelley, Laurie <Laurie.Kelley@fda.hhs.gov>
Subject: RE: RE Urgent Request For Teleconference with Dr Ash Rao on 6 June

Matt

Thank you for this. I will be looking out for the protocol.

Laurie

From: Matthew Rael [<mailto:MRael@Sarepta.com>]
Sent: Wednesday, June 08, 2016 1:01 PM
To: Kelley, Laurie
Cc: Choy, Fannie (Yuet); Shamim Ruff; Ware, Jacqueline H
Subject: RE: RE Urgent Request For Teleconference with Dr Ash Rao on 6 June

Hi Laurie,

In regard to request #2 concerning identity of the normal controls, here is our preliminary response:

Sufficient numbers of normal control biopsy blocks are available from the neuromuscular histology laboratories at Nationwide Children's Hospital (b) (4). We will screen between 5 to 7 biopsies from each center. As of today, June 8, we have initial patient information available for the samples. As the sites obtain more detailed patient records for the samples, we plan to provide more complete patient information by Friday June 10.

Data available as of today:

- All normal controls are from males, some are in the 4- to 18-year-old range, others are older
- All normal controls are from diagnostic muscle biopsies, and therefore have been collected and processed using comparable protocols to study 4658-301
- Pathologic diagnosis of muscle biopsy: in general, mild, nonspecific changes from normal
- One normal control is from biceps, 14 years of age, no pathologic muscle diagnosis
- The remaining biopsies are from quadriceps, which is the most common muscle biopsied in diagnostic cases

We are working to provide the draft blinding and other protocols for review later today.

Regards,

Matt

Matthew Rael, MS

Senior Manager, Regulatory Affairs

p 617.274.4029 (b) (6) f 617.812.0509

e mrael@sarepta.com



215 First Street, Cambridge, MA 02142 USA

From: Kelley, Laurie [<mailto:Laurie.Kelley@fda.hhs.gov>]

Sent: Tuesday, June 07, 2016 5:37 PM

To: Matthew Rael <MRael@Sarepta.com>

Cc: Choy, Fannie (Yuet) <Fannie.Choy@fda.hhs.gov>; Shamim Ruff <SRuff@Sarepta.com>; Ware, Jacqueline H <Jacqueline.Ware@fda.hhs.gov>

Subject: Re: RE Urgent Request For Teleconference with Dr Ash Rao on 6 June

Matt

Thank you for the minutes. We are currently working on ours and will have them to you as soon as possible.

With regards action items from the tcon. Could you please send 1) the per-testing (blinding) protocol and 2) the identity of the normal controls?

Regards

Laurie

From: Matthew Rael

Sent: Tuesday, June 7, 2016 3:03 PM

To: Kelley, Laurie

Cc: Choy, Fannie (Yuet); Shamim Ruff; Ware, Jacqueline H

Subject: RE: RE Urgent Request For Teleconference with Dr Ash Rao on 6 June

Dear Laurie,

Please find attached our minutes from the teleconference between Sarepta and the FDA yesterday.

We ask that the FDA communicate any feedback/agreement on these minutes by end of day Thursday June 9th .

We also ask that Dr. Rao provide comments/feedback on the two draft protocols that we provided as soon as possible.

Regards,

Matt

Matthew Rael, MS

Senior Manager, Regulatory Affairs

p 617.274.4029 (b) (6) f 617.812.0509

e mrael@sarepta.com



215 First Street, Cambridge, MA 02142 USA

From: Matthew Rael

Sent: Monday, June 06, 2016 12:42 PM

To: Ware, Jacqueline H <Jacqueline.Ware@fda.hhs.gov>

Cc: Kelley, Laurie <Laurie.Kelley@fda.hhs.gov>; Choy, Fannie (Yuet) <Fannie.Choy@fda.hhs.gov>; Shamim Ruff <SRuff@Sarepta.com>

Subject: RE: RE Urgent Request For Teleconference with Dr Ash Rao on 6 June

Importance: High

Dear Jackie,

Our slides for the teleconference at 1:00 pm EDT today are attached.

Our attendees will be as follows:

- Edward M. Kaye, MD, Chief Medical Officer, Senior Vice President, and Interim Chief Executive Officer
- Shamim Ruff, Senior Vice President, Regulatory Affairs and Quality
- Diane Frank, PhD, Senior Director, Translational Research
- Jon Voss, Senior Director, Quality
- Fred Schnell, PhD, Senior Scientist, Research Biology
- Matthew Rael, Senior Manager, Regulatory Affairs

Regards,

Matt

Matthew Rael, MS

Senior Manager, Regulatory Affairs

p 617.274.4029 (b) (6) f 617.812.0509

e mrael@sarepta.com



215 First Street, Cambridge, MA 02142 USA

From: Shamim Ruff
Sent: Sunday, June 05, 2016 8:56 PM
To: Ware, Jacqueline H <Jacqueline.Ware@fda.hhs.gov>
Cc: Matthew Rael <MRael@Sarepta.com>; Kelley, Laurie <Laurie.Kelley@fda.hhs.gov>; Choy, Fannie (Yuet) <Fannie.Choy@fda.hhs.gov>
Subject: Re: RE Urgent Request For Teleconference with Dr Ash Rao on 6 June

We will get them to you by the end of day today.

On Jun 5, 2016, at 5:00 PM, Ware, Jacqueline H <Jacqueline.Ware@fda.hhs.gov> wrote:

Dear Matt,

Could you please confirm that the dystrophin protocols, requested in FDA's June 3, 2016 letter, will be amongst the "further details" (see email from Shamim below) that Sarepta will provide tomorrow (Monday, June 6th)? Dr. Rao has requested that he have time to look over them prior to the 1p EST call.

Also, I confirm receipt of the dial-in number for the call. Thank you for sending that information.

Kind regards,
Jackie

Jacqueline H. Ware, Pharm.D.
Captain, United States Public Health Service
Supervisory Regulatory Health Project Manager
FDA/CDER/OND/ODEI/Division of Neurology Products
WO22 Rm. 4346; phone: 301-796-1160

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From: Shamim Ruff [<mailto:SRuff@Sarepta.com>]
Sent: Friday, June 03, 2016 8:24 PM
To: Ware, Jacqueline H; Choy, Fannie (Yuet)
Cc: Kelley, Laurie; Matthew Rael
Subject: RE: RE Urgent Request For Teleconference with Dr Ash Rao on 6 June

Thank you. We will provide further details about the discussion topics by Monday morning.

Best,
Shamim

Shamim Ruff
SVP Regulatory Affairs and Quality
p 617-274-4009 (b) (6)
e sruff@sarepta.com

<image001.jpg>
215 First Street, Cambridge, MA 02142

From: Ware, Jacqueline H [<mailto:Jacqueline.Ware@fda.hhs.gov>]
Sent: Friday, June 03, 2016 8:03 PM

To: Shamim Ruff <SRuff@Sarepta.com>; Choy, Fannie (Yuet) <Fannie.Choy@fda.hhs.gov>
Cc: Kelley, Laurie <Laurie.Kelley@fda.hhs.gov>; Matthew Rael <MRael@Sarepta.com>; Ware, Jacqueline H <Jacqueline.Ware@fda.hhs.gov>
Subject: RE: RE Urgent Request For Teleconference with Dr Ash Rao on 6 June

Dear Shamim,

We propose a 1:00 pm EST call on Monday, June 6th. Please let me know if that time is acceptable for your team.

Also, if you are able, please share additional details about what is to be discussed (beyond that which is described below).

Best regards,

Jacqueline H. Ware, Pharm.D.
Captain, United States Public Health Service
Supervisory Regulatory Health Project Manager
FDA/CDER/OND/ODEI/Division of Neurology Products
WO22 Rm. 4346; phone: 301-796-1160

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From: Shamim Ruff [<mailto:SRuff@Sarepta.com>]
Sent: Friday, June 03, 2016 6:36 PM
To: Choy, Fannie (Yuet)
Cc: Kelley, Laurie; Ware, Jacqueline H; Matthew Rael
Subject: RE Urgent Request For Teleconference with Dr Ash Rao on 6 June

Dear Fannie,

Sarepta would like to request a tcon with Dr Ash Rao on Monday 6 June to discuss some key points on the dystrophin protocols. Please let us know some times he is available.

Thanks for your help.

Regards,
Shamim

Shamim Ruff
SVP Regulatory Affairs and Quality
p 617-274-4009 (b) (6)
e sruff@sarepta.com

<image001.jpg>
215 First Street, Cambridge, MA 02142

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/s/

LAURIE A KELLEY
06/10/2016

From: [Matthew Rael](#)
To: [Choy, Fannie \(Yuet\)](#)
Cc: [Shamim Ruff](#)
Subject: RE: FDA Information: re: NDA 206488 / eteplirsen
Date: Wednesday, June 01, 2016 11:20:43 AM

Hi Fannie,

I acknowledge receipt.

We'll get back to you as soon as possible.

Regards,

Matt

Matthew Rael, MS

Senior Manager, Regulatory Affairs

p 617.274.4029 (b) (6) f 617.812.0509

e mrael@sarepta.com



215 First Street, Cambridge, MA 02142 USA

From: Choy, Fannie (Yuet) [mailto:Fannie.Choy@fda.hhs.gov]
Sent: Wednesday, June 01, 2016 10:54 AM
To: Shamim Ruff <SRuff@Sarepta.com>
Cc: Matthew Rael <MRael@Sarepta.com>; Choy, Fannie (Yuet) <Fannie.Choy@fda.hhs.gov>
Subject: FDA Information: re: NDA 206488 / eteplirsen
Importance: High

Dear Shamim:

We refer to NDA 206488 for eteplirsen submitted on June 26, 2015.

As you know, we were unable to complete our review by the PDUFA date of May 26, but we are committed to completing our review process in a timely manner. A critical component of our ongoing review is whether there is substantial evidence that eteplirsen increases the production of dystrophin, as such a finding could potentially support an accelerated approval. As you know, the dystrophin biomarker data from Study 201/202 include only two pre/post biopsy samples from boys originally randomized to Study 201, and these samples, and all but one of the samples from external

control boys, were obtained from a different muscle group. On May 5, you responded to our request for information about completed biopsies from the ongoing Promovi trial. You reported that baseline biopsies have been obtained from 62 boys in the eteplirsen-treated arm and that 10 boys each have undergone a biopsy following 24 and 48 weeks of eteplirsen treatment. Analysis of the data for immunohistochemistry and Western blotting from these additional biopsies would substantially enhance our assessment of whether eteplirsen treatment leads to dystrophin production. You suggested that a protocol amendment would require 3-6 months, because of the time needed to amend the protocol, distribute it to the sites, and gain IRB approvals. We are eager to work with you to explore ways we can collaborate to expedite the timeline for making these data available for review and will do all we can to assist you in this effort. We would like to schedule a teleconference with you in the next day or two to explore the most efficient options to obtain these analyses.

Please confirm receipt of email.

Regards,
Fannie

Fannie Choy, RPh.
Regulatory Project Manager
Division of Neurology Products
ODE I/OND/CDER
Food and Drug Administration
10903 New Hampshire Avenue, WO22 Rm. 4215
Silver Spring, MD 20993-0002
301-796-2899 phone
fannie.choy@fda.hhs.gov

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/s/

YUET L CHOY

06/03/2016

At the request of Dr. Billy Dunn, DNP Director



NDA 206488

GENERAL ADVICE

Sarepta Therapeutics, Inc.
Attention: Shamim Ruff, MSc.
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) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Exondys 51 (eteplirsen) injection, 50 mg per mL.

This letter is in response to your email of June 2, 2016, to Janet Woodcock, M.D., in which you agreed to perform Western blots on baseline and Week 48 biopsies from eteplirsen-treated patients to assess dystrophin content. We will work with you on the protocol and analysis plan, and on the dates for FDA observers to be present during the procedures.

We agree to have an FDA observer present at the (b) (4) site to monitor tissue sampling and blinding procedures, and to have an observer present at the Corvallis site during performance of the Western blot procedure. We also understand that Corvallis is not a GLP facility.

We understand that a new normal control will need to be established to generate the standard curve of a serially-diluted normal comparator as part of these procedures. Please confirm the healthy dystrophin genotype and phenotype of this new control and compare side-by-side with the limited previous healthy control you have available. Confirm that the validation parameters and acceptance criteria for the new healthy control are comparable to those for the previous healthy control used with the Week 180 samples (e.g., linearity of the serially diluted sample, %RSD).

You should provide each of the relevant protocols for our review that describe the methods you propose to use for testing dystrophin, including those related to tissue acquisition at the clinical site(s), processing, blinding, and shipping procedures at the (b) (4) or elsewhere, tissue quality control before analysis, validation of the new normal control, and Western blotting at the Corvallis location.

You should implement appropriate quality control measures including strict blinding procedures to ensure that the integrity of the other primary and secondary assessments is not compromised as a result of this specific dystrophin investigation.

If you are successful in showing, to FDA's satisfaction, a meaningful increase in dystrophin by Western blot analysis between the paired pre-and post-treatment samples, we expect to be able to

grant an accelerated approval within four business days of receiving the data (assuming all other aspects of the application are approvable).

To allow for prompt approval, should your dystrophin analysis prove successful, we will work with you over the next several weeks on completing labeling negotiations to the degree possible and on necessary postmarketing requirements and commitments.

We request that you not publicly communicate the specific details of this plan until after completion in order to allow maximum procedural efficiency.

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

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
06/03/2016

From: [Shamim Ruff](#)
To: [Choy, Fannie \(Yuet\)](#)
Cc: [Matthew Rael](#)
Subject: RE: FDA Information: re: NDA 206488
Date: Tuesday, May 24, 2016 11:35:38 AM

Dear Fannie,

I confirm receipt.

Shamim Ruff

SVP Regulatory Affairs and Quality

p 617-274-4009 (b) (6)

e sruff@sarepta.com



215 First Street, Cambridge, MA 02142

From: Choy, Fannie (Yuet) [mailto:Fannie.Choy@fda.hhs.gov]
Sent: Tuesday, May 24, 2016 11:33 AM
To: Shamim Ruff <SRuff@Sarepta.com>
Cc: Matthew Rael <MRael@Sarepta.com>; Choy, Fannie (Yuet) <Fannie.Choy@fda.hhs.gov>
Subject: FDA Information: re: NDA 206488
Importance: High

Dear Shamim,

We refer to NDA 206488 for eteplirsen submitted on June 26, 2015.

We are continuing our review and internal discussions related to your pending NDA for eteplirsen and will not be able to complete our work by the PDUFA goal date of May 26, 2016. We will continue to work past the PDUFA goal date and strive to complete our work in as timely a manner as possible. A decision on the application has not been reached at this time. In accordance with our typical review process, we will be soon sharing some preliminary comments from the review team on the proposed labeling for your review and feedback. We will continue to communicate updates on the progress of our review as they become available.

Kindly confirm receipt of email.

-
Regards,
Fannie

Fannie Choy, RPh.
Regulatory Project Manager

Division of Neurology Products
ODE I/OND/CDER
Food and Drug Administration
10903 New Hampshire Avenue, WO22 Rm. 4215
Silver Spring, MD 20993-0002
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/s/

YUET L CHOY

05/25/2016

at the request of Dr. Eric Bastings, DNP Deputy Director

Rare Pediatric Disease Priority Review Voucher eligibility checklist

Under section 529 of the Food, Drug, and Cosmetic Act, the sponsor of a human drug application (as defined in section 735(1) of the FD&C Act) for a rare pediatric disease drug product may be eligible for a voucher that can be used to obtain a priority review for a subsequent human drug application submitted under section 505(b)(1) of the FD&C Act or section 351 of the Public Health Service (PHS) Act after the date of approval of the rare pediatric disease drug product.

This checklist is intended to help determine if an NDA or BLA is eligible for a **Rare Pediatric Disease Priority Review Voucher**.

NDA/BLA	Review Division
NDA 206488 eteplirsen	DNP
Requirement	Meets? (yes/no)
For prevention or treatment of a <i>rare pediatric disease</i> ? (<i>OOPD makes determination</i>)	OOPD RPD designated
Contains no active ingredient (including any ester or salt of the active ingredient) that has been previously approved in any other application under section 505(b)(1), 505(b)(2), or 505(j) of the FD&C Act or section 351(a) or 351(k) of the PHS Act?	Yes
FDA deems eligible for priority review?	Yes 8/4/15
Submitted under section 505(b)(1) (includes 505(b)(2) applications) of the FD&C Act or section 351(a) of the Public Health Service Act?	Yes
Relies on clinical data derived from studies examining a pediatric population and dosages of the drug intended for that population?	Yes
Does not seek approval for an adult indication in the original rare pediatric disease product application?	Yes

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/s/

ALTHEA CUFF
05/16/2016

From: [Choy, Fannie \(Yuet\)](#)
To: [Shamim Ruff](#)
Cc: [Matthew Rael](#); [Choy, Fannie \(Yuet\)](#)
Subject: FDA Information Request: re: NDA 206488 / eteplirsen
Date: Friday, May 06, 2016 11:42:48 AM
Importance: High

Dear Shamim:

We refer to NDA 206488 for eteplirsen submitted on June 26, 2015. We have the following request for information.

Section 6.3 of the protocol of Study 202, relating to efficacy assessments describes that “Detailed instructions for performing these assessments are provided in the Study Operations Manual (SOM)”. Please provide that SOM by close of business today.

Kindly confirm receipt of email and let me know if you have any questions.

Regards,
Fannie

Fannie Choy, RPh.
Regulatory Project Manager
Division of Neurology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, WO22 Rm. 4215
Silver Spring, MD 20993-0002
301-796-2899 phone
301-796-9842 fax
fannie.choy@fda.hhs.gov

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From: [Shamim Ruff](#)
To: [Choy, Fannie \(Yuet\)](#)
Cc: [Matthew Rael](#)
Subject: RE: FDA Information Request: re: NDA 206488 / eteplirsen
Date: Thursday, May 05, 2016 10:02:30 AM

Dear Fannie,

I confirm receipt.

Shamim

From: Choy, Fannie (Yuet) [mailto:Fannie.Choy@fda.hhs.gov]
Sent: Thursday, May 05, 2016 9:47 AM
To: Shamim Ruff <SRuff@Sarepta.com>
Cc: Matthew Rael <MRael@Sarepta.com>; Choy, Fannie (Yuet) <Fannie.Choy@fda.hhs.gov>
Subject: FDA Information Request: re: NDA 206488 / eteplirsen
Importance: High

Dear Shamim:

We refer to NDA 206488 for eteplirsen submitted on June 26, 2015. We have the following request for information.

Please provide the following status update regarding the PROMOVI study:

1. Number of DMD patients amenable to exon 51 skipping that have entered the study
2. Number of DMD patients amenable to exon 51 skipping that had a baseline biopsy
3. Number of DMD patients amenable to exon 51 skipping that have had a Week 24 biopsy
4. Number of DMD patients amenable to exon 51 skipping that have had a Week 48 biopsy.

We ask the information by close of business today.

Please confirm receipt of email and let me know if you have any questions.

Regards,
Fannie

Fannie Choy, RPh.
Regulatory Project Manager
Division of Neurology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, WO22 Rm. 4215
Silver Spring, MD 20993-0002
301-796-2899 phone
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fannie.choy@fda.hhs.gov

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From: [Choy, Fannie \(Yuet\)](#)
To: [Shamim Ruff](#)
Cc: [Choy, Fannie \(Yuet\)](#); [Matthew Rael](#)
Subject: RE: FDA Information Request: re: NDA 206488 / eteplirsen
Date: Thursday, May 05, 2016 12:33:20 PM

Dear Shamim,

Do you have any update on the Division's information request #1 dated May 3, 2016 (attached below)?

Regards,
Fannie

Fannie Choy, RPh.
Regulatory Project Manager
Division of Neurology Products

From: Matthew Rael [mailto:MRael@Sarepta.com]
Sent: Wednesday, May 04, 2016 12:40 PM
To: Choy, Fannie (Yuet)
Cc: Shamim Ruff
Subject: RE: FDA Information Request: re: NDA 206488 / eteplirsen

Dear Fannie,

Please find attached our response to information request #2 below.

Regards,

Matt

Matthew Rael, MS
Senior Manager, Regulatory Affairs
p 617.274.4029 (b) (6) f 617.812.0509
e mrael@sarepta.com



215 First Street, Cambridge, MA 02142 USA

From: Choy, Fannie (Yuet) [<mailto:Fannie.Choy@fda.hhs.gov>]
Sent: Tuesday, May 03, 2016 4:47 PM
To: Shamim Ruff <SRuff@Sarepta.com>

Cc: Matthew Rael <MRael@Sarepta.com>; Choy, Fannie (Yuet) <Fannie.Choy@fda.hhs.gov>

Subject: FDA Information Request: re: NDA 206488 / eteplirsen

Importance: High

Dear Shamim:

We refer to NDA 206488 for eteplirsen submitted on June 26, 2015. We have the following request for information.

1. Reference is made to our Information Request of 4/15/16 & 4/19/16, and to your response dated 4/19/16 & 4/20/16. Please indicate when the Week 240 results will be provided to FDA.
2. Please describe the role of (b) (4) in Week 180 western blot testing.

We ask that you please provide the response by 12 noon tomorrow May 4, 2016.

Please confirm receipt of email and let me know if you have any questions.

Regards,
Fannie

Fannie Choy, RPh.

Regulatory Project Manager

Division of Neurology Products

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Avenue, WO22 Rm. 4215

Silver Spring, MD 20993-0002

301-796-2899 phone

301-796-9842 fax

fannie.choy@fda.hhs.gov

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/s/

YUET L CHOY

05/06/2016

at the request of Dr. Eric Bastings, DNP Deputy Director

From: [Choy, Fannie \(Yuet\)](#)
To: [Matthew Rael](#)
Cc: [Shamim Ruff](#); [Choy, Fannie \(Yuet\)](#)
Subject: RE: FDA Information Request: re: NDA 206488 / eteplirsen
Date: Tuesday, April 19, 2016 7:53:30 PM

Dear Matt,

Thank you for your email. We ask that you provide the raw data for the 11 patients tested. Please let me know if you have any questions.

Regards,
Fannie

Fannie Choy, RPh.
Regulatory Project Manager
Division of Neurology Products

From: Matthew Rael [mailto:MRael@Sarepta.com]
Sent: Tuesday, April 19, 2016 3:27 PM
To: Choy, Fannie (Yuet)
Cc: Shamim Ruff
Subject: RE: FDA Information Request: re: NDA 206488 / eteplirsen

Hi Fannie,

Eleven of the 12 patients were assessed by the end of last week. The visit for the 12th patient is still pending. We will submit the data as soon as we can.

Regards,

Matt

Matthew Rael, MS
Senior Manager, Regulatory Affairs
p 617.274.4029 (b) (6) f 617.812.0509
e mrael@sarepta.com



215 First Street, Cambridge, MA 02142 USA

From: Choy, Fannie (Yuet) [mailto:Fannie.Choy@fda.hhs.gov]
Sent: Tuesday, April 19, 2016 12:52 PM

To: Shamim Ruff <SRuff@Sarepta.com>
Cc: Matthew Rael <MRael@Sarepta.com>; Choy, Fannie (Yuet) <Fannie.Choy@fda.hhs.gov>
Subject: RE: FDA Information Request: re: NDA 206488 / eteplirsen
Importance: High

Dear Shamim,

I would like to follow up on our April 15, 2016 request for information (attached below). We ask that you please provide an update by COB today April 19, 2016.

[Please confirm receipt of email.](#)

Regards,
Fannie

Fannie Choy, RPh.
Regulatory Project Manager
Division of Neurology Products

From: Choy, Fannie (Yuet)
Sent: Friday, April 15, 2016 4:47 PM
To: Shamim Ruff
Cc: Matthew Rael; Choy, Fannie (Yuet)
Subject: RE: FDA Information Request: re: NDA 206488 / eteplirsen

Dear Shamim,

We refer to our information request of February 12, 2016, and also to the teleconference between representatives of your firm and the Division on February 18, 2016.

You noted that you will expedite reporting of the requested functional endpoints (6MWT, NSAA total score and rise time) for the Week 240 assessments in Study 201/202. Please provide an update on when the submission is anticipated.

[Kindly acknowledge receipt of email.](#)

Regards,
Fannie

Fannie Choy, RPh.
Regulatory Project Manager
Division of Neurology Products

From: Choy, Fannie (Yuet)
Sent: Friday, February 12, 2016 1:27 PM
To: Shamim Ruff
Cc: Matthew Rael; Choy, Fannie (Yuet)

Subject: FDA Information Request: re: NDA 206488 / eteplirsen
Importance: High

Dear Shamim:

We refer to NDA 206488 for eteplirsen submitted on June 26, 2015. The Division's review team has the following request for information.

- 1. On what dates are the patients in Study 201/202 scheduled for their next study endpoints exam?**
- 2. Please describe how you will expedite reporting of the Week 240 endpoint data.**

Please confirm receipt of email and let me know if you have any questions.

Regards,
Fannie

Fannie Choy, RPh.
Regulatory Project Manager
Division of Neurology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, WO22 Rm. 4215
Silver Spring, MD 20993-0002
301-796-2899 phone
301-796-9842 fax
fannie.choy@fda.hhs.gov

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/s/

YUET L CHOY

04/20/2016

at the request of Dr. Eric Bastings, DNP Deputy Director



NDA 206488

**CARTON LABELING AND CONTAINER LABEL
DISCUSSION COMMENTS**

Sarepta Therapeutics, Inc.
Attention: Shamim Ruff, MSc.
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, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Exondys 51 (eteplirsen) injection, 50 mg per mL.

We have reviewed your revised container labels and carton labeling submitted on December 17, 2015, in response to our December 9, 2015, comment and recommendations. We are providing the following comment pertaining to the revised carton and container labeling.

All Container Labels and Carton Labeling

1. We note that your updated container labels and carton labeling no longer includes space notated for the product lot and expiration date. Please add this information to both the container labels and carton labeling.

All Carton Labeling

2. We note that as requested you bolded the storage statement on the carton labeling. However, the statement as currently displayed “**Refrigerate at 2-8 °C (36-46 °F)**” is missing the degree and centigrade symbols (°C) after the number 2, and the degree Fahrenheit (°F) after the number 36, and includes an extra space between the numbers 8 and 46 and their degree symbol. Please revise this bolded statement to read “**Refrigerate at 2°C-8°C (36°F-46°F)**.”

10 mL Container Labels

3. Revise the Storage statements on the 10 mL container label, by inserting the degree and centigrade symbols (°C) after the number 2 and degree Fahrenheit (°F) after the number 36, to read “**Refrigerate at 2°C-8°C (36°F-46°F)**.”

We request that you resubmit the carton labeling and container labels that address these issues by March 31, 2016.

If you have any questions, please contact me by phone or email at (301) 796-2899 or fannie.choy@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Fannie Choy, R.Ph.
Regulatory Project Manager
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

YUET L CHOY
03/15/2016

From: [Shamim Ruff](#)
To: [Choy, Fannie \(Yuet\)](#)
Cc: [Matthew Rael](#)
Subject: RE: FDA Information Request: re: NDA 206488
Date: Friday, March 11, 2016 9:15:24 AM

Dear Fannie,
I confirm receipt.

I have just sent your request through to the site and will get back to you as soon as we have the information.

Regards,
Shamim

Shamim Ruff

SVP Regulatory Affairs and Quality

p 617-274-4009 (b) (6)

e sruff@sarepta.com



215 First Street, Cambridge, MA 02142

From: Choy, Fannie (Yuet) [mailto:Fannie.Choy@fda.hhs.gov]
Sent: Friday, March 11, 2016 9:06 AM
To: Shamim Ruff <SRuff@Sarepta.com>
Cc: Choy, Fannie (Yuet) <Fannie.Choy@fda.hhs.gov>; Matthew Rael <MRael@Sarepta.com>
Subject: FDA Information Request: re: NDA 206488
Importance: High

Dear Shamim,

We refer to NDA 206488 for eteplirsen submitted on June 26, 2015. We have the following request for information.

Please send the Name of the Investigator / Site City for the following Italian subjects in the natural history registry:

SUBJID = (b) (6)

Send this information by close of business 1 day from receiving this information request.

Kindly confirm receipt of email.

Regards,
Fannie

Fannie Choy, RPh.

Regulatory Project Manager

Division of Neurology Products

ODE I/OND/CDER

Food and Drug Administration

10903 New Hampshire Avenue, WO22 Rm. 4215

Silver Spring, MD 20993-0002

301-796-2899 phone

fannie.choy@fda.hhs.gov

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/s/

YUET L CHOY

03/11/2016

w/ concurrence: Dr. Eric Bastings, DNP Deputy Director

From: [Choy, Fannie \(Yuet\)](#)
To: [Shamim Ruff](#)
Cc: [Matthew Rael](#); [Choy, Fannie \(Yuet\)](#)
Subject: FDA Information Request: re: NDA 206488
Date: Thursday, February 25, 2016 4:14:03 PM

Dear Shamim,

We refer to NDA 206488 for eteplirsen submitted on June 26, 2015. We also refer to the participants in the natural history cohort of your NDA and the teleconference on February 18, 2016. We are requesting contact information for the sites that enrolled the subjects who participated in the natural history studies.

Provide the following information for each site. We ask that you provide the information on or before February 29, 2016.

Site Name:

Clinical Investigator:

Contact Name:

Address:

Phone:

Email:

Number of exon 51 skippable patients from site (inclusive - all ages, durations of observation, ambulatory status):

Number of exon 51 skippable patients selected as matches to the eteplirsen patients (from the 13 selected as matched):

Kindly confirm receipt of email.

Regards,
Fannie

Fannie Choy, RPh.

Regulatory Project Manager

Division of Neurology Products

ODE I/OND/CDER

Food and Drug Administration

10903 New Hampshire Avenue, WO22 Rm. 4215

Silver Spring, MD 20993-0002

301-796-2899 phone

fannie.choy@fda.hhs.gov

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/s/

YUET L CHOY

02/25/2016

at the request of Dr. Ron Farkas, DNP Clinical TL

From: [Choy, Fannie \(Yuet\)](#)
To: [Shamim Ruff](#)
Cc: [Matthew Rael](#); [Choy, Fannie \(Yuet\)](#)
Subject: FDA Information Request: re: NDA 206488 / eteplirsen
Date: Friday, February 12, 2016 1:27:01 PM
Importance: High

Dear Shamim:

We refer to NDA 206488 for eteplirsen submitted on June 26, 2015. The Division's review team has the following request for information.

- 1. On what dates are the patients in Study 201/202 scheduled for their next study endpoints exam?**
- 2. Please describe how you will expedite reporting of the Week 240 endpoint data.**

Please confirm receipt of email and let me know if you have any questions.

Regards,
Fannie

Fannie Choy, RPh.
Regulatory Project Manager
Division of Neurology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, WO22 Rm. 4215
Silver Spring, MD 20993-0002
301-796-2899 phone
301-796-9842 fax
fannie.choy@fda.hhs.gov

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/s/

YUET L CHOY

02/16/2016

at the request of Dr. Ron Farkas, DNP Clinical TL

From: [Choy, Fannie \(Yuet\)](#)
To: [Shamim Ruff](#)
Cc: [Matthew Rael](#); [Choy, Fannie \(Yuet\)](#)
Subject: RE: FDA Information Request: re: NDA 206488 / eteplirsen
Date: Tuesday, February 09, 2016 1:08:40 PM

Dear Shamim,

We refer to NDA 206488 for eteplirsen submitted on June 26, 2015. We also refer to your submission of Feb 8, 2016, requesting for clarification on FDA comment #5 sent on Jan 29, 2016.

Sarepta Response: Sarepta would like to request clarification on this question. Is FDA seeking the date for when the external control data were selected according to the (b) (4) criteria" (i.e. age ≥7 years, at least 24 weeks of stable steroid dose, and mutation amenable to skipping exon 51)?

FDA Response: Yes, we would like the date, for each subject in the natural history cohort, when you decided that subject would be eligible to serve as a control.

Kindly confirm receipt of email.

Regards,
Fannie

Fannie Choy, RPh.
Regulatory Project Manager
Division of Neurology Products

From: Choy, Fannie (Yuet) [<mailto:Fannie.Choy@fda.hhs.gov>]
Sent: Friday, January 29, 2016 1:12 PM
To: Shamim Ruff <SRuff@Sarepta.com>
Cc: Matthew Rael <MRael@Sarepta.com>; Choy, Fannie (Yuet) <Fannie.Choy@fda.hhs.gov>
Subject: FDA Information Request: re: NDA 206488 / eteplirsen
Importance: High

Dear Shamim,

We refer to NDA 206488 for eteplirsen submitted on June 26, 2015. The review team has the following request for information.

-
- For the participants in the natural history cohort of your New Drug Application (b) (6) please provide all source documents and records that relate to assessments of the 6-minute walk test and NSAA. These

documents should include:

- All medical records related to assessments of ambulation, 6-minute walk test, and rise time
- All medical records related to assessments of physical disability and NSAA
- Records of all phone calls between the study site(s) and the participants related to the registry
- All spreadsheets and data files used to record test results
- Please send the protocol for the natural history registry study as well as any amendments and records of protocol violations or deviations.
- NSAA values were not provided for some participants and time points in the natural history cohort. Please provide the NSAA values, or an explanation of why these values are not available.
- Please provide the individual item scores for each NSAA total score.
- For each subject in the historical cohort, please indicate the date the decision was made to include them, and provide documentation of the date if such documentation exists.

Please provide this information within 7 business days from receipt of this communication.

Kindly confirm receipt of email. Please feel free to contact me if you have any questions.

Regards,
Fannie

Fannie Choy, RPh.

Regulatory Project Manager

Division of Neurology Products

ODE I/OND/CDER

Food and Drug Administration

10903 New Hampshire Avenue, WO22 Rm. 4215

Silver Spring, MD 20993-0002

301-796-2899 phone

fannie.choy@fda.hhs.gov

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/s/

YUET L CHOY

02/09/2016

w/ concurrence: Dr. Eric Bastings, DNP Deputy Director



NDA 206488

**REVIEW EXTENSION –
MAJOR AMENDMENT**

Sarepta Therapeutics, Inc.
Attention: Shamim Ruff, MSc.
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, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Exondys 51 (eteplirsen) injection, 50 mg/mL.

Please also refer to your January 8, 2016, amendment to this application. As described in your materials prepared for the advisory committee, your principal basis for establishing the effectiveness of eteplirsen is a comparison of patients in Study 201/202 to a historical control group, a comparison for which your submission provides additional information. We consider the January 8, 2016, submission a major amendment and are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is May 26, 2016.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with “PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2013 THROUGH 2017.” If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by April 29, 2016.

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
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

WILLIAM H Dunn
02/05/2016

From: [Choy, Fannie \(Yuet\)](#)
To: [Shamim Ruff](#)
Cc: [Matthew Rael](#); [Choy, Fannie \(Yuet\)](#)
Subject: FDA Information Request: re: NDA 206488 / eteplirsen
Date: Friday, January 29, 2016 1:12:01 PM
Importance: High

Dear Shamim,

We refer to NDA 206488 for eteplirsen submitted on June 26, 2015. The review team has the following request for information.

-
- For the participants in the natural history cohort of your New Drug Application [REDACTED] (b) (6) [REDACTED] please provide all source documents and records that relate to assessments of the 6-minute walk test and NSAA. These documents should include:
 - All medical records related to assessments of ambulation, 6-minute walk test, and rise time
 - All medical records related to assessments of physical disability and NSAA
 - Records of all phone calls between the study site(s) and the participants related to the registry
 - All spreadsheets and data files used to record test results
 - Please send the protocol for the natural history registry study as well as any amendments and records of protocol violations or deviations.
 - NSAA values were not provided for some participants and time points in the natural history cohort. Please provide the NSAA values, or an explanation of why these values are not available.
 - Please provide the individual item scores for each NSAA total score.
 - For each subject in the historical cohort, please indicate the date the decision was made to include them, and provide documentation of the date if such documentation exists.

Please provide this information within 7 business days from receipt of this communication.

Kindly confirm receipt of email. Please feel free to contact me if you have any questions.

Regards,
Fannie

Fannie Choy, RPh.
Regulatory Project Manager
Division of Neurology Products
ODE I/OND/CDER
Food and Drug Administration
10903 New Hampshire Avenue, WO22 Rm. 4215
Silver Spring, MD 20993-0002
301-796-2899 phone
fannie.choy@fda.hhs.gov

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/s/

YUET L CHOY

01/29/2016

at the request of Dr Eric Bastings, DNP Deputy Director

From: [Choy, Fannie \(Yuet\)](#)
To: [Matthew Rael](#)
Cc: [Shamim Ruff](#); [Choy, Fannie \(Yuet\)](#)
Subject: RE: FDA Information Request: re: NDA 206488 / eteplirsen
Date: Wednesday, January 20, 2016 1:26:45 PM
Importance: High

Dear Matt,

Thank you for the response. The review team has the following request for information/clarification.

In your 8 January 2016 submission, you state that you provided newly obtained updated 6-minute walk test (6MWT) data for the external control patients.

1. We would like to confirm that the new 6MWT data were obtained through the visit of the patients to the clinic, and measurement of 6MWT per the study protocol.
2. Was any data on 6MWT or any ambulatory ability collected about the patients by the investigator by any other method, for example outside of the usual study visit procedures?

We ask that you promptly respond to this request.

Kindly confirm receipt of email.

Regards,
Fannie

Fannie Choy, RPh.
Regulatory Project Manager
Division of Neurology Products

From: Matthew Rael [mailto:MRael@Sarepta.com]
Sent: Wednesday, January 20, 2016 8:33 AM
To: Choy, Fannie (Yuet)
Cc: Shamim Ruff
Subject: RE: FDA Information Request: re: NDA 206488 / eteplirsen

Good morning Fannie,

Our responses to the questions are below:

1. *In your 8 January 2016 submission you state that you provided newly obtained updated 6-minute walk test (6MWT) data for the external control patients. Can you confirm that the most recent time points (or 2 most recent, for some patients) were collected by telephone.*

We received the raw data as Microsoft Excel files directly from the investigators.

2. *Your slide 8 at the late cycle meeting stated that 8/13 untreated EC-51 patients were on continuous corticosteroids, and 5/13 were on intermittent corticosteroids. Our datasets show 4/13 continuous and 9/13 intermittent. Please clarify.*

In the original EC-51 dataset submitted in the NDA, 9/13 subjects were listed as being on intermittent corticosteroid regimens. This included 3 Leuven subjects (patient IDs (b) (6)) whose steroid use was flagged in the dataset as "3 – on steroids but frequency unknown". Based in updated information from the investigator, these 3 patients are now confirmed to be on continuous regimens (updated data submitted in NDA Sequence No. 0028, dated 17 Dec 2015). In addition, the Italian subject (b) (6) who was indicated as being on intermittent steroid treatment in the original dataset, is now indicated as being on continuous steroid treatment based on the updated data from the investigator (NDA Sequence No. 0021, dated 02 Nov 2015). With the change of status of these 4 patients, the current dataset as summarized at the Late-Cycle Meeting contains 5/13 subjects on intermittent corticosteroids.

Best regards,

Matt

Matthew Rael, MS

Senior Manager, Regulatory Affairs

p 617.274.4029 (b) (6) f 617.812.0509

e mrael@sarepta.com



215 First Street, Cambridge, MA 02142 USA

From: Choy, Fannie (Yuet) [<mailto:Fannie.Choy@fda.hhs.gov>]

Sent: Monday, January 18, 2016 4:34 PM

To: Matthew Rael <MRael@Sarepta.com>

Cc: Shamim Ruff <SRuff@Sarepta.com>; Choy, Fannie (Yuet) <Fannie.Choy@fda.hhs.gov>

Subject: RE: FDA Information Request: re: NDA 206488 / eteplirsen

Good afternoon,

Any update on when you'd expect to respond to our 1/15/16 request for information.

Regards,
Fannie

From: Matthew Rael [<mailto:MRael@Sarepta.com>]
Sent: Friday, January 15, 2016 4:41 PM
To: Choy, Fannie (Yuet)
Cc: Shamim Ruff
Subject: RE: FDA Information Request: re: NDA 206488 / eteplirsen

Hi Fannie,

We acknowledge receipt of this request. Apologies for the delay in getting back to you, we are all currently busy preparing for the FDA advisory committee meeting next week.

We are following up with our statistician to obtain the requested information, and will provide it as soon as possible.

Best regards,

Matt

Matthew Rael, MS

Senior Manager, Regulatory Affairs

p 617.274.4029 (b) (6) f 617.812.0509

e mrael@sarepta.com



215 First Street, Cambridge, MA 02142 USA

From: Choy, Fannie (Yuet) [<mailto:Fannie.Choy@fda.hhs.gov>]
Sent: Friday, January 15, 2016 12:44 PM
To: Shamim Ruff <SRuff@Sarepta.com>
Cc: Matthew Rael <MRael@Sarepta.com>; Choy, Fannie (Yuet) <Fannie.Choy@fda.hhs.gov>
Subject: FDA Information Request: re: NDA 206488 / eteplirsen
Importance: High

Dear Shamim:

We refer to NDA 206488 for eteplirsen submitted on June 26, 2015. The team has the following request for information.

1. In your 8 January 2016 submission you state that you provided newly obtained updated 6-minute walk test (6MWT) data for the external control patients. Can you confirm that the most recent time points (or 2 most recent, for some patients) were collected by telephone.

2. Your slide 8 at the late cycle meeting stated that 8/13 untreated EC-51 patients were on continuous corticosteroids, and 5/13 were on intermittent corticosteroids. Our datasets show 4/13 continuous and 9/13 intermittent. Please clarify.

We ask that you please provide the response right away.

Kindly confirm receipt of email. Please feel free to contact me if you have any questions.

Regards,
Fannie

Fannie Choy, RPh.
Regulatory Project Manager
Division of Neurology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, WO22 Rm. 4215
Silver Spring, MD 20993-0002
301-796-2899 phone
301-796-9842 fax
fannie.choy@fda.hhs.gov

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/s/

YUET L CHOY

01/26/2016

at the request of Dr Ron Farkas, DNP Clinical TL

From: [Choy, Fannie \(Yuet\)](#)
To: [Shamim Ruff](#)
Cc: [Matthew Rael](#); [Choy, Fannie \(Yuet\)](#)
Subject: FDA Information Request: re: NDA 206488 / eteplirsen
Date: Friday, January 15, 2016 12:44:25 PM
Importance: High

Dear Shamim:

We refer to NDA 206488 for eteplirsen submitted on June 26, 2015. The team has the following request for information.

1. In your 8 January 2016 submission you state that you provided newly obtained updated 6-minute walk test (6MWT) data for the external control patients. Can you confirm that the most recent time points (or 2 most recent, for some patients) were collected by telephone.
2. Your slide 8 at the late cycle meeting stated that 8/13 untreated EC-51 patients were on continuous corticosteroids, and 5/13 were on intermittent corticosteroids. Our datasets show 4/13 continuous and 9/13 intermittent. Please clarify.

We ask that you please provide the response right away.

Kindly confirm receipt of email. Please feel free to contact me if you have any questions.

Regards,
Fannie

Fannie Choy, RPh.

Regulatory Project Manager
Division of Neurology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, WO22 Rm. 4215
Silver Spring, MD 20993-0002
301-796-2899 phone
301-796-9842 fax
fannie.choy@fda.hhs.gov

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/s/

YUET L CHOY

01/15/2016

at the request of Dr. Ron Farkas, DNP Clinical TL

From: [Matthew Rael](#)
To: [Choy, Fannie \(Yuet\)](#)
Cc: [Shamim Ruff](#)
Subject: RE: FDA Information Request: re: NDA 206488 / eteplirsen
Date: Wednesday, December 09, 2015 9:22:28 AM

Dear Fannie,

The biopsy images presented in the figures on pages 141-142 of the briefing document are “invert base100” images. This image format was chosen for display purposes to minimize the influence of computer monitors and viewing environment.

Best regards,

Matt

Matthew Rael, MS

Senior Manager, Regulatory Affairs

p 617.274.4029 (b) (6) f 617.812.0509

e mrael@sarepta.com



215 First Street, Cambridge, MA 02142 USA

From: Shamim Ruff
Sent: Tuesday, December 08, 2015 7:44 PM
To: Choy, Fannie (Yuet)
Cc: Matthew Rael
Subject: Re: FDA Information Request: re: NDA 206488 / eteplirsen

Dear Fannie

I confirm receipt.

Shamim

On Dec 8, 2015, at 6:24 PM, Choy, Fannie (Yuet) <Fannie.Choy@fda.hhs.gov> wrote:

Dear Shamim,

We refer to NDA 206488 for eteplirsen submitted on June 26, 2015. We also refer to your Advisory Committee (AC) Briefing Document for the Jan 22, 2016 PCNS AC. The

review team has the following request for information.

In the figure on page 142 of your briefing document were the images created through “invertbase100” – that is, scaling the r,g,b fluorescent values using the following formula: $I' = 1 - 100^{(-I)}$ normalized by the max value of $1 - 100^{(-1)}$ for each of the channels independently. If not, please explain how the inverted images were derived.

We ask that you please respond to this request right away.

Please confirm receipt of email.

Regards,
Fannie

Fannie Choy, RPh.
Regulatory Project Manager
Division of Neurology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, WO22 Rm. 4215
Silver Spring, MD 20993-0002
301-796-2899 phone
301-796-9842 fax
fannie.choy@fda.hhs.gov

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/s/

YUET L CHOY

12/09/2015

at the request of Dr Ron Farkas, DNP Clinical TL



NDA 206488

**CARTON LABELING AND CONTAINER LABEL
DISCUSSION COMMENTS**

Sarepta Therapeutics, Inc.
Attention: Shamim Ruff, MSc.
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, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Exondys 51 (eteplirsen) injection, 50 mg per mL.

We are providing the following comment and recommendation pertaining to the carton and container labeling.

A. Carton Labeling

1. As currently presented, the NDC number is located on the side panel of the carton labeling. Since NDC number is often used as an additional verification method in the pharmacy, it is an important safety feature. Relocate the NDC so that it is displayed in the top third of principal display panel (PDP) of the labeling in accordance with 21 CFR 207.35(b)(3)(i).
2. The "Rx Only" statement is currently presented on the side panel of the carton labeling; consider relocating this statement to the PDP.
3. Revise the middle digits ("-051-") of the NDC (i.e.; the "product code") for the 2 mL and 10 mL vials so that they are not identical. Although the vials contain the same product concentration, they contain different total amount of drug in the container because of differences in the fill volume. When the same product code number is used for different size containers, healthcare providers have had difficulty distinguishing the difference in total drug content. Therefore, revise the product code (middle digits of the NDC number) such that they are different between these products to prevent wrong dose medication errors. See *Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*. Food and Drug Administration. 2013.
4. Add the net quantity statement (i.e., 1 vial) to the carton PDP in accordance with 21 CFR 201.51. Ensure that the net quantity statement appears away from the product strength and is less prominent.

5. Bold the statement “**Refrigerate at 2°C-8°C (36°C-46°F).**” We recommend this to increase the prominence of this important information and minimize the risk of the storage information being overlooked.
6. [REDACTED] (b) (4) “Single Dose”.

B. Container Labels

1. See A.3. above.
2. [REDACTED] (b) (4) “Single Dose”.

We request that you resubmit the carton labeling and container labels that address these issues by December 30, 2015.

If you have any questions, please contact me by phone or email at (301) 796-2899 or fannie.choy@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Fannie Choy, R.Ph.
Regulatory Project Manager
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

YUET L CHOY
12/09/2015

From: [Matthew Rael](#)
To: [Choy, Fannie \(Yuet\)](#)
Cc: [Shamim Ruff](#)
Subject: RE: FDA Information Request: re: NDA 206488 / eteplirsen
Date: Friday, December 04, 2015 9:27:58 AM

Hi Fannie,

I confirm receipt.

Best regards,

Matt

Matthew Rael, MS

Senior Manager, Regulatory Affairs

p 617.274.4029 (b) (6) f 617.812.0509

e mrael@sarepta.com



215 First Street, Cambridge, MA 02142 USA

From: Choy, Fannie (Yuet) [mailto:Fannie.Choy@fda.hhs.gov]
Sent: Friday, December 04, 2015 9:15 AM
To: Shamim Ruff
Cc: Matthew Rael; Choy, Fannie (Yuet)
Subject: FDA Information Request: re: NDA 206488 / eteplirsen
Importance: High

Dear Shamim:

We refer to NDA 206488 for eteplirsen submitted on June 26, 2015. The review team has the following request for information.

Please send the western blot results for the eteplirsen-treated subjects for the 4th biopsy which include the actual estimated values of those below the limit of quantification.

We ask that you provide this information as soon as possible.

Please confirm receipt of email.

Regards,
Fannie

Fannie Choy, RPh.

Regulatory Project Manager
Division of Neurology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, WO22 Rm. 4215
Silver Spring, MD 20993-0002
301-796-2899 phone
301-796-9842 fax

fannie.choy@fda.hhs.gov

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/s/

YUET L CHOY

12/04/2015

at the request of Dr Ron Farkas, DNP Clinical TL

From: [Matthew Rael](#)
To: [Choy, Fannie \(Yuet\)](#)
Cc: [Shamim Ruff](#)
Subject: RE: FDA Information Request: re: NDA 206488 / eteplirsen
Date: Thursday, December 03, 2015 1:43:05 PM

Hi Fannie,

I confirm receipt.

Best regards,

Matt

Matthew Rael, MS

Senior Manager, Regulatory Affairs

p 617.274.4029 (b) (6) f 617.812.0509

e mrael@sarepta.com



215 First Street, Cambridge, MA 02142 USA

From: Choy, Fannie (Yuet) [mailto:Fannie.Choy@fda.hhs.gov]
Sent: Thursday, December 03, 2015 1:34 PM
To: Shamim Ruff
Cc: Matthew Rael; Choy, Fannie (Yuet)
Subject: FDA Information Request: re: NDA 206488 / eteplirsen
Importance: High

Dear Shamim:

We refer to NDA 206488 for eteplirsen submitted on June 26, 2015. The clinical reviewer has the following request for information.

- 1) In my prior information request (27 November 2015) I had asked what the AEs of myoglobinuria in Study 33 were based on and your response said "Laboratory results", however in the same response you said that only Study 28 had performed this lab. Please clarify this apparent discrepancy.
- 2) In the same IR you stated that Anti-Dystrophin Antibodies were assessed in Study 28. There are no results for this lab in this Study in the 120 Day Safety Update ADLB dataset. Please

provide the location of these results.

We ask that you provide this information as soon as possible.

Please confirm receipt of email.

Regards,
Fannie

Fannie Choy, RPh.

Regulatory Project Manager
Division of Neurology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, WO22 Rm. 4215
Silver Spring, MD 20993-0002
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fannie.choy@fda.hhs.gov

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/s/

YUET L CHOY

12/03/2015

w/ concurrence: Dr Ron Farkas, DNP Clinical TL

From: [Shamim Ruff](#)
To: [Choy, Fannie \(Yuet\)](#)
Cc: [Matthew Rael](#)
Subject: Re: FDA Information Request: re: NDA 206488 / eteplirsen
Date: Monday, November 30, 2015 5:15:16 PM

Dear Fannie

I confirm receipt.

Regards
Shamim

On Nov 30, 2015, at 9:40 PM, Choy, Fannie (Yuet) <Fannie.Choy@fda.hhs.gov> wrote:

Dear Shamim:

We refer to NDA 206488 for eteplirsen submitted on June 26, 2015. The review team has the following request for information.

In your study report 4658-US-202-SR-CR-15-005, section 7, you state that sequencing of the PCR product confirmed the expected and correct skipping of exon 51. Please clarify if you observed a difference in the nucleotide sequences of the PCR product between pre-treated and post-treated samples to indicate that the PCR product you detected in post-treated samples was truly a novel transcript and not a precursor of revertant or trace dystrophin.

Please confirm receipt of email.

Regards,
Fannie

Fannie Choy, RPh.
Regulatory Project Manager
Division of Neurology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, WO22 Rm. 4215
Silver Spring, MD 20993-0002
301-796-2899 phone
301-796-9842 fax
fannie.choy@fda.hhs.gov

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From: [Shamim Ruff](#)
To: [Choy, Fannie \(Yuet\)](#)
Cc: [Matthew Rael](#)
Subject: Re: FDA Information Request: re: NDA 206488 / eteplirsen
Date: Monday, November 30, 2015 5:27:01 PM

Dear Fannie
Yes, I confirm receipt.

Regards
Shamim

On Nov 30, 2015, at 10:24 PM, Choy, Fannie (Yuet) <Fannie.Choy@fda.hhs.gov> wrote:

Dear Shamim,

Kindly confirm whether you have received this request.

Thank you,
Fannie

From: Choy, Fannie (Yuet)
Sent: Monday, November 30, 2015 10:15 AM
To: Shamim Ruff
Cc: Choy, Fannie (Yuet); Matthew Rael
Subject: RE: FDA Information Request: re: NDA 206488 / eteplirsen
Importance: High

Dear Shamim:

We refer to NDA 206488 for eteplirsen submitted on June 26, 2015. The review team has the following request for information. APPEARS THIS WAY ON ORIGINAL

- <!--[if !supportLists]-->**1)** <!--[endif]-->**Please send a copy of the images for the Western blots in Study 28 with all lanes labeled as to what is in each on the horizontal axis and also any relevant size markers on the vertical axis.**
- <!--[if !supportLists]-->**2)** <!--[endif]-->**Please verify which studies had testing for Anti-dystrophin antibodies and the location of this data in the NDA submission.**
- <!--[if !supportLists]-->**3)** <!--[endif]-->**Please verify which studies had testing for urine Myoglobin and the location of this data in the NDA submission.**

We ask that you provide this information by Noon on Tuesday, December 1, 2015. Please also provide your response to our Information Request, dated 11/27/15 (attached below), by Noon on December 1, 2015.

-

Please confirm receipt of email.

Regards,
Fannie

Fannie Choy, RPh.
Regulatory Project Manager
Division of Neurology Products

From: Matthew Rael [<mailto:MRael@Sarepta.com>]
Sent: Friday, November 27, 2015 11:40 AM
To: Choy, Fannie (Yuet)
Cc: Shamim Ruff
Subject: RE: FDA Information Request: re: NDA 206488 / eteplirsen

Hi Fannie,

I confirm receipt.

Best regards,

Matt

Matthew Rael, MS
Senior Manager, Regulatory Affairs
p 617.274.4029 (b) (6) f 617.812.0509
e mrael@sarepta.com

[<image001.jpg>](#)
215 First Street, Cambridge, MA 02142 USA

From: Choy, Fannie (Yuet) [<mailto:Fannie.Choy@fda.hhs.gov>]
Sent: Friday, November 27, 2015 6:53 AM
To: Shamim Ruff
Cc: Matthew Rael; Choy, Fannie (Yuet)
Subject: FDA Information Request: re: NDA 206488 / eteplirsen
Importance: High

Dear Shamim:

We refer to NDA 206488 for eteplirsen submitted on June 26, 2015. The review team has the following request for information.

- 1) Please provide the date of the Sarepta dose immediately prior to the SAEs for subject 28-01-108 (Ankle fracture) and 201/202-01-009 femur fracture**
- 2) In Study 33, what were the specific basis (e.g., laboratory, particular complaint,**

etc...) of the adverse of myoglobinuria for the 4 subjects with this adverse event?

We ask that you please provide your responses promptly.

Please confirm receipt of email.

Regards,

Fannie

Fannie Choy, RPh.

Regulatory Project Manager

Division of Neurology Products

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Avenue, WO22 Rm. 4215

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301-796-9842 fax

fannie.choy@fda.hhs.gov

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/s/

YUET L CHOY

11/30/2015

w/ concurrence: Dr Ron Farkas, DNP clinical TL

From: [Choy, Fannie \(Yuet\)](#)
To: [Shamim Ruff](#)
Cc: [Matthew Rael](#); [Choy, Fannie \(Yuet\)](#)
Subject: FDA Information Request: re: NDA 206488 / eteplirsen
Date: Friday, November 27, 2015 9:52:32 AM
Importance: High

Dear Shamim:

We refer to NDA 206488 for eteplirsen submitted on June 26, 2015. The review team has the following request for information.

- 1) Please provide the date of the Sarepta dose immediately prior to the SAEs for subject 28-01-108 (Ankle fracture) and 201/202-01-009 femur fracture**
- 2) In Study 33, what were the specific basis (e.g., laboratory, particular complaint, etc...) of the adverse of myoglobinuria for the 4 subjects with this adverse event?**

We ask that you please provide your responses promptly.

Please confirm receipt of email.

Regards,

Fannie

Fannie Choy, RPh.

Regulatory Project Manager

Division of Neurology Products

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Avenue, WO22 Rm. 4215

Silver Spring, MD 20993-0002

301-796-2899 phone

301-796-9842 fax

fannie.choy@fda.hhs.gov

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From: [Choy, Fannie \(Yuet\)](#)
To: [Shamim Ruff](#)
Cc: [Matthew Rael](#); [Choy, Fannie \(Yuet\)](#)
Subject: FDA Information Request: re: NDA 206488 / eteplirsen
Date: Monday, November 23, 2015 12:46:45 PM
Importance: High

Dear Shamim:

We refer to NDA 206488 for eteplirsen submitted on June 26, 2015. The review team has the following request for information.

Information request

1. For Study 28, specifically regarding Table 11-4 (pp. 63-4) of your study report, what do the pre-treatment numbers represent for the Western blot analysis.
2. For study 201/202, In Table 4 of your study report SR-CR-15-004 and Table 9 of your response to our Oct 23rd 2015 information request, you have provided numbers for % dystrophin protein that are below your proposed limit of quantitation (BLOQ). For some samples, you state that the average was BLOQ (01013 and 01015) but provide actual numbers below LOQ for others (DMD7 and DMD9). Please clarify this discrepancy and update Table 4 to consistently reflect your proposed BLOQ by providing average numbers for all samples and adding an asterisk or other designation to clarify if they were BLOQ.

Please provide your response by [Wednesday Nov 26th](#), close of business.

Please confirm receipt of email.

Regards,

Fannie

Fannie Choy, RPh.

Regulatory Project Manager

Division of Neurology Products

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Avenue, WO22 Rm. 4215

Silver Spring, MD 20993-0002

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/s/

YUET L CHOY

11/27/2015

w/ concurrence Dr Ron Farkas, DNP Clinical TL



NDA 206488

MID-CYCLE COMMUNICATION

Sarepta Therapeutics, Inc.
Attention: Shamim Ruff, MSc.
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) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Exondys 51 (eteplirsen) injection, 50 mg/mL.

We also refer to the teleconference between representatives of your firm and the FDA on October 22, 2015. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

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}

Ronald Farkas, M.D., Ph.D.
Clinical Team Leader
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time: October 22, 2015, 3:30 – 4:30 p.m. EST

Application Number: NDA 206488

Product Name: Exondys 51 (eteplirsen)

Indication: Treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping

Applicant Name: Sarepta Therapeutics, Inc.

Meeting Chair: Ronald Farkas, M.D., Ph.D.

Meeting Recorder: Fannie Choy, R.Ph.

FDA ATTENDEES

Division of Neurology Products

Ronald Farkas, MD, PhD, Clinical Team Leader
Christopher Breder, MD, PhD, Clinical Reviewer
Fannie Choy, RPh, Regulatory Project Manager

Office of Biotechnology Products

Ashutosh Rao, RPh, PhD, Acting Chief, Laboratory of Applied Biochemistry, Division of Biotechnology Review and Research III

Office of Clinical Pharmacology

Atul Bhattaram, PhD, Pharmacometric Reviewer

Eastern Research Group

Marc Goldstein, Independent Assessor

APPLICANT ATTENDEES

Sarepta Therapeutics, Inc.

Edward M. Kaye, MD, Chief Medical Officer, Senior Vice President, Clinical Development, and Interim Chief Executive Officer

Shamim Ruff, Vice President, Regulatory Affairs and Quality

Helen Eliopoulos, MD, Senior Director, Strategic Medical Advisor

Diane Frank, PhD, Senior Director, Translational Research

James Shao, Director, Biostatistics

Uditha DeAlwis, PhD, Director, Quality Control and Analytical Development

Matthew Rael, MS, Senior Manager, Regulatory Affairs

1.0 INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

A Mid-Cycle Communication agenda was sent to Sarepta on October 21, 2015. Sarepta sent discussion slides via email on October 22, 2015.

2.0 SIGNIFICANT ISSUES

We continue to have concerns regarding the strength of efficacy evidence that are similar to those that we communicated to you at the End of Phase 2 meeting on March 13, 2013, and at other meetings prior to submission of the NDA.

A. Clinical Endpoints

- Study 201: There was essentially no difference between drug- and placebo-treated patients based on the intent-to-treat population, and *post hoc* analyses conducted at later time points in a subset of patients lack credibility. Study 201 does not appear to provide any evidence of efficacy.
- Study 202: We understand that you argue that the decline in function of eteplirsen-treated patients is not as severe as what would be expected from natural history. It is not clear that the differences you highlight between eteplirsen-treated patients and natural history in Study 202 provide interpretable evidence of efficacy because such open-label studies are subject to considerable bias, and the decline in function of eteplirsen-treated patients appears generally similar to what would be expected from natural history.

Meeting Discussion:

- The applicant indicated that it thought the most persuasive evidence of efficacy for eteplirsen was from the multi-year Study 202, and that the less clear results of the 6-month Study 201 were not surprising because dystrophin served a protective role that was more apparent in decreasing functional decline over longer time periods.
- The applicant indicated that it thought differences between the clinical course of patients in the open-label Study 202 compared to that of the historical controls indicated eteplirsen was effective. FDA explained that the current findings of the primary review team suggested that the clinical course of eteplirsen patients was, in the context of the uncertainty inherent in

historical comparisons, similar to expected natural history. The applicant expressed concern that FDA did not accept the clinical meaningfulness of what it perceived to be large differences in clinical course between eteplirsen patients and historical controls, but FDA explained that the issue was not one of clinical meaningfulness, but rather whether the differences between groups were due to drug or to other differences between patient groups unrelated to eteplirsen.

- There was additional discussion about baseline and treatment differences between the eteplirsen patients and natural history controls, including factors that, if meaningfully different, would have been likely to affect clinical course, such as the specific type of corticosteroid and dosing regimen used. The applicant acknowledged that detailed information about corticosteroid use was not currently available for the natural history patients, and stated that more information was being sought. FDA commented that some differences between patient groups were more difficult to quantify but potentially important.
- The applicant asserted that placebo controlled trials of eteplirsen and similar drugs were not feasible because long-term administration of placebo to children through central venous catheters was not ethically acceptable. FDA clarified that it did not agree that placebo controlled studies were infeasible, and recommended that other types of access devices that did not enter central veins be used.

B. Biomarker Endpoints

- Most of the data from the first 3 biopsies is unreliable because of serious shortcomings of the experimental methodology. Improved methods were used for the 4th biopsy, but reliability is decreased by factors such as the small number of samples from only a subset of treated patients, many patients without matched baseline samples, and non-linearity of quantification at the very low dystrophin levels that may be present.

Meeting Discussion:

The applicant acknowledged the collaborative effort with the Agency on this aspect of the application.

FDA discussed the validation report for the western blot bioassay used for the fourth biopsy, including why the normal data samples were not considered to be 100% of normal intensity. The applicant explained that such a result could occur because of the way that the standard curve was generated, in combination with inherent variability in the western blot method and in dystrophin levels among different normal individuals. FDA also inquired about an apparent discrepancy in the identity of the Becker samples between different tables within the validation report. The applicant agreed to look into the issue and provide clarification after the teleconference. FDA also noted that submission of raw images was still needed for the validation report for the western Blots. After the teleconference, an information request was sent on October 23, 2015, with specific questions raised by FDA during the meeting.

3.0 INFORMATION REQUESTS

On October 26, 2015, Sarepta submitted response to the information request, dated October 16, 2015, concerning technical questions about dystrophin assay parameters.

[Meeting Discussion:](#) There was no meeting discussion.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

There are no major safety concerns identified at this time and there is currently no plan for a REMS.

[Meeting Discussion:](#) There was no meeting discussion.

5.0 ADVISORY COMMITTEE MEETING

We have tentatively scheduled an advisory committee meeting on January 22, 2016.

6.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

The review classification for this application is Priority. This application is also subject to the provisions of “the Program” under the Prescription Drug User Fee Act (PDUFA) V (refer to:

<http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>).

Therefore, the user fee goal date is February 26, 2016. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by January 25, 2016.

In addition, the planned date for the Late-Cycle Meeting is January 11, 2016, 3:00 p.m. – 4:00 p.m. EST. This meeting can be either a face to face meeting or a teleconference.

7.0 ATTACHMENT

Sarepta discussion slides titled “Discussion Items” received via email on October 22, 2015.

31 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

RONALD H FARKAS
11/20/2015

From: [Choy, Fannie \(Yuet\)](#)
To: [Shamim Ruff](#)
Cc: [Matthew Rael](#); [Choy, Fannie \(Yuet\)](#)
Subject: FDA Information Request: re: NDA 206488 / eteplirsen
Date: Thursday, November 12, 2015 12:24:19 PM
Importance: High

Dear Shamim:

We refer to NDA 206488 for eteplirsen submitted on June 26, 2015. The review team has the following request for information.

In Table 4 of your study report SR-CR-15-004 and Table 9 of your response to our Oct 23rd 2015 information request, you have provided numbers for % dystrophin protein that are below your proposed limit of quantitation (BLOQ). For some samples, you state that the average was BLOQ (01013 and 01015) but provide actual numbers below LOQ for others (DMD7 and DMD9). Please clarify this discrepancy and update Table 4 to consistently reflect your proposed BLOQ by providing average numbers for all samples and adding an asterisk or other designation to clarify if they were BLOQ.

We ask that you please provide your responses promptly.

Please confirm receipt of email.

Regards,

Fannie

Fannie Choy, RPh.

Regulatory Project Manager

Division of Neurology Products

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Avenue, WO22 Rm. 4215

Silver Spring, MD 20993-0002

301-796-2899 phone

301-796-9842 fax

fannie.choy@fda.hhs.gov

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/s/

YUET L CHOY

11/12/2015

at the request of Dr. Ron Farkas, Clinical TL

From: [Choy, Fannie \(Yuet\)](#)
To: [Shamim Ruff](#)
Cc: [Matthew Rael](#); [Choy, Fannie \(Yuet\)](#)
Subject: FDA Information Request: re: NDA 206488 / eteplirsen
Date: Thursday, November 05, 2015 2:15:47 PM
Importance: High

Dear Shamim:

We refer to NDA 206488 for eteplirsen submitted on June 26, 2015. The review team has the following request for information.

Please indicate the study date of start and resolution for the 9 Severe AEs in 6 subjects described in your Summary of Clinical Safety. Please consider the days relative to the subjects first dose, if treated OR from the day of randomization if not treated (e.g., Subject 301-216 003).

We ask that you please provide your responses within 7 business days of receiving the information request.

Please confirm receipt of email.

Regards,

Fannie

Fannie Choy, RPh.

Regulatory Project Manager

Division of Neurology Products

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Avenue, WO22 Rm. 4215

Silver Spring, MD 20993-0002

301-796-2899 phone

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fannie.choy@fda.hhs.gov

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/s/

YUET L CHOY

11/06/2015

at the request of Dr. Ron Farkas, DNP Clinical TL



NDA 206488

**METHODS VALIDATION
MATERIALS RECEIVED**

Sarepta Therapeutics
Attention: Shamim Ruff
215 First Street
Cambridge, MA 02142
sruff@sarepta.com

Dear Shamim:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Exondys 51 (eteplirsen) 50 mg/mL i.v. and to our 9/2/2015, letter requesting sample materials for methods validation testing.

We acknowledge receipt on 11/3/2015, of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have questions, you may contact me by telephone (314-539-3811), FAX (314-539-2113), or email (michael.hadwiger@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael E. Hadwiger, Ph.D.
MVP Coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

MICHAEL E HADWIGER
11/04/2015
Materials received letter

MICHAEL L TREHY
11/04/2015



NDA 206488

INFORMATION REQUEST

Sarepta Therapeutics
Attention: Shamin Ruff
Vice President, Regulatory Affairs and Quality
215 First Street. Cambridge, MA 02142

Dear Ms. Ruff:

Please refer to your New Drug Application (NDA) dated 13 July 2015, received 13 July 2015 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for EXONDYS 51.

We are reviewing the Drug Substance section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA by Friday, 30 October 2015.

LIST COMMENTS AND INFORMATION REQUESTS

- 1) You have agreed to revise the target fill volume for the 10.0 mL drug product configuration (b) (4) to be in accordance with USP <1151>. You state that 3.2.P.3 is not revised since the change is implemented via the quality change system. However, you still need to update section 3.2.P.3 accordingly per 314.50(d)(1)(ii)(a). Additionally, we request that you update section 3.2.P.1 to include the amount of overfill for each vial configuration.
- 2) Provide specific CFR citation for direct food contact (for example, 21CFR 177 and 178 with applicable sub paragraph numbers) for each formulation contacting equipment used in the manufacturing of the drug product. Provide a summary of the venter conducted extractable study results and safety evaluations (b) (4) (b) (4). Elaborate on why the initially assigned high risks (b) (4) carry low safety risk during the manufacturing of the drug product.

- 3) (b) (4)

(b) (4)

(b) (4). The release assay data from 15 batches manufactured so far are (b) (4) than the 100% label claim with only two exceptions. Indicate the corrective and preventive actions undertaken to provide adequate assurance that the assay is targeted at 100% of label claim for future commercial production.

- 4) Dr. Michael Hadwiger from the Office of Testing and Research, St. Louis, MO sent a material requisition to Ms. Shamim Ruff on 02-Sep-2015. However, we have not received this material so far. To facilitate completion of the method validation process, we recommend that you ship this material to our St. Louis laboratory as soon as possible.

If you desire, we could arrange for a tele conference with the CMC review team to discuss the above comments.

If you have any questions, please contact Dahlia A. Woody, Regulatory Business Process Manager, at (301) 796-8427.

Sincerely,

{See appended electronic signature page}

Wendy I.
Wilson -S

Digitally signed by Wendy I.
Wilson -S
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
0 9.2342.19200300.100.1.1=13
00396790, cn=Wendy I. Wilson
-S
Date: 2015.10.23 13:58:13
-04'00'

Wendy I. Wilson-Lee, Ph.D.
Branch Chief, Branch I (Acting)
Division of New Drug Products I
Office of New Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

From: [Choy, Fannie \(Yuet\)](#)
To: [Shamim Ruff](#)
Cc: [Matthew Rael](#); [Choy, Fannie \(Yuet\)](#)
Subject: FDA Information Request: re: NDA 206488 / eteplirsen
Date: Friday, October 23, 2015 12:21:34 PM
Importance: High

Dear Shamim:

We refer to NDA 206488 for eteplirsen submitted on June 26, 2015. The review team has the following request for information.

Clinical

1. Please provide the performance characteristics of the Becker patients on standardized physical function tests (e.g., 6 Minute walk test, NSAA, Rise time), previous biopsy information, medical history, medications etc.
2. Please provide all available data that you may have on the 6 DMD controls including information on standardized physical function tests (e.g., 6 Minute walk test, NSAA, Rise time), previous biopsy information, medical history, medications etc.

Bioassay

1. In your study report SR-CR-15-002, please clarify the discrepancy in the genotype for the BMD patients listed in Tables 2 and 3. In the related data sets in report SR-CR-15-004 (Tables 4-5), clarify which BMD, DMD, and healthy samples were identified as BMD 1,2,3 etc.
2. In your validation report SR-15-023,
 - a. Provide a scientific justification for each of the RSD acceptance criteria listed in Table 2.
 - b. Provide the gel images for each of the raw data to support Table 3. Please include the alpha-actinin gel images and accompanying densitometric quantitation for the dystrophin band for each gel.
 - c. (b) (4)
 - d. (b) (4). Provide a scientific justification as to why you choose to continue to use both 20 and 30 minute exposures with your week-180 samples.
 - d. Clarify why data for the 15 minute exposure was not analyzed.
3. In study report SR-CR-15-004, clarify exactly how you calculated the numbers provided in Tables 4 and 5.
 - a. Provide labeled gel images for all the data in Tables 4 and 5 and clarify how the quantitation was calculated. We are unclear about the comparator used to express

- the average percent dystrophin for each of these data. For instance, why did the three healthy control samples not have a 100% level compared to themselves?
- b. Provide a table showing the raw data for each of the BMD/DMD/control samples with columns showing levels of test sample dystrophin, test sample actinin, comparator dystrophin (e.g. pooled healthy, pooled DMD, control 2) and comparator actinin.

We ask that you please provide your responses **within one week** of receiving the information request.

Please confirm receipt of email.

Regards,

Fannie

Fannie Choy, RPh.

Regulatory Project Manager

Division of Neurology Products

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Avenue, WO22 Rm. 4215

Silver Spring, MD 20993-0002

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/s/

YUET L CHOY

10/23/2015

w/ concurrence: Dr Ron Farkas, DNP Clinical TL

From: [Choy, Fannie \(Yuet\)](#)
To: [Shamim Ruff](#)
Cc: [Matthew Rael](#); [Choy, Fannie \(Yuet\)](#)
Subject: FDA Information Request: re: NDA 206488 / eteplirsen
Date: Thursday, October 15, 2015 4:27:37 PM
Importance: High

Dear Shamim:

We refer to NDA 206488 for eteplirsen submitted on June 26, 2015. The review team has the following request for information.

Were any patients using orthoses or other devices during measurement study endpoints?

Please provide this information by [Monday 10/19/15](#). It is acceptable for you to email your response to me in advance of a formal, archival submission as long as both communications (email & archive) contain identical information.

Please confirm receipt of email.

Regards,

Fannie

Fannie Choy, RPh.

Regulatory Project Manager

Division of Neurology Products

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Avenue, WO22 Rm. 4215

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From: [Choy, Fannie \(Yuet\)](#)
To: [Shamim Ruff](#)
Cc: [Matthew Rael](#); [Choy, Fannie \(Yuet\)](#)
Subject: FDA Information Request: re: NDA 206488 / eteplirsen
Date: Friday, October 16, 2015 12:50:36 PM
Importance: High

Dear Shamim:

We refer to NDA 206488 for eteplirsen submitted on June 26, 2015. The review team has the following request for information.

Please clarify why you state that the upper and lower limits of quantitation (ULOQ and LLOQ) for your western blot are 4% and 0.25% of healthy control. Provide the supporting validation report showing the relationship between serially diluted healthy sample loading and densitometric quantitation of the bands. Include all healthy sample concentrations tested.

Additionally, clarify how you quantitated BMD and healthy samples at levels higher than 4% when your proposed assay ULOQ is 4%.

We ask that you please provide the response by [Wednesday 10/21/15](#). It is acceptable for you to email your response to me in advance of a formal, archival submission as long as both communications (email & archive) contain identical information.

Kindly confirm receipt of email.

Regards,

Fannie

Fannie Choy, RPh.

Regulatory Project Manager

Division of Neurology Products

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10903 New Hampshire Avenue, WO22 Rm. 4215

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fannie.choy@fda.hhs.gov

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/s/

YUET L CHOY

10/18/2015

w/ concurrence: Dr Ron Farkas, DNP Clinical TL

From: [Choy, Fannie \(Yuet\)](#)
To: [Shamim Ruff](#)
Cc: [Matthew Rael](#); [Choy, Fannie \(Yuet\)](#)
Subject: FDA Information Request: re: NDA 206488 / eteplirsen
Date: Thursday, October 08, 2015 1:11:33 PM
Importance: High

Dear Shamim:

We refer to NDA 206488 for eteplirsen submitted on June 26, 2015. The review team has the following request for information.

In data set ADBI for Western blot analysis Mandys106, you have listed quantitation of dystrophin at weeks 12/24/48 relative to normal control (as specified in column "VISIT"). However, there is no accompanying description that clarifies how you estimated this relative quantitation in the absence of a serial dilution of a healthy control on the same gels, as done with the 4th biopsy samples (per study protocol SR-CR-15-004). Please describe how you estimated the % dystrophin relative to normal control, clarify the SOP you used for this estimation, and provide the supporting images used for the quantitation listed in the datasheet. Please also provide clarifying detail on the difference between "Biopsy" and "Re-analysis Biopsy" in the LBGRPID column with respect to the Western Blot Analyses.

Please provide this information in an email no later than [Monday \(10/12/15\) at noon](#) before a formal submission to the electronic Gateway.

Please confirm receipt of email.

Regards,

Fannie

Fannie Choy, RPh.

Regulatory Project Manager

Division of Neurology Products

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Avenue, WO22 Rm. 4215

Silver Spring, MD 20993-0002

301-796-2899 phone

301-796-9842 fax

fannie.choy@fda.hhs.gov

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/s/

YUET L CHOY

10/09/2015

w/ concurrence: Dr. Ron Farkas, DNP clinical TL



NDA 206488

INFORMATION REQUEST

Sarepta Therapeutics
Attention: Shamin Ruff
Vice President, Regulatory Affairs and Quality
215 First Street, Cambridge, MA 02142

Dear Ms. Ruff:

Please refer to your New Drug Application (NDA) dated 13 July 2015, received 13 July 2015 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for EXONDYS 51.

We are reviewing the Drug Product section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA by Tuesday, 13 October 2015.

Drug Process:

1. Establish an upper limit for the API (b) (4) equilibrium time at room temperature.
2. Revise the target fill volume for the 10 mL configuration consistent with the overfill recommendations in USP Chapter <1151>. Alternatively, provide justification for the current target fill per FDA guidance "Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products" [June 2015].
3. Provide compatibility data for the formulation contacting equipment used in the manufacturing of the drug product, to demonstrate that they are not additive, reactive, and adsorptive. Indicate whether components used comply with pertinent CFR regulation for direct food contact as applicable.
4. Provide the latest manufacturing procedure including set points or ranges for all operational parameters, in-process controls, time for unit operation and total production including all holding times, and summary of supporting data. This information may be submitted in either an updated master batch record or an adequately detailed description in section 3.2.P.3.
5. Provide the procedure and validation report for the in-process (b) (4) test.

6. Provide a tabulated summary consisting of batch number, size, purpose, manufacturing time, in-process (b) (4) testing results (b) (4) (b) (4) for all batches used for clinical, registration, and stability study. (b) (4)
7. Revise the pertinent sections of the NDA, including batch formula, to reflect the scaled down sizes for the commercial production, which should not be larger than the largest process validation batches manufactured to date.
8. Update the application to include a detailed description the revised control for dissolution of the API in either the master batch record or section 3.2.P.3.

Facility:

Update section 3.2.P.3.1 to clarify which drug product release tests are performed at each facility listed in the application.

Drug Product:

- 1) Your justification for the acceptance criteria of 90-115% for the drug product assay is not adequate. We acknowledge that batch# 90GD-DR01 showed an assay of (b) (4)% at release. However, your in-process control (b) (4) (b) (4) should be sufficient to assure that the drug product assay is close to 100% on release. Tighten the acceptance criteria of the drug product assay at release or provide adequate justification.
- 2) Provide a copy of the data set (text or excel format) that was used for the statistical analysis of the stability data of the drug product

If you have any questions, please contact Dahlia A. Woody, Regulatory Business Process Manager, at (301) 796-8427.

Sincerely,

Martha R.
Heimann -S

Digitally signed by Martha R. Heimann -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=1300091527,
cn=Martha R. Heimann -S
Date: 2015.10.05 09:35:35 -04'00'

Martha R. Heimann, Ph.D.
CMC Lead, Neurology Products
Division of New Drug Products I
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 206488

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Sarepta Therapeutics, Inc.
215 First Street
Cambridge, MA 02142

ATTENTION: Shamim Ruff,
Vice President, Regulatory Affairs and Quality

Dear Mr. Ruff:

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

We also refer to your correspondence, dated and received August 28, 2015, requesting review of your proposed proprietary name, Exondys 51.

We have completed our review of the proposed proprietary name, Exondys 51 and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your August 28, 2015, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Ermias Zerislassie, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0097. For any other information regarding this application, contact Fannie Choy, Regulatory Project Manager in the Office of New Drugs, at (301) 796-2899.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES
10/03/2015



NDA 206488

INFORMATION REQUEST

Sarepta Therapeutics
Attention: Shamin Ruff
Vice President, Regulatory Affairs and Quality
215 First Street. Cambridge, MA 02142

Dear Ms. Ruff:

Please refer to your New Drug Application (NDA) dated 13 July 2015, received 13 July 2015 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for EXONDYS 51.

We are reviewing the Drug Substance section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA by Tuesday, 8 September 2015.

LIST COMMENTS AND INFORMATION REQUESTS

Drug Process:

1. Provide data supporting the maximum holding time (b) (4) for (b) (4) the sterile (b) (4) drug product (b) (4).
2. Establish an upper limit for the API (b) (4) (b) (4).
3. Explain (b) (4) (b) (4) described in the executed batch records.
4. Revise the target fill volume for the 10ml configuration to comply with the overfill limits described in the USP <1151>.
5. Provide compatibility data for the formulation (b) (4) (b) (4) (b) (4). Indicate whether components used comply with pertinent CFR regulation for direct food contact as applicable.

Drug Product:

- 1) Your justification for the acceptance criteria of 90-115% for the drug product assay is not adequate. We acknowledge that batch# 90GD-DR01 showed an assay (b) (4)% at release. However, your in-process control (b) (4) (b) (4) should be sufficient to assure that the drug product assay is close to 100% on release. Either tighten the acceptance criteria of the drug product assay at release or provide adequate justification.
- 2) Provide a description of the above (b) (4) method along with its validation data.
- 3) Provide the result from the statistical analysis of the stability data (b) (4) (b) (4) of the eteplirsen injection drug product. Also, provide us a copy of the data set in the SAS format along with the SAS code that was used for the analysis.

If you have any questions, please contact Dahlia A. Woody, Regulatory Business Process Manager, at (301) 796-8427.

Sincerely,

Martha R.
Heimann -S

Digitally signed by Martha R. Heimann -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=1300091527,
cn=Martha R. Heimann -S
Date: 2015.09.30 17:32:28 -04'00'

Martha R. Heimann, Ph.D.
CMC Lead, Neurology Products
Division of New Drug Products I
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

From: [Choy, Fannie \(Yuet\)](#)
To: [Shamim Ruff](#)
Cc: [Matthew Rael](#); [Choy, Fannie \(Yuet\)](#)
Subject: FDA Information Request: re: NDA 206488 / eteplirsen
Date: Monday, September 28, 2015 3:24:12 PM
Importance: High

Dear Shamim:

We refer to NDA 206488 for eteplirsen submitted on June 26, 2015. The review team has the following request for information.

Your Study 201 Analysis Dataset Define files are not clear regarding which of your datasets support your MANDYS106 intensity data I Table 11-2 of the CSR. In the LABCAT column of the dataset ADBI, there is a variable " IF MANDYS106" and also "Bioquant MANDYS106". In the dataset ADBI2, there are variables for "INTENSITY READOUT BQ – ORIGINAL" and "INTENSITY READOUT BQ".

Please explain the differences between these 4 variables, including a specific answer to which of your datasets support your MANDYS106 intensity data I Table 11-2 of the CSR.

Please provide this information ASAP in an email before submitting to the electronic Gateway no later than Wednesday (9/30/15) at noon.

Please confirm receipt of email.

Regards,

Fannie

Fannie Choy, RPh.

Regulatory Project Manager

Division of Neurology Products

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Avenue, WO22 Rm. 4215

Silver Spring, MD 20993-0002

301-796-2899 phone

301-796-9842 fax

fannie.choy@fda.hhs.gov

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/s/

YUET L CHOY

09/28/2015

concurrence: Dr Ron Farkas, DNP clinical TL

From: [Choy, Fannie \(Yuet\)](#)
To: [Shamim Ruff](#)
Cc: [Matthew Rael](#); [Choy, Fannie \(Yuet\)](#)
Subject: FDA Information Request: re: NDA 206488 / eteplirsen
Date: Wednesday, September 16, 2015 12:53:08 PM
Importance: High

Dear Shamim:

We refer to NDA 206488 for eteplirsen submitted on June 26, 2015. The clinical reviewer has the following request.

After review of the laboratory values for Study 201/202, it appears that the normal values shifted between the week 28 and 32 labs. For example the LDH high normal shifted from 1250 to 400 and the low values shifted from 250 to 100. Some labs have more than one change. Furthermore review of some labs, e.g., PT suggests a significant change in lab procedure since all of the resulting values of subjects seem to have shifted lower. I'd like a brief telephone call to discuss the laboratory tests for this application.

Please confirm receipt of email. It is preferable to have the call as soon as the appropriate members of your team are available.

Regards,

Fannie

Fannie Choy, RPh.

Regulatory Project Manager

Division of Neurology Products

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Avenue, WO22 Rm. 4215

Silver Spring, MD 20993-0002

301-796-2899 phone

301-796-9842 fax

fannie.choy@fda.hhs.gov

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/s/

YUET L CHOY

09/17/2015

concurrence: Dr. Ron Farkas, Clinical TL



NDA 206488

**FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED**

Sarepta Therapeutics, Inc.
Attention: Shamim Ruff, MSc.
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, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Exondys 51 (eteplirsen) injection, 50 mg/mL.

We also refer to your amendments dated July 13, 2015, July 24, 2015, July 31, 2015, August 20, 2015, August 28, 2015, and September 1, 2015, and to our August 20, 2015, Priority Review Designation letter.

As noted in our August 20, 2015, letter, we are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by January 25, 2016.

In addition, the planned date for our internal mid-cycle review meeting is October 13, 2015. We are currently planning to hold an advisory committee meeting to discuss this application.

At this time, we are notifying you that, we have not identified any additional potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We further refer to your submission of August 28, 2015. We note your commitment to provide a response to the FDA requests for information communicated to you by email on August 6, 2015,

and August 11, 2015. Specifically, you will be submitting the marked immunohistochemistry images from the 201/202 rescore and the fourth biopsy.

We have the following new request for information:

Drug Product

- 1) Provide data from freeze-thaw cycling studies (3 cycles) for both the fill configurations of the drug product.
- 2) Provide any additional stability data for the primary stability batches of the drug product along with the statistical evaluation to support the extension of shelf life.

Comparability Protocol

The comparability protocol submitted for the eteplirsen drug substance (b) (4) (b) (4) (b) (4) is unacceptable.

Several of the proposed changes (numbered per your proposal) are specifically identified as *major changes* in the FDA Guidance “Changes to an Approved NDA or ANDA (April 2004)” <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm077097.pdf> . (b) (4)

(b) (4)

These are changes considered to have a substantial potential to have an adverse effect on the identity, strength, quality, or purity of the drug substance thereby requiring submission of a *Prior Approval Supplement* (§ 314.70(b)).

As to the other two proposed changes (#1 and #6), additional information should be provided.

Each change should be specified and the acceptance criteria for evaluating the effect of the changes should be well defined. Acceptance criteria (numerical limits, ranges, or other criteria) should be included for each specified test and study that will be used to assess the effect of the CMC changes on the product or other material and/or demonstrate equivalence between pre- and post-change material.

Submit the analytical method of MALDI-TOF MS for Analysis of Impurities and validation to support its intended use in the comparability protocol. If the information is already in the NDA, please clarify the location.

The comparability protocol should include a plan for the stability studies that will be performed to demonstrate the equivalence of pre- and post-change product.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances, and
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

During our preliminary review of your submitted labeling, we have the following labeling comments:

General

- Remove all page numbers throughout the labeling.

Table of Contents

- The statement “*Sections or subsections omitted from the full prescribing information are not listed” should not be bolded.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by September 29, 2015. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

We will review this application under the provisions of 21 CFR 314 Subpart H – *Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses*. Unless we otherwise inform you, as required by 21 CFR 314.550, you must submit during the preapproval review period copies of all promotional materials, including promotional labeling and advertisements, intended for dissemination or publication within 120 days following marketing approval (i.e., your launch campaign). During the preapproval review period, please submit, in triplicate, a detailed cover letter (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (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>).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

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 the drug for this indication has orphan drug designation, you are exempt from this requirement.

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
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

WILLIAM H Dunn
09/04/2015



NDA 206488

**REQUEST FOR METHODS
VALIDATION MATERIALS**

Sarepta Therapeutics
Attention: Shamim Ruff
Vice President, Regulatory Affairs and Quality
215 First Street
Cambridge, MA 02142
sruff@sarepta.com

Dear Shamim:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Exondys 51 (eteplirsen) 50 mg/mL i.v.

We will be performing methods validation studies on Exondys 51 (eteplirsen) 50 mg/mL i.v., as described in NDA 206488.

In order to perform the necessary testing, we request the following sample materials and equipments:

Method, current version

Method	Analyte
ID, Molecular Weight by LC/MS (ESI)	Drug Product
Assay, Purity and Impurities by IP-HPLC	Drug Product
(b) (4) Impurity by SCX Chromatography	Drug Product
ID, Molecular Weight by LC/MS (ESI)	Drug Substance
Assay, Purity and Impurities (b) (4)	Drug Substance

Samples and Reference Standards

Eteplirsen Drug Product (50 mg/mL i.v. soln)	(b) (4)	mL
Eteplirsen Drug Substance		mg
Eteplirsen Drug Reference Standard	(b) (4)	mg
		mg
		mg
		g

Equipment

Item	Quantity
Agilent ES Tuning solution ((b) (4)	1
Waters Xbridge BEH 300, (b) (4)	2
Waters Xbridge C-18, (b) (4)	2
Thermo Scientific ProPac SCX-1 HPLC ((b) (4)	2
Thermo Scientific ProPac SCX-1 Guard (b) (4)	2

Please include the MSDSs and the Certificates of Analysis for the sample and reference materials.

Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: MVP Sample Custodian
645 S Newstead
St. Louis, MO 63110

Please notify me upon receipt of this communication. You may contact me by telephone (314-539-3811), FAX (314-539-2113), or email (michael.hadwiger@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael E. Hadwiger, Ph.D.
MVP coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

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/s/

MICHAEL E HADWIGER
09/02/2015

From: [Matthew Rael](#)
To: [Kelley, Laurie](#)
Cc: [Shamim Ruff](#); [Choy, Fannie \(Yuet\)](#)
Subject: NDA 206488: Response to Information Request - CK Data
Date: Tuesday, August 11, 2015 2:47:44 PM

Hi Laurie,

In response to Dr. Dunn's verbal request this morning regarding what creatine kinase data was included in our NDA:

Longitudinal CK data are described in the study 4658-us-202 Week 168 interim clinical study report, Section 12.4.2.1, beginning on page 112. Below is a brief quote from the relevant section:

Consistent with the underlying disease, test results for CK, ALT, AST, and LDH were generally above normal range limits but well within the expected range for patients with DMD (Table 12-6). A consistent downward trend of the mean values over the course of treatment was observed; it cannot be determined, based on the current data, whether this was due to the underlying disease or eteplirsen treatment (Listing 16.2.8.1.1.1).

Updated safety data through the Week 185 cutoff are provided in the CSR appendices, Table 14.3.4.1.1.1 entitled "Summary and Change from Baseline of Serum Chemistry Laboratory Parameters."

Best regards,

Matt

Matthew Rael, MS

Manager, Regulatory Affairs

p 617.274.4029 (b) (6) f 617.812.0509

e mrael@sarepta.com



215 First Street, Cambridge, MA 02142 USA

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/s/

YUET L CHOY
08/24/2015

Kelley, Laurie

From: Kelley, Laurie
Sent: Friday, August 21, 2015 2:52 PM
To: Shamim Ruff
Cc: Matthew Rael; Choy, Fannie (Yuet); Kelley, Laurie
Subject: NDA 206488 Information Request

Shamim

With regards to NDA 206488, our Clinical Reviewer has a request for information. For questions 2-5 please provide the information by August 28, 2015. For question 1, please provide the information by September 18, 2015.

Regards,
Laurie

1. Please submit a final study report for the Week 180 4th biopsy. Also submit all tabulation and analysis datasets with data from the 4th biopsy at 180 week. Provide an analysis set for each parameter (e.g., Western blots, Fiber counts) that contains data from all visits (e.g., 1, 13.9, 25.9, 140.02 and 180). A define file is requested formatted with consideration to the 8/11/15 teleconference, where we discussed the clarity needed in defining variables and codes.
2. In the raw western blot images provided with report SR-CR-15-004, the identity of the samples labeled 'NegCT' is not clear. Please indicate the specific DMD samples used as negative control for each gel. Please provide the gel that compares subject 01013 and 01015 untreated and week 180 treated samples side-by-side.
3. Please provide the corresponding beta-actinin loading control images for all western blot data shown in report SR-CR-15-004.
4. Do you estimate that the skipped product mRNA production seen at week 180 was comparable, lesser, or greater than the weeks 12/24 or 48 samples? Please clarify with a scientific basis for your estimation.
5. Please clarify if you co-stained any of the dystrophin slides with beta sarcoglycan, nNOS or other members of the dystrophin associated protein complex. If so, please send us these images and associated descriptions or narratives.

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/s/

LAURIE A KELLEY
08/21/2015



NDA 206488

INFORMATION REQUEST

Sarepta Therapeutics
Attention: Shamin Ruff
Vice President, Regulatory Affairs and Quality
215 First Street. Cambridge, MA 02142

Dear Mr. Ruff:

Please refer to your New Drug Application (NDA) dated 13 July 2015, received 13 July 2015 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for EXONDYS 51.

We are reviewing the Drug Substance section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA by Tuesday, 8 September 2015.

LIST COMMENTS AND INFORMATION REQUESTS

1. Provide Certificates of Analysis from the manufacturer (b) (4)
[Redacted]
2. Provide a more thorough discussion of the potential genotoxic/carcinogenic impurities arising from (b) (4)
[Redacted]
3. Provide an explanation for the up to (b) (4)% difference in yield obtained for commercial batches of eteplirsen drug substance (e.g., Lot 7001848 – (b) (4); Lot 7001509 – (b) (4)).
4. Provide identification numbers for all non-compendial analytical methods used in the eteplirsen drug substance specification.
5. Provide identification numbers for all non-compendial validation protocols used in the testing of the eteplirsen drug substance.

If you have any questions, please contact Dahlia A. Woody, Regulatory Business Process Manager, at (301) 796-8427.

Sincerely,

**Martha R.
Heimann -S**

Digitally signed by Martha R. Heimann-S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=1300091527,
cn=Martha R. Heimann -S
Date: 2015.08.18 15:50:31 -04'00'

Martha R. Heimann, Ph.D.
CMC Lead, Neurology Products
Division of New Drug Products I
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



NDA206488

PRIORITY REVIEW DESIGNATION

Sarepta Therapeutics, Inc.
Attention: Shamim Ruff, MSc.
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, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Exondys 51 (eteplirsen) injection, 50 mg/mL.

We also refer to your submissions dated June 25, 2015, July 13, 2015, July 24, 2015, and July 31, 2015.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Priority**. Therefore, the user fee goal date is February 26, 2016.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by January 25, 2016.

While conducting our filing review, we identified potential review issues that were communicated to you on August 6, 2015, by email.

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
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

LAURIE A KELLEY
08/20/2015

WILLIAM H Dunn
08/20/2015

Kelley, Laurie

From: Kelley, Laurie
Sent: Tuesday, August 11, 2015 2:07 PM
To: Shamim Ruff; Matthew Rael
Cc: Kelley, Laurie; Choy, Fannie (Yuet)
Subject: NDA 206488 Information Request

Categories: With Sponsor

Shamim and Matt

Please see the information request below from Drs Breder and Rao:

1. In order to assist in the review of the dystrophin rescore numbers submitted, provide the supporting marked immunohistochemistry images from studies 201/202 that indicate fibers that were considered positive or negative for dystrophin by the independent pathologists. For each subject, for the visit numbers 1, (13 or 25.9), 140.02, for Mandys106, for each field counted (using some nomenclature that is associated with the dataset row so the corresponding value can be found), and for each reviewer, send the image demonstrating the fibers counted as positive and negative (overlay of counting mask over fiber image) in either JPEG or PDF format, whichever gives the highest resolution and allows visualization of the scoring.
 - a. Use the naming convention, Subject_visit number_reviewer initials_field variable that ties it to the row on the dataset with the value.
2. We anticipate that we will need to review the marked immunohistochemistry images to support the numeric data you recently submitted for the inverted images with the week-180 biopsy samples stained with Mandys106. If you have already submitted this as part of the metadata, please point to the location of the overlaid metadata. If you have not, please plan to prioritize sending the supporting images from 201/202 first, followed by images from the week 180 biopsy. Within each data set, you may prioritize sending the images for the twelve treated patients and DMD/BMD controls first, followed by healthy positive and staining controls.

The requested information will need to be submitted to the NDA within 2 months on the date of receipt of this e-mail. Please acknowledge receipt of this request and provide your commitment to meet this deadline with 2 business days.

Regards,
Laurie

Laurie Kelley, PA-C
Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4380
10903 New Hampshire Ave.
Silver Spring, Maryland 20993-0002

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/s/

LAURIE A KELLEY
08/12/2015

From: [Choy, Fannie \(Yuet\)](#)
To: [Matthew Rael](#)
Cc: [Shamim Ruff](#); [Choy, Fannie \(Yuet\)](#); [Kelley, Laurie](#)
Subject: FDA Information Request: re: NDA 206488 / eteplirsen
Date: Thursday, August 06, 2015 3:30:51 PM
Attachments: [NDA206488_eteplirsen_IR_080615.pdf](#)
Importance: High

Dear Matt:

We refer to NDA 206488 for eteplirsen submitted on June 26, 2015. The review team has the attached request for information (Info Request dated 8/6/15). We ask that you respond to this request by August 14, 2015.

Please confirm receipt of email, and feel free to contact Laurie/me if you have any questions.

I will be on leave starting Monday Aug 10 through Friday Aug 21, returning on Aug 24, 2015. For any response related to this email and any urgent matters, please contact Laurie Kelley who is copied on this email. Kindly copy me on the email and I will respond upon my return.

Regards,

Fannie

Fannie Choy, RPh.

Regulatory Project Manager

Division of Neurology Products

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Avenue, WO22 Rm. 4215

Silver Spring, MD 20993-0002

301-796-2899 phone

301-796-9842 fax

fannie.choy@fda.hhs.gov

This electronic message is intended to be for the use only of the named recipient, and may contain information that is confidential or privileged. If you are not the intended recipient, you are hereby notified that any disclosure, copying, distribution or use of the contents of this message is strictly prohibited. If you have received this message in error or are not the named recipient, please notify us immediately by contacting the sender at the electronic mail address noted above, and delete and destroy all copies of this message.

We refer to NDA 206488 for eteplirsen submitted on June 26, 2015. The review team has the following comments and information requests. We ask for a prompt response by Friday August 14, 2015. If any of these comments and requests are unclear, you should contact us immediately.

A. Potential Filing Issues

1. Define files for datasets are deficient
 - a. The define file must provide an interpretable description of the contents of the datasets and, when necessary for interpretability, the relationships between different columns. The "Comments" column in the current Define files is not interpretable.
 - b. A brief (1 or 2 sentence) description of each dataset should be included in the define file.
2. The NDA does not contain adequate description of supportive clinical care for patients in study 201/202. As discussed at the Pre-NDA meeting, detailed information on supportive care, such as use of orthoses, physical therapy, and pulmonary therapy is necessary for meaningful comparisons to historical control patients.
3. The NDA does not contain the marked immunohistochemistry images that would indicate fibers that were considered positive for dystrophin by the independent pathologists.
4. MedDRA Versions need to be indicated for all AEs in the AE tables. The study AEs remain in the version from when they were coded (but should all be in 1 version per study), a combination of different MedDRA versions ranging from 14.0 to 17.1. The ISS AE dataset should be updated to the most recent (or recent) version, e.g., 17.1.
5. Study report hyperlinks affecting navigability. There are study report hyperlink errors, e.g. the hyperlink on p. 63 of 150 of the ISS for subject 28-02-202 (Severe AE that led to d/c) connects to the Section 9.6 Data Quality Assurance of Study Report 28. This is only one example. We request your comment on your quality assurance plan for correct and navigable hyperlinks.

B. Outstanding data and information

1. Full data for 4th biopsy, including datasets.

2. Please provide the SAS programs used to generate the tables and figures for the primary and key secondary efficacy endpoints for Study 201/202. If the SAS programs use any SAS macro, please provide all necessary macro programs.
3. According to the Analysis Plan for Study 202, ANCOVA for ranked data will be utilized if there is strong evidence suggesting that the 6MWT results deviate from normal distribution. Please provide discussion on whether the normality assumption has been met and on which analysis (MMRM vs. ANCOVA) conclusions should be based.
4. The raw concentration datasets for study 28 and study 202 were submitted, but the PK analysis datasets could not be located.
5. Please submit SAS codes used in the analyses comparing Studies 201/202 findings with historical controls.

C. Issues that slow review

1. Datasets do not comply with CDISC standards. For example, the units for values should be placed in their own variable column, not placed with another variable.
2. Hyperlinks from the Define file do not connect to datasets.

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/s/

YUET L CHOY

08/06/2015

Concurrence: Dr. Billy Dunn, DNP Director

From: [Matthew Rael](#)
To: [Choy, Fannie \(Yuet\)](#)
Cc: [Shamim Ruff](#)
Subject: RE: FDA Information Request: re: NDA 206488 / eteplirsen
Date: Wednesday, July 15, 2015 5:30:08 PM

Hi Fannie,

I confirm receipt of this email.

We'll get back to you as soon as possible.

Best regards,

Matt

Matthew Rael, MS

Manager, Regulatory Affairs

p 617.274.4029 (b) (6) f 617.812.0509

e mrael@sarepta.com



215 First Street, Cambridge, MA 02142 USA

From: Choy, Fannie (Yuet) [mailto:Fannie.Choy@fda.hhs.gov]
Sent: Wednesday, July 15, 2015 5:12 PM
To: Matthew Rael
Cc: Shamim Ruff; Choy, Fannie (Yuet)
Subject: FDA Information Request: re: NDA 206488 / eteplirsen
Importance: High

Dear Matt:

We refer to NDA 206488 for eteplirsen submitted on June 26, 2015. The review team has the following information request.

Please provide the LTBP4 haplotype for the patients in study 201/202 or indicate where in this information can be found in your NDA.

Please confirm receipt of email, and feel free to contact me if you have any questions.

Regards,

Fannie

Fannie Choy, RPh.

Regulatory Project Manager

Division of Neurology Products

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Avenue, WO22 Rm. 4215

Silver Spring, MD 20993-0002

301-796-2899 phone

301-796-9842 fax

fannie.choy@fda.hhs.gov

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/s/

YUET L CHOY

07/17/2015

at the request of Dr. Ron Farkas, Clinical TL



NDA 206488

NDA ACKNOWLEDGMENT

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

Dear Ms. Ruff:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Exondys 51 (eteplirsen) Injection, 50 mg per mL

Date of Application: June 26, 2015

Date of Receipt: June 26, 2015

Our Reference Number: **NDA 206488**

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on August 25, 2015, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neurology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, please contact me by phone or email at (301) 796-2899 or fannie.choy@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Fannie Choy, R.Ph.
Regulatory Project Manager
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

YUET L CHOY
07/09/2015



IND 077429

MEETING MINUTES

Sarepta Therapeutics, Inc.
Attention: Matthew Rael, MS
Manager, Regulatory Affairs
215 First Street, Suite 415
Cambridge, MA 02142

Dear Mr. Rael:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for eteplirsen (AVI-4658).

We also refer to the meeting between representatives of your firm and the FDA on May 19, 2015. The purpose of the meeting was to continue discussion regarding the content of a New Drug Application for eteplirsen.

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

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
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type C
Meeting Category: Guidance pre-NDA

Meeting Date and Time: May 19, 2015, at 10:00 – 11:00 a.m. EDT
Meeting Location: FDA White Oak Campus, Building 22, Rm 1415

Application Number: IND 077429
Product Name: Eteplirsen (AVI-4658)
Indication: Treatment of Duchenne muscular dystrophy
Sponsor/Applicant Name: Sarepta Therapeutics, Inc.

Meeting Chair: Billy Dunn, M.D.
Meeting Recorder: Fannie Choy, R.Ph.

FDA ATTENDEES

Office of the Center Director

Robert Temple, MD, Deputy Director for Clinical Science

Division of Neurology Products

Billy Dunn, MD, Director
Eric Bastings, MD, Deputy Director
Ronald Farkas, MD, PhD, Clinical Team Leader
Christopher Breder, MD, PhD, Clinical Reviewer
Nick Kozauer, MD, Clinical Team Leader
Lois Freed, PhD, Supervisory Pharmacologist
Barbara Wilcox, PhD, Nonclinical Reviewer
Dave Hawver, PhD, Nonclinical Reviewer
Laurie Kelley, PA-C, Regulatory Project Manager
Fannie Choy, RPh, Regulatory Project Manager

Office of Biotechnology Products

Ashutosh Rao, RPh, PhD, Acting Team Leader, Product Quality

Office of Clinical Pharmacology

Angela Men, MD, PhD, Clinical Pharmacology Team Leader
Bei Yu, PhD, Clinical Pharmacology Reviewer
Atul Bhattaram, PhD, Pharmacometrics Reviewer

Office of Biostatistics

Sue-Jane Wang, PhD, Associate Director for Adaptive Design and Pharmacogenomics/Pharmacogenetics

Kun Jin, PhD, Biometrics Team Leader, Division of Biometrics I

Xiang Ling, PhD, Statistical Reviewer, Division of Biometrics I

Rare Diseases Program

Larry Bauer

SPONSOR ATTENDEES

Sarepta Therapeutics

Edward M. Kaye, MD, Interim Chief Executive Officer, Chief Medical Officer and Senior Vice President Clinical Development

Jay Saoud, PhD, Senior Director, Biometrics

Shamim Ruff, MSc, Vice President, Regulatory Affairs and Quality

Matthew J. Rael, MS, Manager, Regulatory Affairs

Geno Clemenzi, Associate Director, Regulatory Operations

(b) (4)

1.0 BACKGROUND

Sarepta is developing eteplirsen for the treatment of Duchenne muscular dystrophy (DMD). Eteplirsen is a phosphorodiamidate morpholino oligomer (PMO). Its putative mechanism of action is to selectively bind to exon 51 of dystrophin pre-mRNA.

The Agency granted orphan drug designation and fast track designation for eteplirsen for the treatment of DMD on October 23, 2007, and November 27, 2007, respectively.

On March 13, 2013, an end-of-phase 2 (EOP2) meeting was held between the Agency and the sponsor. The sponsor had requested the Agency's opinion on the suitability of filing a New Drug Application (NDA) for eteplirsen to treat DMD.

On July 23, 2013, a Type C meeting was held between the Agency and the sponsor. The meeting was a follow-up to the EOP2 meeting, to continue discussion regarding the acceptability of the proposed NDA filing. Issues requiring further discussion from the Type C meeting were for the sponsor to generate additional data to support filing, and to start a controlled trial as soon as possible with the newly manufactured drug.

The Agency and the sponsor held follow-up meetings on November 8, 2013, November 15, 2013, December 19, 2013 and March 19, 2014. The purpose of the meetings was to discuss the evidence supporting the efficacy of eteplirsen for the treatment of DMD, and the design of future studies.

On April 15, 2014, the Agency provided the sponsor with a guidance letter describing FDA's view of the clinical and biomarker data currently available for eteplirsen and proposed a strategy to consider regarding the submission of an NDA for eteplirsen.

A Type B, CMC pre-submission meeting was held on September 3, 2014. On September 18, 2014, a Type B, pre-submission meeting was held to discuss the strategy and content of an NDA submission for eteplirsen. The sponsor and the FDA did not reach agreement on the content of a complete application at the meeting on September 18, 2014.

The purpose of this Type C Guidance meeting is to hold additional discussion with the Agency to determine the data that would constitute a complete NDA.

FDA sent Preliminary Comments to Sarepta on May 15, 2015.

2.0 DISCUSSION

Question 1:

Sarepta intends to submit an NDA for eteplirsen injection in mid-2015. In support of this NDA submission, Sarepta will submit all the data agreed with the FDA at the 18 September 2014 Pre-NDA meeting (FDA Memorandum of Meeting Minutes dated 20 October 2014, Reference ID 3644985), including the additional data requested by FDA at this meeting. Therefore, topics previously discussed at the 18 September 2014 meeting will not be included in this briefing document. For ease of review, the Agency's meeting minutes referenced above are provided in [Appendix 1](#) of this briefing document.

In addition to the topics agreed to at the Pre-NDA meeting on 18 September 2014, Sarepta will also include the additional items requested by the FDA for inclusion in the NDA submission. We believe that this will constitute a complete NDA as defined by the FDA; items are listed below.

- Week 168 data for Studies 4658-201/202 (previously submitted for FDA review; IND Sequence No. 0112, 24 February 2015)
- Historical control data for 6MWT and pulmonary function testing
- Safety data from new patients
 - 3-month safety data from at least 12 newly exposed patients
 - Additional safety data from later time points and from additional newly-enrolled patients will be submitted in the 120-Day Safety Update
- Dystrophin data, images and analyses as defined by FDA
- Independent assessment of dystrophin-positive fibers from Studies 4658-201/202 and Study 4658-28

- Review of available historical data regarding dystrophin expression and phenotype in Becker muscular dystrophy focusing on the natural history of Becker genotypes that would be created by skipping exon 51
- Analysis of muscle fat fraction by magnetic resonance spectroscopy (MRS) from patients evaluated in Studies 4658-201/202 compared to appropriate natural history controls

Does the Agency concur?

FDA Preliminary Response to Question 1:

Your proposal is generally acceptable but we should discuss and agree on the following:

- Biomarker data:
 - We should discuss your progress to date with analyses from the 4th muscle biopsy from patients in study 201/202, and when these data will be submitted.
 - Regarding your question about “dystrophin data, images, and analyses as defined by FDA” you should be guided by the following:
 - You should include in the NDA datasets for all raw and derived numerical data, including all biomarker and clinical data. For example, for dystrophin fiber counts, you should provide the independent rater analysis for each of the three raters that were included in the reassessment summary provided in Section 9.5 of the briefing document. Similarly, you should submit results from each biomarker assay conducted (including non-dystrophin biomarkers), for example density readings for each western blot, and intensity readings from each image analyzed by Bioquant or similar programs (including a description of results of assays that might not have been numerically read because of technical shortcomings, on-face lack of signal, or other reasons).
 - Regarding dystrophin images, you should submit all images from study 201/202 and study 28 that were captured in a standard format (such as .tif or .jpg). You should *not* submit images captured in non-standard format; however, we should discuss at the meeting what images are in non-standard format and if it is necessary or possible to convert the images to a standard format for submission.
 - Regarding analyses, you should include in the NDA an adequately detailed description and justification of each analysis performed on biomarker and clinical data. For example, for dystrophin fiber counts, you should describe and justify the statistical approach for inter-rater reliability (IRR) analysis of concordance as you have proposed by using the interclass correlation coefficient (ICC) values.
 - Regarding your proposal for electronic submission of the image data files, you should note the following:

- You need to notify the CDER electronic submission staff at ESUB@fda.hhs.gov in advance of your NDA submission.
 - To submit via physical media, it is recommended that you submit a paper copy of the cover letter (with contact information) and FDA form, in case the physical media proves to be unreadable. For more information on submitting via physical media, please refer to: [Specification for Transmitting Electronic Submissions using eCTD Specifications](#).
 - It is not clear that there is a hierarchical organization of your proposed table of contents for the images from study 201/202; if not, please include such an organization to improve usability.
 - The reason for organizing RT-PCR data images in sub-folders D2 and MD, corresponding to antibody names, is not clear.
 - You state that you will submit fat fraction analyses from study 201/202, but it is not clear if other magnetic resonance data was collected. You should not delay your NDA submission to include other magnetic resonance data, but should describe what other data was collected, what analyses are ongoing, and when such results are predicted to be available for submission to the NDA. It is important for interpretability that you submit the original protocols and statistical analysis plans for all magnetic resonance studies, including those that might be ongoing. You should also submit information that supports the validity of the approaches used.
- Clinical data:
 - We should discuss what ongoing testing is being conducted on patients in study 201/202, and when these data will be submitted. You should not delay submission of the NDA to include clinical data from time points later than week 168 but, if possible, such data should be submitted with the original NDA, and should be submitted as an amendment to the NDA as soon as possible.
 - You appear to indicate that you will only submit “tables, listings and figures” for ongoing studies 4658-us-301 and 4658-204. We should discuss the data that will be available at the time of the NDA submission and during the review cycle, and the specifics of your proposal.
 - We should discuss the description of baseline and ongoing clinical care of patients in study 201/202 that will be included in the NDA. To aid comparisons to historical controls, it is important to understand details of care such as steroid use (overall duration, dose, frequency, etc.) other medication use (e.g., cardiac medications), physical therapy (e.g., stretching, splints), and pulmonary therapy (e.g., breathing exercises).

Meeting Discussion:

The sponsor commented on several aspects of the proposed NDA content:

- It was unable to obtain natural history pulmonary function data from the Cooperative International Neuromuscular Research Group (CINRG). The Division requested that Sarepta continue efforts to obtain these data.
- Sarepta informed the Division that in the natural history data it had, rise time data may not be available, but it should be able to submit total NSAA scores.
- The sponsor informed the Division that it would not be able to have the fourth biopsy results until August. The Division stated that it could accept the NDA without this in the original submission; however, these data should be sent as soon as possible. The sponsor was advised to provide an update on the western blotting method validation activities. The Division also strongly advised the sponsor to consult with the Agency if there were any assay-related problems being encountered that might preclude the Division from performing a robust review of the western blotting data when submitted.
- The analysis of the Week 192 data should be available by mid-July. These data should be sent in with the original NDA submission, even if it was not yet integrated with other safety and efficacy data.
- The sponsor and Division agreed that a meeting to orient the review team to the contents of the submission would be useful. The Division commented that it would be most helpful to have this before the submission.
- The sponsor requested discussion on the acceptable file format for dystrophin images. The Division stated that it may be possible to view files generated in MetaMorph or ImageJ but the sponsor should submit a sample file with instructions to make sure it can be opened and reviewed by the Division. The sponsor was advised to follow-up with the Division to confirm that the file format is acceptable before submitting other raw image files to determine whether the software to view them should be included with the raw data files.

Question 2:

Sarepta intends to submit data received (as MS excel spreadsheets) from external academic institutions that include observational DMD patient data for 6MWT, MRS, and potentially pulmonary function testing. Sarepta will submit the datasets as .txt files and SDS-compliant .xpt files along with define.pdf and notes for reviewers.

Does the Agency find this acceptable?

FDA Preliminary Response to Question 2:

The apparent issues with data format may not be clear to us, and should be discussed at the meeting. The acceptability of the historical data itself for supporting your efficacy arguments is a review issue, and we will continue to work with you to obtain informative historical data.

Meeting Discussion:

The Division requested the following:

- Sarepta should send in the original excel datasets, as well as the SAS transport (.XPT) files. All data set entries that have the time of events, i.e., a start and stop time, should also include a variable column for the duration of the event. Examples of this include but are not limited to adverse events, concomitant medications, and dosing durations.

3.0 FDA ADDITIONAL COMMENTS

We note that a Type B pre-submission meeting was held on September 18, 2014, to discuss the content of a complete application for eteplirsen. We refer you to the minutes of that meeting for any additional agreements that may have been reached.

Post Meeting Note:

There is a possibility that your product may qualify for a Rare Pediatric Disease priority review voucher. If you are interested in pursuing this possibility, please consult the guidance, “Rare Pediatric Disease Priority Review Vouchers, Draft Guidance for Industry” (<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM423325.pdf>). Please see section “C” page 13 which describes the process for requesting a voucher. Please note that the requirement to include prevalence estimates is a critical element of the request.

PREA REQUIREMENTS

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 these requirements. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items identified during the meeting.

6.0 ATTACHMENTS AND HANDOUTS

Sarepta submitted slides titled, "Eteplirsen Injection Type B Pre-NDA Meeting | IND77429 | Pre-NDA 206488 | 19 May 2015".

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/s/

WILLIAM H Dunn
06/09/2015



IND 077429

MEETING MINUTES

Sarepta Therapeutics, Inc.
Attention: Matthew Rael, MS
Manager, Regulatory Affairs
215 First Street, Suite 415
Cambridge, MA 02142

Dear Mr. Rael:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for eteplirsen (AVI-4658).

We also refer to the meeting between representatives of your firm and the FDA on September 18, 2014. The purpose of the meeting was to discuss and reach agreement on the format and content of a complete NDA application.

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

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.
Acting Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: September 18, 2014, at 2:00 p.m. EST
Meeting Location: FDA White Oak Campus, Building 22, Rm 1315

Application Number: IND 077429
Product Name: Eteplirsen (AVI-4658)
Indication: Treatment of Duchenne muscular dystrophy
Sponsor/Applicant Name: Sarepta Therapeutics, Inc.

Meeting Chair: Billy Dunn, M.D.
Meeting Recorder: Fannie Choy, R.Ph.

FDA ATTENDEES

Office of the Center Director

Robert Temple, MD, Deputy Director for Clinical Science
Rich Moscicki, MD, Deputy Director for Science Operations

Office of Drug Evaluation I

Ellis Unger, MD, Director
Colleen Locicero, RPh, Associate Director for Regulatory Affairs (via teleconference)

Division of Neurology Products

Billy Dunn, MD, Acting Director
Eric Bastings, MD, Deputy Director
Ronald Farkas, MD, PhD, Clinical Team Leader
Veneeta Tandon, PhD, Clinical Reviewer
Lois Freed, PhD, Supervisory Pharmacologist
Barbara Wilcox, PhD, Nonclinical Reviewer (via teleconference)
Susan Daugherty, Senior Regulatory Project Manager
Fannie Choy, RPh, Regulatory Project Manager

Office of New Drug Quality Assessment

Martha Heimann, PhD, Neurology CMC Lead
Rao Kambhampati, PhD, Quality Reviewer (via teleconference)

Office of Biotechnology Products

Ashutosh Rao, RPh, PhD, Principal Investigator

Division of Biostatistics

Kun Jin, PhD, Biometrics Team Leader

Xiang Ling, PhD, Statistical Reviewer (via teleconference)

Office of Clinical Pharmacology

Angela Men, MD, PhD, Clinical Pharmacology Team Leader

Ta-Chen Wu, PhD, Clinical Pharmacology Reviewer

Hobart Rogers PharmD, PhD, Genomics and Targeted Therapy Reviewer

Atul Bhattaram, PhD, Pharmacometric Reviewer (via teleconference)

Office of Scientific Investigations

Tony El Hage, PhD, Reviewer, Division of Good Clinical Practice Compliance

Office of Surveillance and Epidemiology

Robert Pratt, PharmD, Reviewer, Division of Risk Management (via teleconference)

Jacqueline Major, PhD, Reviewer, Division of Pharmacovigilance I (via teleconference)

Justine Harris, PharmD, Reviewer, Division of Medication Error Prevention and Analysis
(via teleconference)

Ermias Zerislassie, PharmD, Regulatory Project Manager (via teleconference)

Rare Diseases Program

Devanand Jillapalli, MD, Medical Officer

EUROPEAN MEDICINES AGENCY

Sabine Haubenreisser, MSC, PhD, EMA liaison official at the US FDA

EASTERN RESEARCH GROUP REPRESENTATIVE

Patrick Zhou, Independent Assessor

SPONSOR ATTENDEES

Sarepta Therapeutics

Chris Garabedian, President and Chief Executive Officer

Edward M. Kaye, MD, Chief Medical Officer & Sr. Vice President Clinical Development

Jay Saoud, PhD, Senior Director, Biometrics

Peter Sazani, PhD, Executive Director, Medical Affairs

Diane Berry, PhD, Vice President, Global Health Policy and Government Affairs

Shamim Ruff, MSc, Vice President, Regulatory Affairs and Quality

Matthew J. Rael, MS, Manager, Regulatory Affairs

(b) (4)

1.0 BACKGROUND

Sarepta is developing eteplirsen for the treatment of Duchenne muscular dystrophy (DMD). Eteplirsen is a phosphorodiamidate morpholino oligomer (PMO). Its putative mechanism of action is to selectively bind to exon 51 of dystrophin pre-mRNA.

The Agency granted orphan drug designation and fast track designation for eteplirsen for the treatment of DMD on October 23, 2007, and November 27, 2007, respectively.

On March 13, 2013, an end-of-phase 2 (EOP2) meeting was held between the Agency and the sponsor. The sponsor had requested the Agency's opinion on the suitability of filing a New Drug Application (NDA) for eteplirsen to treat DMD.

On July 23, 2013, a Type C meeting was held between the Agency and the sponsor. The meeting was a follow-up to the EOP2 meeting, to continue discussion regarding the acceptability of the proposed NDA filing. Issues requiring further discussion from the Type C meeting were for the sponsor to generate additional data to support filing, and to start a controlled trial as soon as possible with the newly manufactured drug.

The Agency and the sponsor held follow-up meetings on November 8, 2013, November 15, 2013, December 19, 2013 and March 19, 2014. The purpose of the meetings was to discuss the evidence supporting the efficacy of eteplirsen for the treatment of DMD, and the design of future studies.

On April 15, 2014, the Agency provided the sponsor with a guidance letter describing FDA's view of the clinical and biomarker data currently available for eteplirsen and proposed a strategy to consider regarding the submission of an NDA for eteplirsen.

The sponsor is planning to submit an NDA in December 2014. A Type B, CMC pre-submission meeting was held on September 3, 2014. The purpose of the September 18, 2014, pre-NDA meeting is to discuss and reach agreement with the Agency on the strategy and content of the NDA submission for eteplirsen.

2.0 DISCUSSION

The Agency's responses to the questions presented in the sponsor's background package dated August 14, 2014, and to the additional question submitted on September 8, 2014, are provided below.

2.1. CLINICAL

Question 1: Clinical Safety and Efficacy

At the time of NDA submission, Sarepta will provide CSRs and integrated summaries of safety and efficacy for the complete (AVI-4658-33, AVI-4658-28, and 4658-us-201) and ongoing (4658-us-202) eteplirsen clinical studies conducted to date as described below.

- Final abbreviated CSR for study **AVI-4658-33**, entitled “Restoring Dystrophin Expression in Duchenne Muscular Dystrophy: A Phase I/II Clinical Trial Using AVI-4658”
- Final CSR for study **AVI-4658-28**, entitled “Dose-Ranging Study of AVI-4658 to Induce Dystrophin Expression in Selected Duchenne Muscular Dystrophy (DMD) Patients”
- Final CSR for study **4658-us-201**, entitled “A Randomized, Double-Blind, Placebo-Controlled, Multiple Dose Efficacy, Safety, Tolerability, and Pharmacokinetics Study of AVI-4658 (Eteplirsen), a Phosphorodiamidate Morpholino Oligomer, Administered Over 28 weeks in the Treatment of Ambulant Subjects with Duchenne Muscular Dystrophy”
- Interim CSR for **4658-us-202**, entitled “Open-Label, Multiple-Dose, Efficacy, Safety, and Tolerability Study of Eteplirsen in Subjects with Duchenne Muscular Dystrophy who Participated in Study 4658-us-201,” to cover all available clinical data through Week 144 (data cut-off for the Eteplirsen Injection NDA) of continuous weekly dosing (i.e., from Week 1 of Study 201 through Week 116 of Study 202)
- Integrated summaries of safety and data listings for all safety data, including uniformly coded adverse events and concomitant medications
- Integrated summaries of efficacy and data listings for dystrophin-related (all studies) and select functional clinical efficacy endpoints (Studies 4658-us-201/202)

Does the Agency agree that this information is sufficient for filing the application?

FDA Preliminary Response to Question 1:

No, the following issues need to be resolved before considering your application for filing:

- a) **Extent of Exposure:** In our April 15, 2014, letter we stated that the extent of patient exposure to eteplirsen was insufficient to adequately characterize the safety profile in patients with DMD, and we urged you to begin exposing additional patients as soon as possible, including patients both older and younger than those enrolled in previous eteplirsen studies.

Meeting Discussion:

There was discussion about the sponsor's proposal for exposure data to be included in the NDA. The sponsor proposed that no new exposure data be included at the time of NDA submission, and that data for 30 patients would be submitted in February, 2015, with data for 60 patients at the end of April, 2015 (sponsor slides appended).

After the meeting FDA met internally, and concluded the following:

- The sponsor should include 3-month data from at least 12 to 24 newly exposed patients at the time the NDA is submitted.
- Available data from the other patients enrolled in the new eteplirsen studies (studies 301, 203, 204) should also be included at the time the NDA is submitted, even if exposure is less than 3 months in duration.
- Additional data from later time points and from newly enrolled patients should be submitted in the 120-Day Safety Update.

- b) **Magnetic Resonance Imaging (MRI) Data:** On February 3, 2014, we asked you to submit the results of the MRI muscle study of the patients in study 201/202. You responded that the 2-year data from 11 of 12 patients would be collected by March 3, 2014, and that analysis was anticipated to take 2 additional months. Before we can consider filing, we need to determine that these data will be submitted in sufficient detail to permit substantive review, including, for example, data from comparable patients to serve as a comparator arm.

Meeting Discussion:

The sponsor explained that the MRI muscle study was being conducted by an academic group, and that availability of data was not under the sponsor's control. FDA agreed that if the MRI data could not be obtained it would not be a filing issue. However, FDA strongly urged the sponsor to submit the MRI data with appropriate natural history controls.

- c) **Historical Control Data for Clinical Endpoints:** You claim that open-label data from study 202 show a rate of decline in walking ability and a stabilization of respiratory muscle function that differ from the natural history. As stated in our April 15, 2014, letter, to permit substantive review of these claims, you need to identify historical patients who are appropriately matched to the study 202 patients. As stated in the letter, this requires individual patient-level data for the historical patients including, for example, measures such as rise time and/or similar timed tests (e.g., NSAA), baseline factors including duration and dose of steroids, and intensity of physical therapy and other ancillary care that affect physical function. The specific methods and conventions used to collect historical data also need to be described in detail because, for example, some of your analyses from study 201/202 are based on selecting the higher of two measurements, and comparison to historical data obtained from single measurements or average measurements would not be a valid comparison.

Importantly, as noted by Dr. Mendell and others, preservation of ambulation and other skills is affected by the value that families and caregivers put on maintaining those skills, with such factors as risk of falls and injury from continued ambulation weighed against the safety and speed of allowing patients to use a wheelchair. While it is not clear that such biases can be adequately controlled, you should present data in your application that demonstrate that measures of muscle strength were similarly impaired between eteplirsen patients and historical controls at the time that wheelchair use was adopted.

Meeting Discussion:

The sponsor indicated that it did not have, and did not plan to submit, patient-level natural history data, and that published data would be adequate as a historical control. FDA disagreed on the need for patient-level data, because without such data, there would be no way to be assured that the groups are adequately matched for important baseline and prognostic variables. FDA reiterated that it was the sponsor's responsibility to provide a matched historical control, and that FDA was not able to provide such data.

After the meeting FDA discussed the issue internally. FDA strongly advises the sponsor to obtain and submit patient-level natural history data. FDA is prepared to appeal to the academic groups holding the data to allow the sponsor a means to acquire the data.

- d) **Dystrophin Data and Analyses:** You claim that expression of dystrophin and associated proteins was increased by eteplirsen. To permit substantive review of these claims, the following data must be included in the application at the time of filing:
- i. The source images and key analyses of the expression data for dystrophin and related protein biomarkers from studies 201/202 and AVI-4658-28. This includes the blinded independent assessment of positive fibers for dystrophin immunohistochemistry (IHC) images that we described in our information request of July 29, 2014. Also, as contained in that information request, the Bioquant fluorescence intensity analyses of the 20x images from study 201/202 must be included in the application. To allow adequate assessment of the above results, the application must contain the source IHC and western blot images for both studies 201/202 and AVI-4658-28, along with summarized tables of the data. You must also include the relevant assay protocols, blinding procedures, quantitation methodology, and summarized assay validation information that justifies the acceptance/rejection criteria and controls used for each assay. In cases where multiple antibodies were tested with the same assay, you need to clarify the methodological differences and key quantitative findings with each antibody before submission of the application.

Meeting Discussion:

The sponsor proposed submission of the blinded independent assessment of positive fibers after submitting the NDA. FDA stated the assessment was crucial to FDA's review, and needed to be included when the NDA was submitted.

After the meeting FDA met internally, and concluded the following:

- The study 201/202 clinical site inspection conducted in May 2014, after the issuance of the April 15, 2014, guidance letter, uncovered marked disparities in the immunohistochemistry methodology and concerns about the reproducibility of data. The lack of confirmation of robust dystrophin measurement during the site visit necessitates including the independent assessment of dystrophin-positive fibers and the 168-week efficacy data from study 201/202 in the NDA.
 - Discrepancies remain, and must be resolved, between FDA's understanding from the investigator of the study 201/202 raw immunohistochemistry data that was collected, including images obtained at both 20x and 40x magnification, and the description of the data provided by the sponsor.
 - At the time of preparation of these meeting minutes discussions were ongoing between FDA and the sponsor regarding its proposals to change the method of assessment of dystrophin-positive fibers.
 - Additional discussion between the sponsor and FDA will be necessary to determine what would constitute a complete NDA.
- ii. One of your key arguments is that eteplirsen increases expression of truncated dystrophin to a level similar to that present in the milder Becker muscular dystrophy (BMD). To provide support for this assertion, you must include a thorough presentation and analysis of the historical data available regarding dystrophin expression in Becker and other milder forms of DMD in the application, as well as the correlation between protein expression and phenotype.

Meeting Discussion: There was no meeting discussion.

- iii. In your May 21, 2014, letter, you proposed new bioassay protocols for validating dystrophin assessment methods. Based on a subsequent communication we sent you on July 29, 2014, and discussions during the May 29-30, 2014, site visit to Nationwide Children's Hospital, you should provide your updated approach to dystrophin assessment and any available relevant method validation information supporting your updated approach for future biopsies.

Meeting Discussion: There was no meeting discussion.

Question 2: Integrated Safety Summary

Sarepta proposes to summarize uniformly coded safety data across all clinical studies (AVI-4658-33, AVI-4658-28, 4658-us-201, and 4658-us-202, up to 144 weeks).

Does the Agency agree with Sarepta's approach for summarizing eteplirsen safety data?

FDA Preliminary Response to Question 2:

Summarizing safety data across all studies is acceptable, but the studies vary greatly in design and length; detailed safety data also should be presented for each study separately.

Meeting Discussion: There was no meeting discussion.

Question 3: Primary and Supportive Efficacy Endpoints

Sarepta proposes to use the 6-minute walk test as the primary efficacy endpoint to support the proposed treatment indication for eteplirsen injection. Pulmonary muscle function and forced vital capacity data through Week 144 (study 4658-us-202) as well as percent dystrophin-positive fiber data at Weeks 12, 24, and 48 will be used as key supportive efficacy endpoints.

Does the Agency agree with this approach?

FDA Preliminary Response to Question 3:

As stated in our April 15, 2014, letter, we have significant concerns about the ability of either your clinical or biomarker data to support approval. The overall persuasiveness of the efficacy data is more important than any single endpoint. Data and analyses of all of the efficacy endpoints measured must be included in the application.

Meeting Discussion: There was no meeting discussion.

Question 4: Risk Evaluation and Mitigation Strategy

Sarepta believes that a Risk Evaluation and Mitigation Strategy (REMS) is not necessary to ensure that the benefits of eteplirsen administration outweigh the risks to DMD patients.

Does the Agency agree with Sarepta's approach?

FDA Preliminary Response to Question 4:

We are not currently aware of risks that would appear to require a REMS, but all safety decisions will be contingent on our review.

Meeting Discussion: There was no meeting discussion.

Question 5: Clinical Pharmacology

Question 5a:

Sarepta will provide supportive nonclinical data in the application at the time of NDA submission as follows:

- All available nonclinical pharmacokinetic reports previously submitted to the IND will be included in the NDA submission. These reports include nonclinical studies using human biomaterials (plasma protein binding, cytochrome P450 induction and inhibition, metabolic stability, and interactions with key human drug transporters) as well as a radiolabeled ¹⁴C-etelipirsen absorption, distribution, and excretion study in mice.

Does the Agency agree that these data are sufficient to support the NDA?

FDA Preliminary Response to Question 5a:

- The acceptability of these studies will be a matter of review of the detailed data in the application.
- ADME information in humans is needed to understand the metabolic fate of the parent drug and its metabolites, as well as contributions of various routes of elimination in humans. These data will inform decisions about whether specific studies in organ dysfunction will be necessary. Our view remains the same as communicated to you at the end-of-phase 2 meeting, given that you have not presented any new data.

Meeting Discussion: There was no meeting discussion.

Question 5b:

Sarepta will provide clinical pharmacokinetic data (plasma concentration and estimated PK parameters) in the application at the time of NDA submission as follows:

- Human pharmacokinetic reports from clinical studies AVI-4658-28, 4658-us-201, combined 4658-us-201/4658-us-202 (Week 8 single-draw), and 4658-us-202 (serial assessments at Week 124 ± 2 weeks, which corresponds to Week 152 from Week 1 of study 4658-us-201).

Does the Agency agree that these data are sufficient to support the NDA?

FDA Preliminary Response to Question 5b:

The proposed clinical pharmacokinetic (PK) reports to be included in the application appear sufficient. In addition, given that you planned to perform population PK analysis, the population PK study reports should be submitted. The acceptability of these data will be a matter of review.

Meeting Discussion: There was no meeting discussion.

Question 5c:

Sarepta plans to include requests for deferrals and waivers in the NDA for conducting clinical studies to evaluate eteplirsen in special patient populations, as follows:

- Deferral for the clinical evaluation of patients with renal impairment
- Waiver for the clinical evaluation of patients with hepatic impairment
- Waiver for the clinical evaluation of QT/QTc

Does the Agency agree with this approach?

FDA Preliminary Response to Question 5c:

- Study in renal impairment: The proposal for deferral is acceptable. You should include proposed labeling regarding the use of eteplirsen in renal impaired patients.
- Study in hepatic impairment: Based on the metabolism information for eteplirsen that you have previously submitted, the proposal to waive the study is acceptable. However, you should provide a comprehensive summary of the available scientific information and a justification for not needing a study as part of your application.
- Clinical evaluation of QT/QTc: We are willing to consider arguments in your application that characterization of potential QT effects can be accomplished without the need for a dedicated thorough QT study.

Meeting Discussion: There was no meeting discussion.

Question 6: Updated Safety and Efficacy Data

As discussed with the Agency at the 19 March 2014 meeting, Sarepta proposes submitting the efficacy data from the Week 168 time point (approximately Q1 in 2015) from patients enrolled in the ongoing study 4658-us-202 during the NDA review period.

Furthermore, available safety data from study 4658-us-202 up to and beyond Week 168, as well as any available data from our confirmatory open-label study 4658-301, will also be submitted as part of the 120-Day Safety Update.

Sarepta may also provide additional safety or efficacy data from eteplirsen-treated DMD patients in ongoing clinical studies 4658-203 and 4658-204 during the NDA review period.

Does the Agency agree with Sarepta's proposal for submitting updated safety and efficacy data during the review cycle?

FDA Preliminary Response to Question 6:

Efficacy data: The 168 week data will be collected prior to your planned submission and are critical to our analysis of efficacy. They should be included in the application at the time of submission.

Safety data: See response to Question 1.

Meeting Discussion:

See discussion to Question 1d.

Question 7: Confirmatory Studies to Support Accelerated Approval

In its April 2014 Advice/Information Request letter, the Agency outlined a potential pathway for accelerated approval of an NDA for eteplirsen injection including two confirmatory studies. Sarepta plans to fulfill both approaches suggested by the Agency as follows:

1. Study 4658-301 (Amendment 1 submitted in IND Amendment Sequence No. 0084, dated 28 May 2014), an open-label, historically-controlled study of eteplirsen, is currently being initiated at approximately 39 sites with the expectation that the first patient will be screened in August-September 2014.
2. Study 4045-301, a randomized, double-blind, placebo-controlled study of both SRP-4045 and SRP-4053, could potentially be initiated between early to mid-2015. The timing of this confirmatory study is dependent on (b) (4) agreement with the Division (b) (4), (b) (4). For study 4045-301, Sarepta plans to incorporate both SRP-4045 and SRP-4053 into a master protocol, both to expedite completion of enrollment, and to obtain a more robust placebo controlled clinical and dystrophin dataset in a timely manner in support of Sarepta's broader application of our technology across other rare DMD genotypes. Sarepta will request an expedited meeting with the Division under IND (b) (4) to discuss the development plans for SRP-4045 (and SRP-4053) necessary to enable this study and to seek agreement on its major design aspects.

Does the Agency agree in concept that its request for a randomized, double-blind, placebo controlled confirmatory study with SRP-4045 (4045-301) would be fulfilled if there was agreement from the Agency that the assessment of safety and efficacy were part of a broader master protocol that included both the SRP-4045 and SRP-4053 PMOs?

FDA Preliminary Response to Question 7:

A placebo-controlled trial should be initiated immediately with SRP-4045. A master protocol can be used so long as it does not cause any delay initiating the placebo-controlled study.

We are concerned about the accuracy of your characterization of the possible approval pathway for eteplirsen that we outlined in the April 2014 letter. In addition to the issues raised in our responses to your questions above, the following issues need to be addressed:

- We stated that, after examining the dystrophin source data and images, we were concerned about serious methodological problems and were skeptical that the available data were persuasive. We stated that you should begin exposure of additional patients, and that while we were willing to exercise flexibility, we expected additional dystrophin biomarker data at the time of NDA submission or shortly thereafter.
- We stated that based on our preliminary assessment of the possible effect size of eteplirsen (and other factors), we did not agree that the 48 week open-label trial that you proposed would be likely to provide a definitive demonstration of the efficacy of eteplirsen. Our more recent assessment of the 144 week efficacy data that are now available from study 201/202 suggests that functional decline may not be distinguishable from historical experience. This has increased our concern that any effect of eteplirsen, if present, may not be large enough to provide interpretable evidence of efficacy in an open-label study of a design similar to what you have proposed.

Meeting Discussion: There was no meeting discussion.

2.2. PHARMACOLOGY AND TOXICOLOGY

Question 8: Nonclinical Safety and Toxicology Assessment

Does the Agency agree that the proposed nonclinical safety and toxicity data are sufficient for filing the NDA application?

FDA Preliminary Response to Question 8:

The completed nonclinical studies appear to be sufficient to support filing of an NDA for eteplirsen. The adequacy of the studies will be a matter of review.

Meeting Discussion: There was no meeting discussion.

Question 9: Reproductive Toxicology

Does the Agency agree that the male fertility assessments performed within the repeat-dose toxicity studies fulfill the requirement for filing the application?

FDA Preliminary Response to Question 9:

Although the study in juvenile rat (study #4658-tox-003) and the 39-week study in cynomolgus monkey (Study #4658-tox-001) included assessment of male reproductive organs, it is not clear that these assessments were conducted in a stage-aware manner (*cf.* Meeting Minutes, dated 4/12/2013). We ask that you confirm that the microscopic evaluation of male reproductive organs in these studies was conducted with an awareness of the spermatogenic cycle (*cf.* Lanning LL *et al.* *Toxicologic Pathology*, 30(4): 507-520, 2002).

Meeting Discussion: There was no meeting discussion.

Question 10: Carcinogenicity

Does Agency agree with the planned approach to the assessment of carcinogenicity as described above?

FDA Preliminary Response to Question 10:

Based on the information provided in the briefing package, we cannot conclude that it would be sufficient to assess the carcinogenic potential of eteplirsen in a single species. You should provide justification in the application with supporting data for your planned approach. As previously discussed (Meeting Minutes, dated 4/12/2013), the assessment of carcinogenicity for eteplirsen may be conducted post-approval.

Meeting Discussion: There was no meeting discussion.

2.3. REGULATORY OPERATIONS

Question 11:

Does the Agency agree that the proposed data formats are acceptable for filing the application?

FDA Preliminary Response to Question 11:

Yes, the proposed data format is acceptable. If the raw SDTM data are converted from raw eCRF data, ensure the raw eCRF data are also submitted and provide clear traceability from raw data to SDTM data.

Meeting Discussion: There was no meeting discussion.

2.4. DYSTROPHIN QUANTIFICATION REASSESSMENT

Question 12:

As MANDYS106 was the antibody used for the primary analysis of studies 4658-us-201/202, Sarepta will prioritize reassessment of images generated using this antibody. We plan to have a standalone study report of the reassessment of MANDYS106 images available for submission in January 2015, during the 60-day filing period of the NDA for eteplirsen injection. Reassessment of the Dys2 and Dys3 antibody images, and IHC images from study AVI-4658-28 will follow, with the respective reports submitted post-filing as they become available.

Does the Agency find this approach acceptable?

FDA Preliminary Response to Question 12:

Please see our comments in response to Questions 1 and 7.

Meeting Discussion: There was no meeting discussion.

3.0 ADDITIONAL COMMENTS

3.1. **DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION**

- The content of a complete application was discussed. Additional discussion between the sponsor and FDA is necessary to determine what would constitute a complete NDA.
- 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.

- A preliminary discussion on the need for a REMS was held and it was concluded that FDA is not currently aware of risks that would appear to require a REMS, but all safety decisions will be contingent on our review.
- In addition, we note that a chemistry pre-submission meeting was held on September 3, 2014. We refer you to the minutes of that meeting for any additional agreements that may have been reached.

3.2. PREA REQUIREMENTS

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 these requirements. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

3.3. 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](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- 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 42 important format items from labeling regulations and guidances.

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

3.4. ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or

cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, “Guidance for Industry Assessment of Abuse Potential of Drugs”, available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>.

3.5. 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.				
2.				

Corresponding names and titles of onsite contact:

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

4.0 ISSUES REQUIRING FURTHER DISCUSSION

Additional discussion between the sponsor and FDA is necessary to determine what would constitute a complete NDA.

5.0 ATTACHMENTS AND HANDOUTS

Sarepta submitted slides titled, “Eteplirsen Injection | Type B Pre-NDA Meeting | IND 077429 / Pre-NDA 206,488 | 18 September 2014”.

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

/s/

WILLIAM H Dunn
10/17/2014

MEMORANDUM OF TELECONFERENCE

Teleconference Date: October 15, 2014, 9:30 a.m.
Dial-in Number: (b) (4)
Application Number: IND 077429
Product Name: Eteplirsen
Sponsor/Applicant Name: Sarepta
Subject: Discuss dystrophin data

FDA Participants

Ellis Unger, MD, Director, ODE1
Ronald Farkas, MD, PhD, Clinical Team Leader, DNP
Ashutosh Rao, RPh, PhD, Principal Investigator, OBP
Fannie Choy, RPh, Regulatory Project Manager, DNP

Sponsor/Applicant Participants

Sarepta
Edward M. Kaye, MD, Chief Medical Officer & Sr. Vice President Clinical Development
Peter Sazani, PhD, Executive Director, Preclinical Development
Shamim Ruff, MSc, Vice President of Regulatory Affairs and Quality
Matthew J. Rael, MS, Senior Regulatory Affairs Associate

1.0 BACKGROUND:

The Agency and the sponsor have had multiple discussions regarding dystrophin data and quantification, following a site visit of the laboratories at National Children's Hospital Research Institute on May 29 and 30, 2014.

The sponsor has asked for an informal teleconference to clarify its proposed methodology for the re-scoring of the dystrophin images from studies 201/202.

2.0 DISCUSSION:

The sponsor's question and related background information are appended to this memo.

Question:

Sarepta would like to provide (b) (4) images to assist in the interpretations of dystrophin-positive fibers may be of utility in the implementation of a multi-reader, multi-site dystrophin positive fiber assessment protocol.

Is this acceptable to FDA?

Meeting Discussion:

The Agency did not find the proposed method of assessing dystrophin-positive fibers to be acceptable. The Agency stated that, for the proposed NDA application, the sponsor should have the native images read by three expert, independent pathologists under the same protocol used by Nationwide Children's Hospital in Columbus, Ohio. The independent re-analyses should also provide information on the inter- and intra-analyst variability. (b) (4)

(b) (4) The sponsor expressed understanding of the discussion.

The sponsor informed the Agency of its plan to submit a full protocol for the positive fiber counting of the MANDYS106 images for the Agency's review on 10/20/14. Sarepta requested an expedited review, as the sponsor is planning to start the re-assessment on 10/27/14. Dr. Rao asked the sponsor to confirm that the protocol submitted would be similar to the protocol used in NCH. The sponsor clarified that there may be minor changes to ensure consistent reading across three laboratories, such as lighting conditions.

Dr. Unger urged the sponsor to start the re-assessment of positive fibers as soon as possible.

The call was ended.

Dear Dr Rao,

Sarepta would like to provide a brief update on the method development for the confirmation of the original dystrophin positive fiber data provided from Study 201/202. We would also like to check in with you on our proposal to minimize inter-reader variability detailed in Q1 below.

The original data represents a rigorous, robust, blinded assessment of dystrophin positive fibers as determined by a single reviewer. As we previously showed you, patients in Studies 201/202 treated with 30 mg/kg/wk eteplirsen demonstrated an increase in the percentage of dystrophin-positive fibers to 23% of normal, relative to baseline ($p \leq 0.004$), at week 24. At week 48, the 8 patients who had received 30 or 50 mg/kg/wk eteplirsen without interruption from week 1 showed a mean increase in the percentage of dystrophin-positive fibers to 47% of normal, relative to baseline ($p \leq 0.001$). Increases at week 48 were similar when the 30 mg/kg/wk (52%; $p \leq 0.001$) and 50 mg/kg/wk (43%; $p \leq 0.008$) cohorts were analyzed separately, suggesting that eteplirsen's effect on the production of novel dystrophin was independent of dose at these higher dose levels.

We are in the process of adapting the original protocol to apply to 3 independent pathologists located in potentially multiple sites. This includes, but is not limited to, ensuring that standard equipment and environmental conditions are used for all three readers. To this end we will be providing identical computers and monitors for each pathologist and will be ensuring that ambient room light levels are consistent in each of the reading rooms.

As MANDYS106 was the antibody used for the primary analysis of studies 4658-us-201/202, Sarepta will prioritize reassessment of images generated using this antibody. We expect to deliver a full protocol for the confirmation of the MANDYS106 images by October 20th for your review. We will be requesting a 2-3 day turnaround time so that we may begin execution of the protocol as soon as possible. We plan to have a standalone study report of the reassessment of MANDYS106 images available around the time of NDA submission, well within the 60-day filing period. Reassessment of the Dys2 and Dys3 antibody images, and IHC images from study AVI-4658-28 will follow, with the respective reports submitted post-filing as they become available.

Question 1

Method development is focused on obtaining high quality data from 3 independent pathologists by ensuring consistent image interpretation among readers and minimizing possible sources of variance.

(b) (4)

(b) (4)

Sarepta would like to provide image readers (b) (4) to assist in the interpretations of dystrophin-positive fibers may be of utility in the implementation of a multi-reader, multi-site dystrophin positive fiber assessment protocol.

Is this acceptable to FDA?

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/s/

YUET L CHOY
10/17/2014



IND 77,429

MEETING MINUTES

Sarepta Therapeutics, Inc.
Attention: Shamim Ruff, MSc, Vice President, Regulatory Affairs and Quality
215 First Street
Suite 7
Cambridge, MA 02142

Dear Ms. Ruff:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for eteplirsen (AVI-4658).

We also refer to the meeting between representatives of your firm and the FDA on September 3, 2014. The purpose of the meeting was to discuss the chemistry, manufacturing, and controls information to be submitted in an NDA for eteplirsen.

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

If you have any questions, contact Teshara G. Bouie, Regulatory Project Manager, at (301) 796-1649.

Sincerely,

{See appended electronic signature page}

Olen Stephens, Ph.D.
Acting Branch Chief
Branch I, Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: September 3, 2014; 2:00 – 3:00 pm
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1415
Silver Spring, Maryland 20903

Application Number: IND 77,429
Product Name: eteplirsen
Indication: Duchenne muscular dystrophy
Sponsor/Applicant Name: Sarepta Therapeutics, Inc.

Meeting Chair: Olen Stephens, Ph.D.
Meeting Recorder: Teshara G. Bouie

FDA ATTENDEES

Office of New Drug Quality Assessment

Olen Stephens, Ph.D., Acting Branch Chief
Martha Heimann, Ph.D., CMC Lead
Rao Kambhampati, Ph.D., Review Chemist
Teshara G. Bouie, Regulatory Health Project Manager

SPONSOR ATTENDEES

Jayant Aphale, PhD, MBA, RAC, Senior Vice President, Technical Operations
Shamim Ruff, MSc, Vice President, Regulatory Affairs and Quality
Ju Li, PhD, Sr. Scientist, Analytical Development
Ahmad Hasan, PhD, Director, Process Development and Scale-Up
William Cover, JD, PhD, Associate Director, CMC Regulatory Affairs
Daniel J. Ferreira, PhD, Associate Director, CMC Regulatory Affairs

1.0 BACKGROUND

IND 77,429 is indicated for the treatment of Duchenne muscular dystrophy. An EOP2 CMC meeting was held on October 17, 2013. The sponsor amended the IND on April 9, 2014, with CMC information to support changes to the drug substance manufacturing process (process A1 to A2). The Agency provided comments and recommendations in an Advice Letter dated May 23, 2014. On June 9, 2014, the sponsor requested a pre-NDA CMC meeting to discuss the chemistry, manufacturing, and controls information to be submitted in an NDA for eteplirsen. Background packages were received on July 29, 2014.

2. DISCUSSION

Question 1

- a. Does the Agency agree that these proposed release tests and acceptance criteria are acceptable for drug substance to be used in the manufacture of commercial drug product?

FDA Response: In general, the release test parameters appear reasonable except for the (b) (4) being controlled and the control strategy for the impurity profile. The release test methods and acceptance criteria will be reviewed upon NDA submission. Also, your justification for omitting testing for some solvents will be a review issue. See our response to question 7 for further comment.

- b. Does the Agency agree that these proposed release tests and acceptance criteria are acceptable for commercial drug product?

FDA Response: In general, the release test parameters appear reasonable except for the control strategy for the impurity profile. The release test methods and acceptance criteria will be reviewed upon NDA submission. See our response to question 7 for further comment.

Meeting Discussion: Sarepta referred to their slide # 5 detailing the synthesis and purification of the drug substance and outlined their justification (b) (4). The Agency advised Sarepta to submit this justification with details of the process description and batch analysis results of some recent lots (b) (4).

Question 2

Does the Agency agree that the proposed chemical stability protocol for the proposed label instructions will support the storage period between dilution and administration if the acceptance criteria are met?

FDA Response: Yes your approach appears reasonable.

Meeting Discussion: No further discussion at the meeting.

Question 3

- a. Does the agency agree that the stability data submission plan for the drug substance is acceptable for filing the NDA, with the commitment to submit additional data on primary stability batches 90 days after the original submission?

FDA Response: Yes, we concur with your stability data submission plan.

Meeting Discussion: No further discussion at the meeting.

- b. Does the agency agree that the stability data submission plan for the drug product is acceptable for filing the NDA with the commitment to submit additional data 90 – 120 days after the original submission?

FDA Response: Yes, we concur with your stability data submission plan.

Meeting Discussion: No further discussion at the meeting.

Question 4

Does the Agency agree [REDACTED] (b) (4)

FDA Response: We concur [REDACTED] (b) (4)
The acceptance criteria for these starting materials will be a review issue.

Meeting Discussion: No further discussion at the meeting.

Question 5

Based upon the calculations provided in the meeting briefing document, does the Agency agree that an environmental categorical exclusion will be granted?

FDA Response: Yes, we concur that you may submit a claim for an environmental categorical exclusion, and it is reasonable to expect that it will be granted.

Meeting Discussion: No further discussion at the meeting.

Question 6

Does the Agency agree Sarepta has acceptable plans to completely characterize the drug substance manufactured by the commercial process?

FDA Response: Yes, your approach appears reasonable.

Meeting Discussion: No further discussion at the meeting.

Question 7

Does the Agency agree Sarepta has acceptable data to support a change [redacted] (b) (4) [redacted] ?

FDA Response: Your change to [redacted] (b) (4) is a reasonable approach [redacted] (b) (4) We still have concerns with using this method [redacted] (b) (4)

As we recommended in our advice letter sent May 23, 2014, we recommend using a HPLC-MS system to better identify the impurities, [redacted] (b) (4) The system suitability testing for this method will be critical, [redacted] (b) (4)

Meeting Discussion: Refer to slides 7 & 8. The sponsor was advised to:

- Incorporate an internal standard for major impurities within defined regions.
- Define column run times and the time span for the pooled regions.
- Test API powder with MALDI-TOF across all batches to show consistency of the impurity profile and monitor batch to batch consistency.
- Write a protocol defining major changes and proposed filing categories. Submit this protocol in the Module 3 Regional section of the NDA.
- Provide justification in the NDA why LCMS is not used in the current method for monitoring impurities within regions.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

5.0 ACTION ITEMS

None.

6.0 ATTACHMENTS AND HANDOUTS

See attached.

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/s/

TESHARA G BOUIE
09/08/2014

OLEN M STEPHENS
09/08/2014



IND 077429

ADVICE/INFORMATION REQUEST

Sarepta Therapeutics, Inc.
Attention: Matthew Rael, MS
Manager, Regulatory Affairs
215 First Street, Suite 415
Cambridge, MA 02142

Dear Mr. Rael:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for eteplirsen (AVI-4658).

We also refer to your submission, dated May 21, 2014, providing an interim update on the new bioassay protocols under development for your validated dystrophin assessment methods.

We further refer to our May 29 and 30, 2014, site visit of the laboratories at Nationwide Children's Hospital Research Institute, where studies 201 and 202 were conducted.

Based on follow-up discussions with you and investigators at Nationwide Children's Hospital, we would like to request the following re-analysis of the stored raw images from previous phase 2 studies, to be completed at the earliest possible time. We have provided our requests, below, but please let us know if we can provide any additional information or clarification. Please submit a timetable for the estimated completion dates of each request.

1. **Percent Dystrophin Positive Fibers by Expert Assessment:** Please obtain blinded, independent assessment of the dystrophin scoring (positive/negative) from three pathologists or other experts.

Please specifically address the following points:

- a. Include images obtained with MandyS106, Dys2, and Dys3 antibodies.
- b. Specify the computer equipment, software, and conditions under which the pathologists will analyze the images. We suggest use of a modern high-resolution LED monitor in a room where lighting is well controlled (i.e., dimly lighted).
- c. Ensure that the 20x image files are renamed and randomized with respect to patient number, block number, section number, and quadrant number, and that all reads are blinded. In other words, the 24 images for each stain/patient/and timepoint should be separated, intermixed with images from all other patients, and read blindly in random

- order. The person(s) responsible for blinding the image files should not be involved in the image analyses.
- d. Assess the inter-analyst and intra-analyst variability for your image analyses between the independent pathologists. We suggest that readers analyze several images on two occasions (mixed in with other images), and that the dual readings can be used to assess intra-reader variability.
2. **Histogram of Pixel intensity:** Please submit the tiff files for a subset of images composed of the first 3 images from each patient and time point (12 patients and 3 time points), and include similar images for your positive and negative controls. For each image, please also provide a histogram of the red intensity of the pixels in the image.
 3. Please provide summarized data of the Bioquant fluorescence intensity analyses from study 201/202 using your 20x images.
 4. Please provide the primary IHC and western blot data for the 12-week open-label phase 2 dose escalation study and conduct the same analyses as described above on the IHC images.

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.
Acting Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

WILLIAM H Dunn
07/29/2014

MEMORANDUM OF TELECONFERENCE

Teleconference Date: April 23, 2014 12:15 – 1:00 p.m. EST
Dial-in Number: (b) (4)
Application Number: IND 077429
Product Name: Eteplirsen
Sponsor/Applicant Name: Sarepta
Subject: Discuss logistics for a Round-table Discussion

FDA Participants

Rich Moscicki, MD, Deputy Director for Science Operations
Ellis Unger, MD, Office Director, Office of Drug Evaluation I
Billy Dunn, MD, Acting Director, Division of Neurology Products (DNP)
Eric Bastings, MD, Deputy Director, DNP
Ronald Farkas, MD, PhD, Clinical Team Leader, DNP
Devanand Jillapalli, MD, Clinical Reviewer, DNP
Susan Daugherty, Regulatory Project Manager, DNP
Ashutosh Rao, RPh, PhD, Principal Investigator, Reviewer-Researcher, OBP

Sponsor/Applicant Participants

Sarepta
Edward M. Kaye, MD, Chief Medical Officer & Sr. Vice President Clinical Development
Peter Sazani, PhD, Executive Director, Preclinical Development
Shamim Ruff, MSc, Vice President of Regulatory Affairs and Quality
Matthew J. Rael, MS, Senior Regulatory Affairs Associate

Nationwide Children's Hospital

Louise R. Rodino-Klapac, Ph.D, Principal Investigator
(b) (4)

1.0 BACKGROUND:

The Agency and the sponsor had multiple discussions regarding dystrophin data and quantification. In order to clarify the quantification methodology of the dystrophin data from the existing trial, the FDA will hold a round-table discussion with the pathologist(s) at Nationwide Children's Hospital who generated the dystrophin-positive fiber data. During the round-table, the FDA would like a step-by-step walk-through of the procedure from image acquisition to data quantitation.

The goal of this teleconference was to agree on the logistics of the best way for FDA to learn how the current dystrophin data were obtained and analyzed.

2.0 DISCUSSION:

Before the discussion began, Dr. Dunn asked Sarepta what could be discussed with the Nationwide Children's Hospital (NCH) representatives on the teleconference. Sarepta asked that the discussion be limited to dystrophin.

Dr. Rao stated that FDA needs to be able to understand how the dystrophin data were acquired and analyzed because there seems to be some lack of agreement on the persuasiveness of those data. Dr. Rao then described how FDA performed their preliminary assessment of the immunohistochemistry and Western blotting data. FDA clarified that the raw data did not seem to fully support the qualitative and quantitative conclusions submitted by Sarepta. Sarepta indicated that the images that they provided were pdf (condensed) vs. full images. Dr. Rao indicated that the pdf-to-pdf comparison from the raw data to the previously submitted representative data in pdf format also did not appear consistent. Sarepta stated that they can try to review the images and the image analysis steps with the FDA to address any concerns.

(b) (4) thought it would be difficult to reproduce the exact conditions that they used to acquire and analyze the dystrophin data. (b) (4) stated that it is sometimes difficult to get consistent outcomes from immunohistochemistry analyses. Dr. Rao agreed and clarified that FDA would like a step-by-step explanation of the image acquisition and analyses performed using ImageJ and Bioquant software for the manual and automated quantitation of dystrophin positive fibers and fluorescence intensity, respectively. Both FDA and Sarepta representatives agreed that the best path forward was to have FDA representatives visit the Nationwide Children's Hospital and view the slides together. The images from previous analyses are available for review as TIF files, which might offer more detail and clarity. (b) (4) indicated that the person that performed the quantitation was blinded.

Dr. Moscicki asked for a high-level explanation of how the images were acquired, how the fields were selected, randomization, and how illumination was set. (b) (4) offered the following description:

- There were three levels of tissue segments.
- Each group of slides had positive and negative controls.
- All slides were stained within 24 hours.
- The person performing the photography was blinded.
- Four quadrants were chosen randomly by coordinates.
- For positive controls, the software chooses the illumination.

Dr. Unger asked for specifics regarding image analysis, specifically the number of gray levels assessed. The sponsor will forward this information.

It was noted that the 48-week biopsy was performed differently than the 12/24-week biopsies. (b) (4) stated that different sets of positive and negative controls were used for quantitation of the 48-week and 12/24-week slides.

Drs. Moscicki and Rao asked the Sponsor to ensure that FDA has the latest version of their immunohistochemistry and Western blotting protocols. The Sponsor agreed to check and provide any updates before FDA visits Nationwide Children's Hospital.

Dr. Moscicki indicated that more data may not be needed if we can be convinced during our visit to NCH. If we are not convinced, then FDA and the sponsor will discuss the possibility of a fourth biopsy.

Dr. Rao said the Western Blot data submitted by the sponsor contributed to our lack of confidence in the overall dystrophin conclusions presented by the sponsor. Issues with the data included over-filled protein gels. The sponsor agreed that the Western Blot data were inadequate. Dr. Rao offered to assist the sponsor in validating the antibodies and standardizing their protocol for Western blotting. The sponsor accepted Dr. Rao's offer to help and agreed to have further discussion.

Sarepta was also informed that the FDA is interested in a broader discussion on DMD and dystrophin as a biomarker. The FDA Critical Path Initiative may be contacting Sarepta to include them in a discussion with other stakeholders on the current state of dystrophin measurement in DMD.

Dr. Dunn indicated that today's teleconference would be the first of many interactions to discuss existing and, perhaps, future data. The goal is to optimize the methodology for assessing dystrophin in order to support a regulatory outcome. Drs. Rao, Moscicki, and Unger will be the FDA experts that will mainly be involved in assessing the biomarker aspects of the drug development program, with input from other FDA experts. Dr. Rao will be the primary technical point-of-contact for the dystrophin assay development and validation; however, all communication should come through the Regulatory Project Manager, Dr. Fannie Choy.

The call was ended.

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/s/

SUSAN B DAUGHERTY
05/02/2014



IND 077429

ADVICE/INFORMATION REQUEST

Sarepta Therapeutics, Inc.
Attention: Matthew Rael, MS
Manager, Regulatory Affairs
215 First Street, Suite 415
Cambridge, MA 02142

Dear Mr. Rael:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for eteplirsen (AVI-4658).

We also refer to the November 8, 2013, November 15, 2013, December 19, 2013, and March 19, 2014, meetings between representatives of your firm and the FDA. The purpose of the meetings was to discuss the evidence supporting the potential efficacy of eteplirsen for the treatment of Duchenne muscular dystrophy and the design of future studies.

Reference is also made to your electronic correspondence dated March 21, 2014, based on discussion with FDA on March 19, 2014, proposing studies to collect additional efficacy and safety data for eteplirsen.

This letter describes FDA's view of the clinical and biomarker data currently available for eteplirsen and proposes a strategy to consider regarding the submission of an NDA for eteplirsen. This letter also serves as the final meeting minutes for the four meetings listed above between FDA and Sarepta, with additional reference to the meeting preliminary comments sent to you on November 6, 2013, prior to our meeting on November 8, 2013, and the meeting preliminary comments sent to you on December 17, 2013, prior to our meeting on December 19, 2013.

BACKGROUND

Sarepta is developing eteplirsen for the treatment of Duchenne muscular dystrophy (DMD). Eteplirsen is a phosphorodiamidate morpholino oligomer (PMO) that selectively binds to exon 51 of dystrophin pre-mRNA.

DISCUSSION

We recognize that you, your academic associates, and others in the DMD patient community believe that the current evidence addressing the efficacy and safety of eteplirsen is sufficient to support NDA review. Although we have described our reservations about your interpretation of

the available data, we believe that with additional data to support the efficacy and safety of eteplirsen for the treatment of DMD, described below, an NDA should be fileable (assuming other aspects of the submitted application meet applicable standards). As we are sure you appreciate, however, our willingness to consider an application for filing cannot be taken to suggest the outcome of our review. We also note that if the application is filed, you should expect public discussion of the NDA at an Advisory Committee meeting.

We see two potential pathways to accelerated approval:

1. The clinical data from Study 201/202 on 6-minute walk could be considered a finding on an intermediate clinical endpoint that could have the potential to support accelerated approval. The basis for accelerated approval might be a conclusion that eteplirsen has some effect on the rate of decline of walking performance, a relatively short-term clinical benefit, that may be reasonably likely to predict a long-term beneficial effect on irreversible morbidity or mortality. That study, however, because of its size, design, and analysis, would fall short of adequately characterizing the effect of eteplirsen to an extent that would support standard approval.

We have significant concerns regarding our ability to draw valid conclusions based on the Study 201/202 data with respect to walking performance and other data for the reasons described below. These issues will be addressed during our review once the NDA is filed.

- a) For Study 201, the intent-to-treat (ITT) analysis, including all randomized patients, for the comparison of the eteplirsen-treated group to placebo was negative. We have previously expressed our skepticism regarding your modified ITT analysis, which excluded two patients randomized to eteplirsen.
 - b) Patients in Study 202 appear to be receiving optimal care, including intensive physical therapy and intensive steroid regimens. You would need to establish that treatment modalities in a historically-controlled population were similar, such that the historical group is appropriately matched to the Study 202 patients, and we would expect you to provide patient-level data for both groups.
 - c) For most of its duration, Study 202 was open-label. Performance on the 6-minute walk test is strongly influenced by motivation and coaching, and open-label trials are susceptible to bias on the part of investigators, patients, and parents.
2. We have discussed the possibility of using a number of modalities to quantify dystrophin in muscle biopsies, and discussed how these biomarkers might be used as a surrogate endpoint(s) to support accelerated approval. After examining the source data and images you provided in support of dystrophin protein expression from eteplirsen treatment, we remain skeptical about the persuasiveness of the data, and concerned about serious methodological problems explained previously.

As discussed during our recent meetings, however, we propose a collaborative effort in which we will work to better understand the methods and analyses used for the existing biomarker data. We will also work together on methods for the collection of additional data that could be more reliable. The goal of the collaborative effort would be to help you apply suitable, consistent, and objective methods for measuring increases in functional dystrophin protein, which should be amenable to independent verification. Whether additional biomarker data come from newly-treated patients, a repeat biopsy of patients currently enrolled in Study 202, or both will be a matter of further discussion.

As indicated above, we are uncertain whether the existing dystrophin biomarker data will be persuasive enough to serve as a surrogate endpoint that is reasonably likely to predict clinical benefit. If we were to find the biomarker data to be adequate upon detailed review, however, they would have the potential to support accelerated approval.

Another approach to demonstrating an effect of eteplirsen on dystrophin protein production would be to obtain a fourth muscle biopsy in patients who are continuing in Study 202, and to compare these samples, in blinded fashion, to samples obtained from a group of treatment-naïve patients with exon 51 DMD.

Stressing that we have not determined whether an application for eteplirsen would be approved, any accelerated approval would necessitate confirmatory studies to verify the clinical benefit. Confirmatory studies should be underway at the time of approval. We envision two approaches for confirmatory trials, and we urge you to initiate **both** of these trials as soon as possible:

1. A historically-controlled trial might be acceptable to confirm clinical benefit following accelerated approval. We note that a historically-controlled study is likely to provide interpretable evidence of efficacy only if the beneficial effect of eteplirsen is large, by clearly showing that performance is better in eteplirsen-treated subjects than could be reasonably expected, based on knowledge of the natural history of the disease. The effect size would have to be sufficient to overcome the uncertainty inherent in historically-controlled trials, and motivational factors that can affect the results.

We note also that the current extent of patient exposure to eteplirsen is insufficient to adequately characterize the safety profile in patients with DMD and that the historically-controlled trial will add substantially to the safety database. We urge you to begin this trial as soon as possible. We see no reason to exclude patients previously treated with drisapersen or to exclude patients older or younger than those enrolled in previous eteplirsen studies, and so we encourage you to include such patients. We would be open to discussing with you a plan to designate certain patients in the historically-controlled trial as the primary analysis population, with other patient subgroups included for secondary analyses and for collection of safety data. You should document the baseline characteristics of all patients and collect biomarker and clinical data in a manner similar to previous studies, allowing for any methodological improvements in the evaluation of dystrophin expression that result from our collaboration described above. We expect that the initial biomarker data from these exposures will start becoming available at about the

time of NDA submission and shortly thereafter. We are willing to exercise flexibility in receiving these emerging biomarker data during the review of the NDA.

2. A randomized, placebo-controlled trial of another PMO with a similar mechanism of action, directed at a different exon (e.g., SRP-4053 or SRP-4045), with demonstration of a correlation between dystrophin production and definitive clinical benefit on 6-minute walk or another measure, could provide confirmatory evidence of eteplirsen's clinical benefit if approval were based on a surrogate endpoint. We strongly suggest that you begin randomizing patients within a placebo-controlled trial(s) as soon as possible, once initial short-term safety data are obtained. We also urge you to include younger patients in these studies and to stratify efficacy analyses by age. As previously discussed with you, we find no credible reason to believe that efficacy cannot be demonstrated in younger patients.

We envision that you would pursue both confirmatory pathways simultaneously if eteplirsen were to receive accelerated approval, noting that the second pathway is in line with your stated business plan for development of other PMO drug candidates. If data from the second pathway became available first and confirmed clinical benefit to support full approval of eteplirsen, we would be open to discussing with you a plan to terminate the historically-controlled trial.

Based on our preliminary assessment of the possible effect size of eteplirsen, we do not agree that the 48-week open-label trial you proposed – eteplirsen versus a concurrent control arm of patients not amenable to an exon 51 skipping treatment – would be likely to provide definitive demonstration of the efficacy of eteplirsen. Unless the effect of eteplirsen is large and occurs soon after starting treatment, we view the concurrent control arm you have described as uninterpretable by design: 1) the natural history of non-exon 51 patients may differ from exon 51 patients; and 2) 48 weeks is not a sufficient period for observation. That said, we would not object to your proceeding with enrollment of a concurrent control group if such enrollment would be advantageous to you as you prepare for clinical trials of your other PMO drug candidates.

As you complete preparations for submission of an NDA, we recommend you carefully review the FDA Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biologic Products, particularly the sections that address reliance on a single adequate and well-controlled trial to support approval.

We understand the serious nature of DMD and the urgent need to develop safe and effective therapies for its treatment. We are committed to working closely with you on your clinical development program. If any points we have discussed above are unclear, please bring them to our attention immediately.

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.
Acting Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURES:

Sarepta proposal for eteplirsen program dated March 21, 2014
List of Meeting Attendees: March 19, 2014

From: [Shamim Ruff](#)
To: [Choy, Fannie \(Yuet\)](#)
Cc: [Matthew Rael](#)
Subject: FW: Sarepta Proposal for Eteplirsen Program
Date: Saturday, March 22, 2014 1:32:03 PM

Dear Fannie,

Further to our recent brainstorming session with FDA, please find attached below the email sent by our CEO, Chris Garabedian, to FDA Management yesterday afternoon.

Please acknowledge receipt.

Regards,

Shamim

Dear Drs. Woodcock, Temple, Jenkins, Unger, and Dunn:

Thank you for the informal brainstorming meeting and the constructive dialogue that took place on Wednesday, March 19th. We have considered the various kinds of input that you provided at this brainstorming session and we propose the following course of activities for you to consider. Once we receive formal guidance from the Agency, we will begin to move forward on finalizing these study protocols and begin the process of IRB approvals so we can begin screening and dosing new patients as soon as possible.

1. Clinical Studies

Sarepta proposes the following clinical trials for further discussion with you:

Proposed Eteplirsen Studies

Study Type	Population	N	Endpoints
Open label with control	Ambulatory exon-51-amenable DMD patients ≥ 7 years; Concurrent control arm of DMD patients with same inclusion/exclusion criteria that are non-exon-51 amenable	Approx. 60:60	6MWT, dystrophin, safety, exploratory functional endpoints
Open label	Exon-51-amenable DMD patients 4-6 years	Approx. 20	Safety, dystrophin, exploratory functional endpoints
Open label	Nonambulatory exon-51-amenable DMD patients ≥ 7 years	Approx. 20	Safety, dystrophin, exploratory functional endpoints
Non-interventional natural history	Non-exon-51 amenable DMD patients; all comers	TBD	Safety

2. Dystrophin Methodology

Thank you for your generous offer for us to engage with FDA experts, and also for your additional offer to allow us access to consult experts from the FDA laboratories as well as access to/use of FDA laboratories to work on standardization and refinement of our dystrophin assay methodology.

In order to clarify the quantification methodology of the dystrophin data from the existing Phase 2 clinical trial, we will ask (b) (4) (b) (4) who generated the dystrophin-positive fiber data to make (b) (4) available to you. This may allow you to better understand how these data were generated and interpreted. We look forward to scheduling these meetings as soon as possible.

Sarepta will work closely with the Agency to reach agreement on our dystrophin quantification methods for use in our upcoming studies. We have a protocol to conduct immunofluorescence, western blot, and RT-PCR assessments at a minimum. If the timing of muscle biopsies are expected to occur before agreement on these methodologies are reached with the Agency, Sarepta will explore freezing the blocks for future analysis. Sarepta will also investigate the potential assessment of nNOS as a confirmatory marker of functional dystrophin and use of new dystrophin detection and quantification methods, such as mass spectrometry, which may supplement but not initially replace our existing immunofluorescence-based assay.

3. NDA Submission

From the views we heard expressed by the Agency, it appears the FDA may be open to an NDA filing based on the clinical outcomes data from the existing Phase 2 study. Sarepta is prepared to submit the NDA this summer, with an understanding that the chances of a positive review would be bolstered by supplemental data, such as 144-week clinical data (e.g., 6MWT, Pulmonary Function tests), early safety data from additional eteplirsen exposed patients in the upcoming studies, and/or a possible fourth muscle biopsy from the ongoing Phase 2 study.

4. Follow-On Exon Skipping Drugs for DMD and Confirmatory Study

As discussed, we are in late preclinical development with two follow-on exon-skipping drugs targeting gene deletions amenable to exons 45 and 53 and we understand the Agency would like us to move these drugs into patients as soon as possible. To this end, we will work with the FDA on the design of this study that would include our drugs, SRPT-4045 and SRPT-4053 and will prepare a design that will include one or both of these drugs against a placebo control. Please note that we are currently at the pre-IND stage for these next 2 compounds and will need to prepare manufacturing scale-up for clinical trials with INDs submissions expected in the 2nd half of this year.

5. Communication to the Public

Upon receipt of formal guidance from the Agency that reflects all of the meetings since November, 2013, as well as FDA's position on the course of activities proposed in this letter, we are prepared to share our planned draft press release with the appropriate contact at the FDA to ensure an alignment of communications between Sarepta and the

Agency for this program.

We thank you for your active and broad engagement on this program across the Agency and the extensive time each of you have provided to assist us in evaluating eteplirsen for DMD boys. We look forward to your response to our proposal and we hope you that you find the approach we have outlined above acceptable, so that we, together with the DMD community, can move forward swiftly.

Sincerely,

Chris Garabedian

President & CEO

617.274.3993 direct

(b) (6)

cgarabedian@sarepta.com



215 First Street, Cambridge MA 02142

The information contained in this message may be confidential, privileged and protected from disclosure. If the reader of this message is not the intended recipient, you are hereby notified that any dissemination, distribution or copying of this communication is strictly prohibited. If you have received this communication in error, please notify us immediately by email or telephone and destroy all copies of the original message. Thank you.

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LIST OF MEETING ATTENDEES

Meeting Date and Time: March 19, 2014 2:00-4:00 P.M. EST
Meeting Location: FDA White Oak Campus, Building 22, Room 1313

FDA ATTENDEES

Office of the Center Director

Janet Woodcock, MD, Director
Robert Temple, MD, Deputy Director for Clinical Science
Robert Guidos, JD, Senior Advisor
Rich Moscicki, MD, Deputy Director for Science Operations

Office of New Drugs

John Jenkins, MD, Director

Office of Drug Evaluation I

Ellis Unger, MD, Director

Division of Neurology Products

Billy Dunn, MD, Acting Director
Eric Bastings, MD, Deputy Director
Ronald Farkas, MD, PhD, Clinical Team Leader
Devanand Jillapalli, MD, Clinical Reviewer
Veneeta Tandon, PhD, Clinical Reviewer
Lois Freed, PhD, Supervisory Pharmacologist
Barbara Wilcox, PhD, Nonclinical Reviewer (via teleconference)
Fannie Choy, RPh, Regulatory Project Manager
Laurie Kelley, PA-C, Regulatory Project Manager (via teleconference)
Aaron Sherman, Consumer Safety Technician (via teleconference)

Office of Biotechnology Products

Ashutosh Rao, RPh, PhD, Principal Investigator, Reviewer-Researcher

Office of New Drug Quality Assessment

Rao Kambhampati, PhD, Quality Reviewer

Office of Clinical Pharmacology

Angela Men, MD, PhD, Clinical Pharmacology Team Leader
Ta-Chen Wu, PhD, Clinical Pharmacology Reviewer (via teleconference)
Hobart Rogers PharmD, PhD, Genomics and Targeted Therapy Reviewer
Vikram Sinha, PhD, Director, Division of Pharmacometrics (via teleconference)
Atul Bhattaram, PhD, Pharmacometric Reviewer

Office of Biostatistics

Kun Jin, PhD, Team Leader, Division of Biometrics I

Office of Pediatric Therapeutics

Skip Nelson, MD, PhD, Deputy Director and Senior Pediatric Ethicist

Rare Diseases Program

Larissa Lapteva, MD, Medical Officer

SPONSOR ATTENDEES

Sarepta Therapeutics

Chris Garabedian, President and Chief Executive Officer

Edward M. Kaye, MD, Chief Medical Officer & Sr. Vice President Clinical Development

Jay Saoud, PhD, Senior Director, Statistics and Data Management

Peter Sazani, PhD, Executive Director, Preclinical Development

Shamim Ruff, MSc, Vice President of Regulatory Affairs and Quality

Matthew J. Rael, MS, Manager, Regulatory Affairs

(b) (4)

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/s/

WILLIAM H Dunn
04/15/2014

MEMORANDUM OF TELECONFERENCE

Teleconference Date: February 7, 2014 12:00 p.m.

Application Number: IND 077429

Product Name: Eteplirsen

Sponsor/Applicant Name: Sarepta

Subject: Discuss dystrophin data

FDA Participants

Billy Dunn, MD, Acting Director, Division of Neurology Products
Ronald Farkas, MD, PhD, Clinical Team Leader, DNP
Devanand Jillapalli, MD, Clinical Reviewer, DNP
Veneeta Tandon, PhD, Clinical Reviewer, DNP
Fannie Choy, RPh, Regulatory Project Manager, DNP
Ashutosh Rao, RPh, PhD, Principal Investigator, Reviewer-Researcher, OBP
Atul Bhattaram, PhD, Pharmacometric Reviewer, Office of Clinical Pharmacology

Sponsor/Applicant Participants

Chris Garabedian, President and Chief Executive Officer
Edward M. Kaye, MD, Chief Medical Officer & Sr. Vice President Clinical Development
Jay Saoud, PhD, Senior Director, Statistics and Data Management
Peter Sazani, PhD, Executive Director, Preclinical Development
Shamim Ruff, MSc, Vice President of Regulatory Affairs and Quality
Matthew J. Rael, MS, Senior Regulatory Affairs Associate

1.0 BACKGROUND:

The Agency and the sponsor had multiple discussions regarding dystrophin data and quantification. The Agency would like to review all the biomarker data for patients treated with eteplirsen. The teleconference is to request all supportive biomarker data that the sponsor might have.

2.0 DISCUSSION:

- a. Dr. Dunn asked the sponsor to submit all immunofluorescence (IF) and Western Blot (WB) data for all patients. Sarepta acknowledged that they have access to WB, RT-PCR, and IF data for all 12 patients at all time points.
- b. Dr. Rao requested the WB data for all 12 patients, including baseline and week 12/24/48 time point samples (see Action Item). The Agency will need the raw data as full-length blot images with an indication of the dystrophin or actin loading control bands and a table with the quantification of the dystrophin and bands from each

- image. Explain post-treatment changes observed in the dystrophin band. If different antibodies were tested, provide a side-by-side comparison of the staining profile for the different antibodies with identical sample(s).
- c. Dr. Rao requested the IF for all 12 patients, including the 24 raw data images from each patient and the quantification for fluorescence intensity and percent positive fibers for each image (see Action Item).
 - d. Dr. Rao requested the raw RT-PCR data as full-length gel images, for all patients, including the baseline and week 12/24/48 samples (see Action Item). Indicate the band(s) corresponding to skipped product and explain any post-treatment changes. Also include your assessment of the correlation between dystrophin quantitation by WB, IF, and RT-PCR.
 - e. Dr. Dunn informed the sponsor to submit the data as soon as possible, in order for the Agency to do a comprehensive analysis of the data. Dr. Dunn explained that this was an informal working teleconference for the purpose of explaining the Agency's data request and that, following completion of the Agency's review of the data to be submitted, the sponsor could expect a follow-up working teleconference or meeting to discuss the Agency's findings.

3.0 ACTION ITEMS:

The sponsor will submit interpretable data as soon as possible, or in modules as early as next week. The sponsor will communicate with the Agency for clarification of the request, if needed.

List of items to submit:

- a. All WB, full length blot images, label and quantify dystrophin/actin, all 12 patients
- b. Comparison of WB with either MandyS106 or Dys1 antibodies and same sample(s)
- c. All IF images and quantification of intensity and percent positive
- d. All RT-PCR, full length gels, label and quantify skipped product, all 12 patients
- e. Correlation between dystrophin quantitation by WB, IF and RT-PCR.

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/s/

YUET L CHOY
02/10/2014



IND 77,429

MEETING MINUTES

Sarepta Therapeutics, Inc.
Attention: Matthew Rael, MS, Senior Regulatory Affairs Associate
215 First Street
Suite 7
Cambridge, MA 02142

Dear Mr. Rael:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for eteplirsen (AVI-4658).

We also refer to the meeting between representatives of your firm and the FDA on October 17, 2013. The purpose of the meeting was to discuss the suitability of Sarepta's CMC plans to support pivotal clinical studies and commercial supplies of eteplirsen (AVI-4658) drug product.

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

If you have any questions, contact Teshara G. Bouie, Regulatory Project Manager, at (301) 796-1649.

Sincerely,

{See appended electronic signature page}

Olen Stephens, Ph.D.
Acting Branch Chief
Branch I, Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: End-of-Phase 2 CMC

Meeting Date and Time: October 17, 2013; 3:00 - 4:00 pm EST
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1309
Silver Spring, Maryland 20993

Application Number: IND 77429
Product Name: eteplirsen (AVI-4658)
Indication: Duchenne muscular dystrophy
Sponsor/Applicant Name: Sarepta Therapeutics, Inc.

Meeting Chair: Olen Stephens
Meeting Recorder: Teshara G. Bouie

FDA ATTENDEES

Office of New Drug Quality Assessment:

Scott Furness, Ph.D., Deputy Director for Review and Operations
Olen Stephens, Ph.D., Acting Branch Chief
Martha Heimann, Ph.D., CMC Lead
Rao Kambhampati, Ph.D., CMC Reviewer
Teshara G. Bouie, Regulatory Health Project Manager

Office Pharmaceutical Science/Microbiology Staff:

John Metcalfe, Ph.D., Microbiology Reviewer

Office of Compliance:

Tara Goen, Branch Chief
Vibhakar Shah, Ph.D., Compliance Officer

Division of Neurology Product:

Ronald Farkas, MD, Medical Officer, Team Leader

SPONSOR ATTENDEES

Chris Garabedian, President and Chief Executive Officer
Jayant Aphale, PhD, MBA, RAC, Senior Vice President, Technical Operations
Shamim Ruff, MSc, CChem, MRSC, Vice President, Regulatory Affairs and Quality
Ahmad Hasan, PhD, Director, Process Development and Scale-Up
Scott Roberts, Associate Director, Quality Control
Josanna Holzapfel, Manager, Subunits
William Cover, PhD, JD, Associate Director, CMC Regulatory Affairs
Jessica Stromme, PMP, Senior Manager, Project Management (DMD Program)

1.0 BACKGROUND

IND 77,429 is indicated for the treatment of Duchenne muscular dystrophy. On August 6, 2013, the sponsor requested an EOP2 CMC meeting to discuss the suitability of Sarepta's CMC plans to support pivotal clinical studies and commercial supplies of eteplirsen (AVI-4658) drug product. Background packages were received on September 17, 2013. Preliminary responses were sent to the sponsor on October 15, 2013.

2. DISCUSSION

Question 1

Sarepta proposes two orthogonal methods to assure the identity of the drug substance. A molecular weight determination of the purified drug substance will be performed using mass spectrometry. Sarepta will sequence samples of the purified drug substance using acid hydrolysis and mass spectrometry. In addition, confirmation of the sequence during synthesis will be determined (b) (4) to

(b) (4) .

Does the Agency agree with the testing scheme for identity testing?

FDA Response: We agree with your proposal of two (b) (4) methods to assure identity of the drug substance.

Meeting Discussion: *No further discussion at the meeting.*

Question 2

Question 2a and 2b

Drug Substance: Sarepta has release test methods and acceptance criteria for the drug substance lots used to make drug product for clinical trials. Sarepta plans to use these methods and acceptance criteria for drug substance release for commercial material.

a. Does the Agency agree that these proposed release tests and acceptance criteria (Table 7-1) are acceptable for drug substance to be used in the manufacture of commercial drug product?

FDA Response to 2a: The list of proposed release tests for the drug substance found in Table 7-1 of your meeting package appear reasonable, however, we recommend you also include moisture content and total heavy metals content in the list of specifications or provide a justification for their absence. Regarding the acceptance criteria for these drug substance release specifications, we do not agree to specifications prior to submission of the NDA, since this is a review decision based on the sum of the data in the application.

Meeting Discussion: *No further discussion at the meeting.*

Drug Product: Sarepta has drug product release test methods and acceptance criteria for clinical trial material. These methods and acceptance criteria will be used for release of commercial material.

b. Does the FDA agree that these proposed release tests and acceptance criteria (Table 7-5) are acceptable for commercial drug product?

FDA Response to 2b: The proposed release tests listed in the drug product specifications (Table 7-5) seem reasonable. Regarding the acceptance criteria for these drug product release specifications, again we do not agree to specifications prior to submission of the NDA, since this is a review decision based on the sum of the data in the application. With that said, we note that the acceptance criterion for Assay (% Lab Claim) and Total impurities content by RP-IP HPLC and SCX-HPLC appear wide at this time.

Meeting Discussion: *No further discussion at the meeting.*

Question 3

Question 3a and 3b

Sarepta has undertaken manufacturing and scale-up process development for the drug substance and plans to make updates to unit operations in order to meet commercial market demand. For clarity, the currently filed process is referred to as “clinical process” or Process A1 and the commercial process is referred to as Process A2. The updates include an increase in batch scale from (b) (4) in the near term, with modifications to improve (b) (4)

(b) (4) No change will be or has been made to the route of chemical syntheses.

Sarepta plans to manufacture (b) (4) drug substance batches under cGMP at (b) (4) scale using Process A2 at the current manufacturer. (b) (4) Process validation batches and commercial material will be manufactured using Process A2. Drug substance from Process A1 manufactured at (b) (4) scale will be compared to the drug substance manufactured at (b) (4) scale using Process A2 to demonstrate product comparability. Once product comparability is demonstrated, the drug substance from Process A2 manufactured at (b) (4)

(b) (4) scale will be compared to the drug substance manufactured at (b) (4) scale using Process A2 to confirm scalability.

a. Based upon the description of the changes and characterization of the drug substance manufactured by the commercial process (Process A2), does the Agency agree that if the current acceptance criteria are met, drug substance made by the commercial process (Process A2) is comparable to the drug substance made by the clinical process (Process A1)?

FDA Response to 3a: Because of multiple significant changes between the Process A1 and Process A2, we will need to evaluate batch data from the two processes to determine comparability.

(b) (4)
(b) (4)
(b) (4) we will need to evaluate the validation data for this method before commenting on the comparison between batches from the two processes. Also, submit a risk assessment of the changes between Process A1 and Process A2 with an evaluation of the potential impact on the final drug substance quality.

Meeting Discussion: *The FDA reiterated the importance of the RP-IP-HPLC method to bridge drug substance manufactured by the A1 and A2 processes and encouraged the sponsor to submit an updated description of the method as well as any validation data for the method. The sponsor agreed to submit the method validation report to the IND for comment by the FDA.*

b. For the NDA submission, Sarepta plans to submit the comparability data of one lot of Drug Substance manufactured by Process A2 at the (b) (4) scale for comparison to A1 batches manufactured at the (b) (4) scale. Additional data from A2 batches will be available for submission during the NDA review cycle. Does the agency agree that this data from Process A2 will be sufficient to support the NDA filing?

FDA Response to 3b: We note that three batches (Lots 7001140, 7001101, 7001144) are reported in Table 7-9 of your meeting package. It is unclear why analytical data from these batches would not be submitted at filing. At the time of filing, we expect all batch data for lots manufactured by Process A1 and Process A2. Additionally, to bridge the two processes, you should provide a side-by-side comparison of process parameters used by both synthetic routes. This also applies when scaling the batch size (b) (4) for Process A2.

Meeting Discussion: *No further discussion at the meeting.*

Question 4
Question 4a and 4b

Sarepta has conducted its drug substance stability evaluations on clinical trial material that is being used in the ongoing clinical trials. Summaries of methods, data and protocols for completed and ongoing stability studies using the current manufacturing process, Process A1 (clinical process) are presented in the briefing document. As noted in [Question 3](#), Sarepta is implementing scale up related manufacturing modifications without changing the chemical synthetic route, Process A2 (the commercial process). Sarepta has established a formal stability program for drug substance manufactured using Process A2 that includes three stability batches from the (b) (4) scale.

Given the chemical synthetic route is the same in Process A1 and A2, Sarepta proposes to use the stability data for drug substance manufactured by Process A1 as the primary stability data.

- a. *Does the agency agree with Sarepta's drug substance stability protocol for drug substance produced by Process A1*
- b. *Does the agency agree with Sarepta's drug substance stability protocol for drug substance produced by Process A2, the commercial process?*

FDA Response to 4a and 4b: We agree with the tests included in the stability protocols for the drug substance, but you should also include a test for impurity profile by strong cation exchange (SCX) HPLC at all time points. Because we noticed multiple significant changes between the Process A1 and Process A2, the primary stability data should be collected on the drug substance lots that were manufactured by using Process A2. The stability data collected on the Process A1 lots may be used as supportive stability data. Also, to be clear, review of the stability data occurs at the time of NDA filing, so we are not commenting on the adequacy of the stability data at this time.

Meeting Discussion: *No further discussion at the meeting.*

Question 5

Sarepta has conducted its drug product stability evaluations on clinical trial material currently being used in Phase II clinical trials using drug substance from Process A1. Summaries of methods, data and protocols for completed and ongoing stability studies using drug product formulated with drug substance manufactured by Process A1 are presented in the briefing document. Sarepta will also establish a formal stability program that includes accelerated stability testing for drug product formulated with drug substance manufactured using Process A2. As noted in [Question 3](#) and [Question 4](#), drug substance manufacturing modifications (Process A2) are being implemented to support scale-up. The drug product formulation will contain the same excipients and container closures.

Does the Agency agree that the data from Sarepta's stability program for drug Product formulated with Process A1 drug substance, in addition to short term (1-3 months) and accelerated temperature stability data from drug product formulated with Process A2 drug

substance, will support the use of drug product formulated with Process A2 drug substance, the commercial process, for pivotal clinical studies?

FDA Response to 5: We agree that it would be preferable for the pivotal clinical studies to use the proposed commercial Process A2 drug substance batches provided any new impurities have been qualified. As with any drug development program, we recommend that you monitor the stability of clinical study materials during development. So long as the drug substance manufactured using Process A2 is comparable to Process A1 drug substance, it would not be necessary to obtain additional stability data on drug product batches prepared with Process A2 drug substance prior to use in clinical studies.

Meeting Discussion: *No further discussion at the meeting.*

Question 6

At the time of the NDA submission, Sarepta plans to submit stability data on the drug substance manufactured by Process A1, the clinical process, as the primary stability data. The chemical synthetic route for manufacturing drug substance in Process A1 is the same as that used in Process A2, the commercial process (see [Question 3](#)). The NDA submission will contain the following stability data:

Drug Substance:

- For Process A1 drug substance, stability data from three (3) batches will be submitted: one at 24 months, one at 9 months and one at 6 months.
- For Process A2 drug substance, stability data from one batch with 1 month accelerated and real time stability test data will be submitted.
- Sarepta proposes to provide to the Agency additional stability data from Process A2 drug substance as it becomes available during the NDA review and subsequently, on a quarterly basis. Sarepta also commits to inform the FDA of any discrepancies in the stability results on a timely basis.

Does the Agency find Sarepta's proposal for the drug substance acceptable?

Drug Product:

- For drug product formulated with Process A1 drug substance, stability data from two (2) batches will be submitted: one at 24 months and one at 9 months.
- For drug product formulated with Process A2 drug substance, one lot with real time and accelerated stability data at 1 month will be submitted.
- Sarepta proposes to provide to the Agency with additional stability data from Process A2 as it becomes available during the NDA review and subsequently on a quarterly basis.

Sarepta also commits to inform the FDA of any discrepancies in the stability results on a timely basis.

Does the Agency find Sarepta's proposal for drug product acceptable?

FDA Response: We would like to discuss this question further during the face-to-face meeting.

Meeting Discussion:

- *The sponsor clarified that the proposed stability package would represent the minimum amount of data they anticipate at the time of filing. Because the drug substance and drug product manufacturers are contract manufacturers, the sponsor has minimal control over the timing of their manufacturing runs.* (b) (4)
(b) (4)
(b) (4) *Therefore, extensive long term stability data may not be necessary to support a viable shelf-life for this product. The sponsor was informed that the limited stability package may be addressed through a combination of post-marketing commitments, post-marketing requirements, and a shortened shelf-life at the time of NDA approval. The sponsor may also extend the shelf-life as additional data become available post-approval. The sponsor agreed that all available stability data would be submitted on filing and that stability updates would be submitted to the NDA as soon as they were available to facilitate review.*
- *The sponsor was reminded that as a part of the NDA approval process under the Agency's pre-approval inspection (PAI) program, the Agency needs to determine whether all facilities responsible for the manufacture of the drug substance and the drug product are capable and ready to produce material with their intended quality characteristics, reproducibly and reliably, while complying to the principles of good manufacturing practices, as applicable. The sponsor was advised that they should expect pre-approval inspection of those facilities that have never been inspected by the FDA, have outdated GMP history, or have irrelevant GMP history. The Agency also informed the sponsor that prior to the submission of the NDA they may request a Pre-Operational Review (POR) of their manufacturing facilities per the Field Management Directive - FMD #135. The purpose of the POR is to provide field guidance (Agency's feedback) on facility design, pre-construction, equipment installation/qualification or pre-production aspects to the Firm prior to commercial production. The FMD #135 is posted at and can be accessed through the following FDA link:*

<http://www.fda.gov/ICECI/Inspections/FieldManagementDirectives/ucm096042.htm>

The Agency clarified that a POR is not performed in lieu of a pre-approval

inspection. The decision of whether to conduct a PAI a separate issue from the POR and is made after the NDA is filed.

Post-Meeting Note:

The stability protocol described in your meeting package will be sufficient for filing your NDA. As discussed in the face-to-face meeting, you will submit all available stability data to the NDA as well as stability updates as soon as they are available.

Additional Comments:

- 1. In order to facilitate our comparison of the two drug substance manufacturing processes, we request that you provide comparative in-process control (IPC) data for a select number of the batches.**

(b) (4)

(b) (4)

Meeting Discussion: *The Agency expressed concerned with bridging the two processes. The sponsor agreed to provide a risk assessment of the changes made between Processes A1 and A2 as well as a detailed comparison of the two manufacturing processes. The sponsor will describe development of the A2 process from the A1 process*

(b) (4)

(b) (4)

- 2. Regarding the drug product stability protocol, sterility testing should be included at the 12 and 24 month time points.**
- 3. We note that the drug product manufacturing**

(b) (4)

(b) (4)

(b) (4)

do not include bioburden monitoring
Upon submission of the NDA, the manufacturing process should include a bioburden monitoring step, and an appropriate bioburden action level.

(b) (4)

(b) (4)

- 4. We note that the drug product is intended to be diluted in normal saline prior to patient administration. If the drug product label will identify a post dilution storage period of more than 4 hours at room temperature or 24 hours at refrigerated temperature, then the NDA should contain data demonstrating the microbiological stability of the diluted product for the intended in-use time (time between product dilution and patient administration).**
- 5. If the drug product will not be administered immediately after dilution, provide in-use stability data to demonstrate the assay and impurity levels do not change prior to administration.**

Additional Meeting Discussion:

The sponsor referred to the Agency's August 15, 2013 Advice letter responding to their July 9, 2013, IND amendment requesting feedback on their CMC strategy for starting materials, specifically questions 1 and 2.

Question 1: Does the Agency agree that [REDACTED] (b) (4)

Question 2: Does the Agency agree that the chemical and functional purity of the nominated API starting materials demonstrates control of these materials?

Meeting Discussion:

- *The sponsor verbally explained the rationale for establishing the starting materials and defining the beginning of the manufacturing process. Because these two questions were not part of the meeting package, the Sponsor was advised to resubmit their questions and justifications for Agency feedback. Specifically, the sponsor will address known and likely impurities [REDACTED] (b) (4)*

- *For manufacture, quality control and quality assurance of starting materials of the drug substance (i.e., active pharmaceutical ingredient, API), the sponsor was referred to the principles of Good Manufacturing Practice as recommended in the ICH Q7 Guidance: "Good Manufacturing Practice Guide For Active Pharmaceutical Ingredients". In particular, the sponsor was recommended to follow a sliding scale approach in terms of GMP requirements for the production of the API starting material as depicted in the Table 1 of the guidance. The ICH Q7 Guidance can be accessed from the following FDA link:*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073497.pdf>

4.0 ISSUES REQUIRING FURTHER DISCUSSION

The Agency is open to future meetings as necessary once the sponsor amends their IND.

5.0 ACTION ITEMS

None.

6.0 ATTACHMENTS AND HANDOUTS

See attached.

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/s/

TESHARA G BOUIE
10/28/2013

OLEN M STEPHENS
10/28/2013



IND 077429

MEETING MINUTES

Sarepta Therapeutics, Inc.
Attention: Matthew J. Rael, M.S.
Senior Regulatory Affairs Associate
215 First Street, Suite 7
Cambridge, MA 02142

Dear Mr. Rael:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for eteplirsen (AVI-4658).

We also refer to the meeting between representatives of your firm and the FDA on July 23, 2013. The purpose of the meeting was to follow-up to the EOP2 meeting held between Sarepta and the Agency on March 13, 2013.

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

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}

Eric Bastings, M.D.
Acting Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type C
Meeting Category: Guidance

Meeting Date and Time: July 23, 2013 4:00 P.M. EST
Meeting Location: FDA White Oak Campus, Building 22, Rm. 1309

Application Number: IND 077429
Product Name: Eteplirsen (AVI-4658)
Indication: Treatment of Duchenne muscular dystrophy
Sponsor/Applicant Name: Sarepta Therapeutics, Inc.

Meeting Chair: Eric Bastings, M.D.
Meeting Recorder: Fannie Choy, R.Ph.

FDA ATTENDEES

Office of New Drugs

John Jenkins, MD, Director

Center for Drug Evaluation and Research

Robert Temple, MD, Deputy Director for Clinical Science

Division of Neurology Products

Eric Bastings, MD, Acting Director
Ronald Farkas, MD, PhD, Clinical Team Leader
Billy Dunn, MD, Clinical Team Leader
Devanand Jillapalli, MD, Clinical Reviewer
Lois Freed, PhD, Supervisory Pharmacologist
Barbara Wilcox, PhD, Nonclinical Reviewer
Jacqueline Ware, PharmD, Chief Project Management Staff (via teleconference)
Fannie Choy, RPh, Regulatory Project Manager

Office of Clinical Pharmacology

Ta-Chen Wu, PhD, Clinical Pharmacology Reviewer
Michael Pacanowski, PharmD, MPH, Associate Director for Genomics and Targeted Therapy
Hobart Rogers, PharmD, PhD, Genomics Reviewer

Division of Biometrics I

Ohidul Siddiqui, PhD, Statistic Reviewer

Rare Diseases Program

Larissa Lapteva, MD, Medical Officer

Office of In-Vitro Diagnostics and Radiological Health (OIR), CDRH

Elizabeth Mansfield, PhD, Director, Personalized Medicine Staff

Caryl Giuliano, PhD, Regulatory Scientist, DIHD

SPONSOR ATTENDEES

Sarepta Therapeutics

Chris Garabedian, President and Chief Executive Officer

Edward M. Kaye, MD, Chief Medical Officer & Sr. Vice President Clinical Development

Shamim Ruff, MSc, Vice President of Regulatory Affairs and Quality

Peter Sazani, PhD, Executive Director, Preclinical Development

Jay Saoud, PhD, Senior Director, Statistics and Data Management

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1.0 BACKGROUND

Sarepta is developing eteplirsen for the treatment of Duchenne muscular dystrophy (DMD). Eteplirsen is a phosphorodiamidate morpholino oligomer (PMO) that selectively binds to exon 51 of dystrophin pre-mRNA.

On March 13, 2013, an end-of-phase 2 (EOP2) meeting was held between the Agency and the sponsor. The sponsor had requested the Agency's opinion on the suitability of filing a New Drug Application (NDA) under Subpart H for eteplirsen to treat DMD. The action item from the EOP2 meeting was for the sponsor to submit a comprehensive discussion of the data discussed at the meeting that were not previously submitted in the meeting package. The Agency agreed to take these additional data into consideration.

The purpose of this Type C meeting is a follow-up to the EOP2 meeting, continuing discussion regarding the acceptability of the proposed Subpart H NDA filing. The sponsor states that the scope of the meeting will be limited to clinical and pharmacology/toxicology issues.

2. DISCUSSION

Question:

The biological relationship between dystrophin and muscle function is well documented and supports the utility of dystrophin as a surrogate endpoint that is reasonably likely to predict clinical benefit in patients with DMD. Eteplirsen has demonstrated a consistent positive effect on dystrophin across all clinical trials conducted to date. Moreover, 48 weeks of treatment with eteplirsen resulted in an unprecedented and clinically meaningful 67.3-meter clinical benefit on the 6MWT compared to placebo for 24 weeks followed by eteplirsen for 24 weeks, and eteplirsen has been well-tolerated at doses of 30 and 50 mg/kg/wk through 74 weeks.

At Week 74, the patients in the eteplirsen treatment cohort remained stable on the 6MWT, with a 65-meter benefit over the placebo/delayed eteplirsen cohort ($p \leq 0.004$). In addition, the placebo/delayed eteplirsen cohort, between Week 36 and Week 74 (the timeframe that reflects a period after dystrophin production was confirmed in these patients), remained stable.

Additional endpoints which support the results of the 6MWT, including pulmonary function tests and other timed-function tests, suggest that eteplirsen is stabilizing or slowing the progression of this disease compared to what would be expected from age-adjusted natural history studies in DMD.

The data from Studies 201/202 with eteplirsen on the primary clinical outcome measure, the supporting clinical outcome measures, along with the favorable

outcomes reported by the parents of the patients in the study, strongly suggest that eteplirsen is producing a treatment effect that is stabilizing or slowing the progression of the disease.

Based on the totality of the data, Sarepta would like to propose submission of an NDA for the treatment of DMD under 21 CFR 314 Subpart H. Does the Agency support Sarepta's proposal?

FDA Preliminary Response to Question

We are open to considering an NDA based on these data for filing; however, we have a number of concerns, and some of these (b, c, and d) should be addressed prior to filing:

- a. You provided data suggesting that treatment with eteplirsen results in expression of truncated but potentially functional dystrophins. The truncated dystrophins may vary in both quality and quantity depending upon the particular mutation skipped. Although your data suggest binding to the dystrophin-associated glycoprotein complex (DAPC) subcomplexes, the functionality of each of these dystrophins *in vivo* is unknown, as is the quantity of dystrophin that must be produced to result in a clinically meaningful change. Therefore, whether the production of a truncated, but potentially functional dystrophin is reasonably likely to predict clinical benefit will be a review issue.

Meeting Discussion:

The sponsor stated that, in Study 201/202, patients with 5 different mutations amenable to exon 51 skipping were included. Data from this study demonstrated that dystrophin production was dependent on duration of treatment, but not dose or mutation. The Agency stated that the data were limited because only a few patients had each mutation type, and that the larger issue of if the production of truncated dystrophin was reasonably likely to predict clinical benefit remained a review issue.

- b. With respect to the immunofluorescence method for detecting truncated dystrophin and dystrophin-associated proteins, we note that all muscle biopsies were obtained and processed by a single technician at a single study center, and immunofluorescence was quantified by a single muscle pathologist. You argue that processing at a single center enhanced the consistency and quality of the data, and that may be so. However, image interpretation is susceptible to bias, and analyses of medical images require scrupulous attention to, and documentation of, blinded analysis. Please include in your NDA a charter that details the planned methodology, standardization, sample handling, archiving of images, etc. We also ask that you confirm, by an independent laboratory, the immunohistochemical findings for dystrophin and associated proteins in the previously collected tissue blocks. We refer you to our Guidance on imaging endpoints, which has some applicability here (FDA Guidance for Industry: Standards for Clinical Trial Imaging Endpoints [draft]),

August, 2011). We will work closely with you to agree on methods to measure fluorescence intensity of dystrophin and associated proteins in tissue sections, to provide assurance with respect to the veracity of the findings.

Meeting Discussion:

The sponsor stated that the detailed procedures that were followed when performing the immunofluorescence method will be included in the NDA, and that there were no tissue blocks from the previous biopsies. In each patient, approximately 1000 muscle fibers were counted in 24 sections, and many images (JPEG format) of these sections were taken. These images will be made available for independent review.

The Agency stated that the utility of the images was limited since they were taken after exposure was adjusted by the positive control, and asked if the original tissue-section slides were available for independent review. The sponsor stated that the tissue slides have all degraded (immunofluorescence stain degrades over time). The sponsor explained that positive-control adjusted exposure leads to a higher dystrophin immunofluorescence intensity and percent positive fiber count, and therefore, pre-treatment counts were subtracted from on-treatment counts to account for this inflation.

The Agency also expressed concern about batch effects and asked if biopsies were batch-processed by treatment day. The sponsor stated all three biopsies obtained at Baseline, Weeks 12 and 24 were processed at the same time. All biopsies were processed at Dr. Mendel's laboratory. Dr. Mendel, who was the Principal Investigator, was not involved with processing the biopsies. Another individual in his laboratory, who was not otherwise involved with the study conduct, processed the biopsies.

Post-meeting additional FDA comments:

- The specificity of antibodies used in IHC studies should be confirmed by Western blot, with submission of the entire gel image (not just the band of interest).
- c. The data on expression of truncated dystrophin and associated proteins is limited in terms of both duration of effect and overall number of patients exposed. To demonstrate that eteplirsen has a sustained effect on expression over a clinically relevant period of time, we ask that you obtain and analyze an additional muscle biopsy from each of the 12 patients who have been on open-label treatment.

Meeting Discussion:

There was a discussion on additional muscle biopsies and how dystrophin immunofluorescence intensity and percent positive fiber count by immunohistochemistry can be interpreted in the absence of baseline biopsy samples. The Agency opined that new biopsies could still provide important information even

in the absence of baseline tissue if the counts were clearly higher than the range seen in pre-treatment counts. Another option was to use pre-treatment biopsies from the confirmatory study to interpret the additional biopsies to be done in the ongoing Study 202, although blinding issues would need to be addressed.

The sponsor described challenges in getting a fourth biopsy from patients currently undergoing open-label treatment, in particular, getting approval from the IRB and consent from reluctant parents. The Agency encouraged the sponsor to communicate to the parents that the Agency considers the data from the additional biopsies important to support previous findings and to evaluate the sustainability of the effect on dystrophin. The sponsor also described plans to stagger biopsies over the duration of treatment in the confirmatory study in order to reduce the number of biopsies from each patient.

d. Accurate quantification of the amount of truncated dystrophin produced by eteplirsen is critical for considering Subpart H approval. We agree that the immunofluorescence method has some advantages over western blot, in particular, permitting the subcellular localization of dystrophin. However, the immunofluorescence method does not incorporate the type of calibration necessary for reliable quantification. We have considered the concerns you raised regarding quantification of dystrophin by western blot (e.g., low expression level, large size of dystrophin, etc), but note that the method is commonly used in similar clinical studies, and that at least some western blot data were collected for eteplirsen-treated patients (e.g., figure 4-5, page 32 of your meeting package). We continue to believe that western blot data with appropriate calibration would be useful to quantify the dystrophin produced by eteplirsen, and will work closely with you to agree on a protocol for conducting these analyses.

Meeting Discussion:

The sponsor stated that the western blot method was used in only one patient (Figure 4-5 in the meeting package), and was not assessed in all patients since the wrong antibody was used to identify dystrophin. The sponsor stated that they consider the immunohistochemistry method superior to western blot for the reasons described in the briefing book. However, the sponsor acknowledged that western blot data could be supportive and stated that the western blot method would be used to quantify dystrophin using the correct antibody in the new biopsies.

The Agency asked whether co-localization of dystrophin with other members of the dystrophin glycoprotein complex was assessed in all patients in Study 201/202. The sponsor replied that it was done only in a few patients in that study but was also assessed in another study (Study 33). In response to a question, the sponsor stated that it was not possible (in the laboratory that the sponsor uses) to use all three stains for co-localization of the subcomplexes in the same slide.

Post-meeting additional FDA comments:

- The ‘dot blot’ method, or similar high-sensitivity protein detection methods, appears to offer some advantages to western blot, such as lower requirements for tissue and increased ability to generate a standard curve for dystrophin and other internal controls. Western blot still appears necessary to demonstrate specificity (including demonstration that increased signal in treated patients is not due to increased levels of non-dystrophin cross-reactive proteins). The Division will work with you to agree on the specific uses of western blot vs. other methods in the new tissue samples that will be studied. The Division recommends that you examine in the new tissue samples the correlation between levels of mRNA for truncated dystrophin (determined by quantitative RT-PCR) and levels of the protein. If a high level of correlation exists, the information could be useful in future studies.
- e. The overall safety database includes only 38 patients exposed to eteplirsen by any route, dose, or duration. We understand that the current supply of eteplirsen is limited, but we want to discuss with you how the available supply (and potentially additional amounts that could be produced on the same scale) could be used to obtain additional data. We also need to discuss the design of the postmarketing confirmatory trial that would be required under subpart H.

Meeting Discussion:

The sponsor stated that the current drug supplies are sufficient to dose the 12 patients enrolled in the ongoing open-label study. The sponsor is currently in mid-scale production of the drug product. Assuming that all regulatory requirements including stability are met, the earliest time drug can be available for any other patients is March 2014 which is also when they expect to begin enrolling patients in the confirmatory study. The Agency stated that there may be some regulatory flexibility regarding the requirement for stability data to make the drug available earlier; however, this will need to be confirmed internally.

Post-meeting Note:

- After the meeting, the Office of New Drug Quality Assessment (ONDQA) was consulted regarding CMC requirements to support use of a new batch in the confirmatory study. ONDQA recommends that stability be monitored during the clinical study. However, if the quality of the new batch is comparable to that of batches used in the previous study, the existing stability data could support initiation of the clinical study concurrently with stability studies.

The sponsor is targeting NDA submission in the 2nd or 3rd quarter of 2014, at which time they hope to include preliminary safety data from patients enrolled in the

confirmatory study, as well as data from the fourth biopsy on patients enrolled in Study 202. The sponsor also stated that they have plans for large-scale production of the drug in the near future and expect to supply the full market upon approval.

There was a discussion on the design of the confirmatory trial. The sponsor proposed a trial with a concurrent untreated control arm composed of subjects not amenable to exon 51 skipping. The sponsor stated that data from multiple countries suggest that the natural history of subjects with deletions that are not amenable to exon 51 skipping is fairly similar to those with deletions that are amenable. The Agency expressed reservation due to the usual difficulty in showing comparability between the study populations in natural history studies. The Agency stated that data from such an open-label design would be difficult to interpret. The sponsor replied that the combination of natural history data on the 6MWT and data from matched controls could help in interpretation. The Agency reiterated that the 6MWT is subjective and therefore susceptible to bias in the proposed design.

There was a brief discussion regarding a potential situation when multiple sponsors apply for approval for the treatment of DMD around the same time frame. The Agency informed the sponsor that if one sponsor was given full approval for the treatment of DMD, the accelerated approval pathway would not be applicable to the other sponsors unless a substantial advantage over existing therapy for the same indication was demonstrated.

The Agency informed the sponsor that the long-term safety database of 12 subjects was very small, and data from additional treated patients would be important.

f. Regarding your request for “submission of an NDA for the treatment of DMD under 21 CFR 314 Subpart H,” we want to emphasize that NDA filing is separate from approval under Subpart H; an NDA can be approved under Subpart H, but is not filed under Subpart H.

Meeting Discussion: None

g. Please also note that our filing the NDA would not indicate that we have accepted dystrophin expression as a biomarker reasonably likely to predict clinical benefit. A filing would only indicate that the question merits review, and that we deem the data to be reviewable.

Meeting Discussion: None

3.0 ADDITIONAL COMMENTS

3.1 DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

4.0 ISSUES REQUIRING FURTHER DISCUSSION

A follow-up meeting will be necessary discuss the procedures for independent review of images of previous biopsies and analysis of new biopsies, and the design of the confirmatory study.

The clearest path forward to provide adequate data to support filing and approval, and for a post-approval confirmatory study would be starting a placebo-controlled trial as soon as possible with newly manufactured drug.

5.0 ACTION ITEMS

There were no action items identified during the meeting.

6.0 ATTACHMENTS AND HANDOUTS

- Sponsor submitted slides titled “Sarepta Therapeutics / EOP2 Follow-Up Meeting / 23 July 2013”
- Sponsor back-up slide titled “Placebo-Controlled Arm Challenges”

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/s/

ERIC P BASTINGS

08/22/2013



IND 077429

MEETING MINUTES

Sarepta Therapeutics, Inc.
Attention: Matthew J. Rael, M.S.
Senior Regulatory Affairs Associate
245 First Street, Suite 1800
Cambridge, MA 02142

Dear Mr. Rael:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for eteplirsen (AVI-4658).

We also refer to the meeting between representatives of your firm and the FDA on March 13, 2013. The purpose of the meeting was to discuss the development plans of eteplirsen in the treatment of Duchenne muscular dystrophy.

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

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}

Russell G. Katz, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: End of Phase 2

Meeting Date and Time: March 13, 2013 4:00 P.M. EST
Meeting Location: FDA White Oak Campus, Building 22, Rm. 1309

Application Number: IND 077429
Product Name: Eteplirsen (AVI-4658)
Indication: Treatment of Duchenne muscular dystrophy
Sponsor/Applicant Name: Sarepta Therapeutics, Inc.

Meeting Chair: Russell G. Katz, M.D.

FDA ATTENDEES

Office of New Drugs
John Jenkins, MD, Director

Center for Drug Evaluation and Research
Robert Temple, MD, Deputy Director for Clinical Science

Office of Drug Evaluation I
Ellis Unger, MD, Director

Division of Neurology Products
Russell Katz, MD, Director
Eric Bastings, MD, Deputy Director
Ronald Farkas, MD, PhD, Clinical Team Leader
Devanand Jillapalli, MD, Clinical Reviewer
Lois Freed, PhD, Supervisory Pharmacologist
Barbara Wilcox, PhD, Nonclinical Reviewer
Jacqueline Ware, PharmD, Supervisory Regulatory Project Manager
Fannie Choy, RPh, Regulatory Project Manager
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Rare Diseases Program
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Salvatore Pepe, PharmD, Regulatory Research Officer
Hong Vu, PhD, Regulatory Researcher Officer

Office of Medical Policy
Leonard Sacks, Associate Director for Clinical Methodology

Division of Medication Error Prevention and Analysis
Irene Z. Chan, PharmD, BCPS, Team Leader
Sue Liu, PharmD, Safety Reviewer

SPONSOR ATTENDEES

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Chris Garabedian, President and Chief Executive Officer
Edward M. Kaye, MD, Chief Medical Officer & Sr. Vice President Clinical Development
Shamim Ruff, MSc, Vice President of Regulatory Affairs and Quality
Matthew J. Rael, MS, Senior Regulatory Affairs Associate
Jay Saoud, PhD, Senior Director, Statistics and Data Management
Peter Sazani, PhD, Executive Director, Preclinical Development

Nationwide Children's Hospital and The Ohio State University
Jerry R. Mendell, MD, Curran-Peters Chair in Pediatric Research, Professor of Pediatrics and Neurology, Director Gene Therapy Center and Director of Paul D. Wellstone Center

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1.0 BACKGROUND

Sarepta is developing eteplirsen for the treatment of Duchenne muscular dystrophy (DMD). Eteplirsen is a phosphorodiamidate morpholino oligomer (PMO) that selectively binds to exon 51 of dystrophin pre-mRNA.

Sarepta has requested the end of phase 2 (EOP2) meeting to seek the Division's opinion on the suitability of filing a New Drug Application (NDA) under Subpart H for eteplirsen to treat DMD. Sponsor is also seeking Division's feedback on the proposed design of a confirmatory clinical trial and the remaining pharmacology/toxicology studies that would be adequate to support an NDA filing and subsequent full approval.

2.0 DISCUSSION

Question 1:

The biological relationship between dystrophin and muscle function is well documented and supports the utility of dystrophin as a surrogate endpoint that is reasonably likely to predict clinical benefit in patients with DMD. Eteplirsen has demonstrated a consistent positive effect on dystrophin across all clinical trials conducted to date. Moreover, 48 weeks of treatment with eteplirsen resulted in an unprecedented and clinically meaningful 67.3-meter clinical benefit on the 6MWT compared to placebo for 24 weeks followed by eteplirsen for 24 weeks, and eteplirsen has been well-tolerated at doses of 30 and 50 mg/kg/wk through 62 weeks.

Based on the totality of the data, Sarepta would like to propose submission of an NDA for the treatment of DMD under 21 CFR 314 Subpart H. Does the Agency support Sarepta's proposal?

FDA Preliminary Response to Question 1:

While the biological relationship between dystrophin and muscle function is well-documented, the specific *quality* and *quantity* of dystrophin produced by a drug is central to the question of if the effect can be considered reasonably likely to predict clinical benefit. Eteplirsen, by design, can only increase the production of truncated dystrophin associated with muscle pathology like BMD. Furthermore, different mutations will result in production of different forms of truncated dystrophin, some of which may not be functional or result in conversion to the BMD phenotype. While we do not believe that you have adequately characterized the quantity of truncated dystrophin produced by eteplirsen treatment (Western blot data is not available), the immunofluorescence data you presented suggests that a much lower quantity of truncated dystrophin is produced by eteplirsen treatment than is present in BMD. Furthermore, as specified in Subpart H, a determination that a biomarker is reasonably likely to predict benefit is based on additional sources of evidence including epidemiologic, therapeutic, pathophysiologic, and other evidence, including clinical evidence of the type provided in study 201/2. From

the information we have we do not find that study 201 provides any interpretable evidence of benefit on 6MWT, as there was essentially no difference between drug and placebo based on the intent-to-treat population (even without consideration of multiple-testing). Similarly, data from study 202 does not provide interpretable evidence of benefit given the limitations of the open-label design for protecting against bias on effort-dependent endpoints like 6MWT. In fact, data from study 202 suggests that decline of 6MWT was similar to that expected from natural history ((Mazzone: 42.3 ± 73.9 m/year; McDonald: 57 ± 104 m/year). We note also that there was no correlation between the dystrophin data and the 6MWD data through Week 62. We therefore do not believe that an NDA filing for eteplirsen under Subpart H could be supported by available data.

Also, while perhaps more readily remediable, to support filing of a Subpart H NDA for eteplirsen, you would have to provide adequate evidence that the data collected on the biomarker is of sufficient quality to support meaningful regulatory review. This standard for data quality is essentially the same for Subpart H as for regular approval, as described under *21 CFR 314.126, Adequate and Well-Controlled Studies*. In particular, you would need to document before we filed an NDA that adequate steps were taken to minimize bias, and that a reliable quantitative assessment of drug effect was provided. Details of methodology, therefore, would be critical to our filing decision. We do not believe that the information submitted to us to date provides adequate reassurance that an NDA would be fileable.

The Subpart H pathway is still possible for eteplirsen if you can provide additional supportive biomarker or clinical data, as described below. It is important to stress, however, that filing an NDA under Subpart H in no way reflects a finding that the surrogate is reasonably likely to predict clinical benefit, instead only reflecting that the question itself merits NDA review. While we are open to discuss additional biomarker data that could support the data on truncated dystrophin that you currently have, demonstrating an improvement in an independent aspect of muscle integrity or physiology might be adequate. Other evidence about the behavior of proteins that interact with dystrophin also may contribute to evidence that the truncated dystrophin produced by eteplirsen is functional. Additional clinical data short of a traditional positive study might also be adequate, noting however adequate protection from bias is key.

If it is true that eteplirsen leads to remarkable clinical benefit in even some patients, there is no doubt that a feasible placebo controlled clinical study can be designed to demonstrate that benefit, and we remain eager to discuss such a possibility. As discussed in Question 2, exposure of additional patients appears necessary to support safety for NDA filing; this provides an opportunity to collect additional clinical efficacy and biomarker data.

There appears to be no reason to limit exposure to ambulatory patients, as other endpoints, like upper body strength, or even pulmonary or cardiovascular outcomes could contribute to efficacy evidence.

Meeting Discussion:

The sponsor presented slides to highlight the mechanism of action of eteplirsen, quantitative methods used to assess dystrophin, overview of study design for Studies 201/202 and results for dystrophin production and 6MWT (through Week 62). The sponsor noted that although there may be some degree of training effect during the first 12 weeks, they were encouraged by the stabilization of the 6MWT in both the original eteplirsen group and the delayed eteplirsen group during the timeframe of meaningful dystrophin expression.

The Agency noted that despite the expected test-retest variability in the 6MWT, even in two trials administered on the same day, there were multiple instances when the 6MWT values were identical in two tests for patients at different time points. For example, patient #002, had values of 416 and 442 meters for trial 1 and 2, respectively, at baseline, and 416 and 442 meters for trial 1 and 2, respectively, at Week 12. The Agency asked if the tester for the 6MWT knew the previous distances, particularly in the context of the knowledge that by Week 36 all patients were being given eteplirsen, and whether the associated source documents were available for data generated in this single site study. The sponsor replied that it was the same physical therapist who administered the 6MWT and who, per protocol, was required not to look back at previous scores. The sponsor also stated that they did not think the test was administered in a way that would favor specific intervals of distance (e.g. 'whole laps'), and that they audited the data and found the test correctly administered. The sponsor agreed to look further into these results.

In response to the Agency's request, the sponsor provided details of the immunohistochemistry (IHC) and provided other data they thought showed that dystrophin produced is functional.

The sponsor stated that dystrophin-positive fibers analyzed using IHC provide information about both the quantity and quality of the dystrophin protein produced, and that it localized at the cell membrane. The methodology used was described. Twenty-four microscope fields with a total of more than 1000 muscle fibers per patient per time point were examined. For each patient the baseline/background signal was established with pre-treatment biopsy and this baseline value was subtracted from on-treatment values. All biopsy examinations were performed by an evaluator who was blinded with regard to biopsy timing (pre-treatment, on-treatment), treatment group and dose of eteplirsen. The blinded evaluator examined each of the 24 microscope fields under an exposure adjusted by the positive control such that only positive fibers were visible, which were then counted systematically. Then the gain on the microscope was adjusted to count the negative fibers, and the percentage of positive fibers was calculated by dividing the number of positive fibers by the total number of fibers. In response to the Agency's question, the sponsor acknowledged that fluorescence images fade over time, and that the biopsy blocks would need to be resectioned and restained if retesting of the samples was necessary. Further, the sponsor stated that although they believe that dystrophin

assessment using the Western Blot was not as informative as the IHC, such assessment could be done.

The sponsor stated that since dystrophin was localized to the cell membrane (by IHC), as is the dystrophin produced in Becker patients that is truncated but localized to the cell membrane, the findings are supportive of the functionality of the dystrophin produced by eteplirsen. Additional supporting evidence on the functionality of the truncated dystrophin produced was the increased staining of nNOS, a component of the dystroglycan protein complex, in muscle biopsies from subjects who received eteplirsen. The Agency asked the sponsor if nNOS expression would theoretically be increased in all 7 of the DMD deletion mutations to be treated with eteplirsen. The sponsor acknowledged that nNOS would likely not be expressed in all of the DMD mutations likely to be amenable to exon 51 skipping. The Agency also inquired if the sponsor was able to attribute BMD phenotypes that were representative of the truncated dystrophin likely produced from exon 51 skipping of the 7 DMD deletion mutations. The sponsor stated that they did not have phenotypic evidence from BMD subjects who would represent the 7 different truncated products produced from the 7 DMD deletion mutations.

There was a discussion on the suitability of dystrophin as a surrogate. In this regard, the Agency noted that it was not clear how supportive the 6MWT data as measured in the study was: although there were prominent differences between treatment groups, the study was very small and it was troubling that there seemed to be no explanation for the identical findings on different days (for two tests) on the 6MWT for a number of patients, a finding that appeared to be inconsistent with the known test-retest variability of that measurement. In addition, there was no good consistency between results on the 6MWT and other related functional clinical endpoints. The Agency requested that the sponsor provide a coherent and comprehensive summary to support dystrophin as a surrogate. In particular, the Sponsor was asked to provide a comprehensive discussion of the experimental methods used to assess dystrophin, and data to show that the dystrophin produced is at the correct anatomic location and functional at a cellular level (separate from clinical effects). The Agency also requested that the sponsor provide a detailed discussion of all clinical outcomes in the eteplirsen program.

There was a brief discussion of the timeline of the proposed NDA filing and ability of the sponsor to provide drug if the NDA is approved. The sponsor stated that the planned NDA submission was the first Quarter of 2014, and that the drug would not be available until after approval, initially in limited quantities. The Agency noted that during the initial post-approval period when limited quantities of eteplirsen are expected to be available, a lottery system could be one potential way to make the drug available in a fair manner to patients, and, if the details were properly designed, data derived from such a random lottery system could be a de facto randomized clinical trial. In the context of this setting (i.e. limited drug availability), a placebo-controlled design for the pivotal confirmatory trial would be justifiable. It is therefore important to consider potential endpoints based on patient/caregiver reported outcomes.

The Agency stated that there were considerable data presented by the sponsor during the meeting that were not included in the briefing package. The sponsor responded that they would formally submit the above requested data in the near future. The Agency stated that they had not made a final decision regarding acceptability of the proposed Subpart H NDA filing, and that the Agency would consider the additional data submitted by the sponsor before making a final decision.

Question 2:

DMD is a rare disease with a US prevalence of approximately 15,000. The proposed DMD indication affects approximately 13% of the overall DMD patient population. At the end of 2013, Sarepta will have safety data from all of the 38 patients treated to date, including data from 12 patients who will have received no less than 96 weeks and up to 120 weeks of treatment at 30 mg/kg/wk or 50 mg/kg/wk eteplirsen.

Given the extremely rare prevalence of patients amenable to this treatment, is the proposed safety database acceptable to the FDA for filing under 21 CFR 314 Subpart H?

FDA Preliminary Response to Question 2:

Exposure of additional patients is necessary to support subpart H filing; even if efficacy can be supported by a ‘reasonably likely’ finding, for approval there must still be enough safety data to conclude that the drug has an acceptable risk/benefit profile. Exposure can occur in patients across a wide range of DMD stage, and need not be limited to ambulatory patients, such that feasibility should not be an issue even considering the low US prevalence.

Meeting Discussion:

The sponsor stated that approximately 400 patients have been treated with the same PMO backbone in different indications, and their data could provide additional support of safety.

The Agency agreed that such data would be considered and noted also that in the event it agrees to file the Subpart H NDA submission, additional safety data to support approval could come from the first few months of the placebo-controlled pivotal confirmatory trial (see discussion under Question 1).

Question 3:

Sarepta is proposing a two-arm, open-label, multi-center, 48-week study to confirm the efficacy and safety of 30 mg/kg/wk of eteplirsen in DMD patients with genotypically confirmed deletions that are amenable to correction by skipping exon

51. The study will use a control arm consisting of DMD patients who are not amenable to correction by skipping exon 51, but who meet all other inclusion and exclusion criteria (Section 6.3 and Appendix D).

Does the Agency agree that:

- **The patient population as defined by the entry criteria is acceptable?**
- **The patient population in the control arm is acceptable?**
- **The selection of the 6MWT as the primary efficacy endpoint and dystrophin-positive fibers as the key secondary efficacy endpoint is acceptable?**
- **The use of a MMRM test statistic for the analysis of the primary efficacy endpoint is acceptable?**

FDA Preliminary Response to Question 3:

This question currently is premature. However, while the natural history of DMD is seemingly well understood, we note that there is considerable variation among individual patients with regard to clinical measures and important milestones. In this context, data from a confirmatory long-term open-label study may only be interpretable if a relevant objective endpoint obviously insulated from bias demonstrates compelling data that is clearly well outside the known variability range for DMD. For modest effects on clinical endpoints including the 6MWD, placebo-controlled data would seemingly be necessary to provide interpretable data.

Meeting Discussion:

As discussed under Question 1, a placebo-controlled design for the pivotal confirmatory trial appears justifiable and practicable. If that study proves impracticable, the proposed study could be interpretable if the effect is large, well outside the known variability of the disease.

Question 4:

Sarepta proposes that the male fertility assessments performed to date are sufficient to address the requirement for assessment of toxicity to male reproductive organs and male fertility (ICH Topic S5(R2) Document “Detection of Toxicity to Reproduction for Medicinal Products and Toxicity to Male Fertility”, November 2005).

Does the Agency agree that no additional fertility assessments are needed to support approval?

FDA Preliminary Response to Question 4:

The 12-week studies of AVI-4658 did not include a focused, stage-aware, evaluation of male reproductive organs. You state that no adverse effects on male fertility parameters were observed in the chronic toxicity study in monkey or in the juvenile animal toxicology study in rat; however, since these study reports have not been submitted, we cannot confirm the adequacy of the analyses. This will be a matter of review.

Meeting Discussion:

The Division asked the status of the study reports for the chronic toxicity studies in mdx mouse and monkey and the juvenile animal toxicology study. The sponsor indicated that the studies have been completed and the reports are being finalized. The Division noted that concern remains regarding the enlarged ventricles reported in the mdx mouse.

Question 5:

Sarepta plans to conduct a series of absorption, distribution, metabolism, and excretion (ADME) studies in vitro and in vivo; these studies will be complete at the time of filing and will be included in the initial NDA submission under 21 CFR 314 subpart H (Appendix H).

Does the Agency agree that if there is no significant turnover of parent eteplirsén compound, and no cytochrome P450 induction or inhibition or p-glycoprotein interaction, that the conducted and planned studies will provide sufficient ADME characterization of eteplirsén for market approval?

FDA Preliminary Response to Question 5:

Nonclinical

We recommend that you conduct a tissue distribution study of AVI-4658 in order to determine extent of distribution and $t_{1/2}$ in target tissues.

Clinical Pharmacology:

The characterizations you outlined are insufficient from a clinical pharmacology perspective. We recommend the additional studies or ADME characterizations as outlined below.

1. In-vitro characterizations:

- The inclusion of CYP2B6 in in-vitro screening for inhibitory potential of eteplirsén on major CYP enzymes
- The in-vitro screening for interaction potential of eteplirsén with other important transporters of interest in liver and kidney.
- For investigating the potential interaction with P-gp, we recommend that you use the Agency recommended strong P-gp inhibitor, such as quinidine

- Please refer to the Agency's Guidance for Industry (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm292362.pdf>) for recommendations that are considered pertinent to eteplirsen. Studies should be conducted using physiological-relevant drug concentrations. Consideration should also be taken based on other co-medications that are necessary or likely to be given to these DMD patients. In the absence of a study, adequate scientific justification will be necessary for the Agency's review.
2. You should provide detailed information regarding the metabolic fate of eteplirsen both in vitro and in humans, including other non-renal route of elimination and the potential Phase II glucuronide conjugates in feces (as mentioned in the original IND submission) in the NDA submission for review.
 3. Since eteplirsen is mainly eliminated via renal route we recommend that you conduct a study to determine the impact of reduced renal function on pharmacokinetics and systemic exposure of eteplirsen. Please refer to the Agency's Guidance for Industry (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm292362.pdf>) for recommendations for proper study design.

Meeting Discussion:

There was no discussion.

Question 6:

Based on eteplirsen's pharmacology/mechanism of action and results from completed toxicity studies in several species, eteplirsen is not considered a carcinogenic hazard. Sarepta would therefore like to propose a single 2 year carcinogenicity study (b) (4). Moreover, since the target population for eteplirsen is limited to males, the proposed carcinogenicity study will be limited to male animals.

Does the Agency agree?

FDA Preliminary Response to Question 6:

You will need to submit a request for waiver of the standard requirement for carcinogenicity assays in two species, which should include a detailed justification for limiting the assessment of carcinogenic potential to a single species.

We agree that for drugs intended for treatment of DMD, nonclinical studies may be conducted in male animals only. However, if a single sex is used, the number of animals per group will need to be doubled.

Meeting Discussion:

There was no discussion.

Question 7:

Sarepta plans to initiate the carcinogenicity study after market approval is granted, consistent with the International Conference on Harmonization (ICH) Safety (S1A, March 1996) and M3 (R2), June 2009 guidelines for pharmaceuticals for life-threatening or severely debilitating diseases, especially where no satisfactory alternative therapy exists.

Does the Agency agree that the carcinogenicity requirement can be delayed until after market approval?

FDA Preliminary Response to Question 7:

Considering the seriousness of the indication, the carcinogenicity study(ies) may be submitted post approval, if the available nonclinical and clinical data support such a strategy.

Meeting Discussion:

There was no discussion.

3.0 ADDITIONAL COMMENTS

Your proposal to limit the indication to a subset of DMD patients defined by a specific group of mutations may meet the definition of a companion diagnostic (<http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm>). Please consult with CDRH to determine whether an IDE is needed for further investigation of this product.

Breakthrough therapy designation is separate from our determination that it is premature to file an NDA for eteplirsen. However, to consider eteplirsen for breakthrough designation you would, at minimum, have to more clearly demonstrate increased expression of truncated dystrophin.

3.1 DIVISION OF MEDICATION ERROR PREVENTION AND ANALYSIS

You propose to supply eteplirsen in a concentration of 50 mg/mL supplied in 2 mL single use vials. The weight range of the pediatric patients included in your clinical studies thus far range from 22 kg to 78 kg. For a 60 kg pediatric patient, the weekly dose of eteplirsen would be 1800 mg (30 mg/kg x 60 kg). Based on your proposed vial strength and volume, a healthcare practitioner will need 18 vials to prepare a dose for this patient. We are concerned the large number of vials needed to prepare a usual dose of your product is burdensome and vulnerable to medication errors during the preparation of your drug. We recommend you develop a packaging for your product that is more congruent

with your dosing, if feasible, or explain how you plan to mitigate this risk for medication errors.

3.2 DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at:
<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

The sponsor will submit a comprehensive discussion of the issues discussed at the meeting that were not previously submitted in the meeting package. The Agency will take this additional discussion into consideration when deciding whether to file the application under Subpart H at this time.

6.0 ATTACHMENTS AND HANDOUTS

- Sarepta submitted slides titled “Duchenne Muscular Dystrophy (DMD)”
- Sarepta handout titled “Dystrophin Quantification Methodology”

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/s/

RUSSELL G KATZ
04/12/2013

LATE-CYCLE COMMUNICATION
DOCUMENTS



NDA 206488

LATE-CYCLE MEETING MINUTES

Sarepta Therapeutics, Inc.
Attention: Shamim Ruff, MSc.
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, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Exondys 51 (eteplirsen) Injection, 50 mg per mL.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on January 11, 2016.

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

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}

Ronald Farkas, M.D., Ph.D.
Clinical Team Leader
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: January 11, 2016, 3:00 p.m. – 4:00 p.m. EST
Meeting Location: FDA White Oak Campus, Building 22 Room 1315

Application Number: NDA 206488
Product Name: Exondys 51 (eteplirsen)
Applicant Name: Sarepta Therapeutics, Inc.

Meeting Chair: Ronald Farkas, M.D., Ph.D.
Meeting Recorder: Fannie Choy, R.Ph.

FDA ATTENDEES

Office of New Drugs
John Jenkins, MD, Director

Office of Drug Evaluation I
Ellis Unger, MD, Director
Robert Temple, MD, Deputy Director

Division of Neurology Products
Billy Dunn, MD, Director
Eric Bastings, MD, Deputy Director
Ronald Farkas, MD, PhD, Clinical Team Leader
Christopher Breder, MD, PhD Clinical Reviewer
Lois Freed, PhD, Supervisory Pharmacologist
David Hawver, PhD, Nonclinical Reviewer
Laura Jawidzik, MD, Medical Officer
Tracy Peters, PharmD, Associate Director of Labeling (via teleconference)
Fannie Choy, RPh, Regulatory Project Manager
Brittany Dustman, PharmD Candidate, Temple University School of Pharmacy

Office of New Drug Products
Martha Heimann, PhD, Neurology CMC Lead

Office of Biostatistics
Kun Jin, PhD, Team Leader, Division of Biometrics I
Xiang Ling, PhD, Statistical Reviewer

Office of Biotechnology Products

Ashutosh Rao, PhD, Acting Chief, Laboratory of Applied Biochemistry, Division of Biotechnology Review and Research III

Office of Clinical Pharmacology

Ta-Chen Wu, PhD, Clinical Pharmacology Reviewer (via teleconference)

Kevin Krudys, PhD, Pharmacometrics Team Leader

Atul Bhattaram, PhD, Pharmacometrics Reviewer

Hobart Rogers, PharmD, PhD, Genomics and Targeted Therapy Reviewer

Division of Advisory Committee and Consultant Management

Diem-Kieu Ngo, PharmD, Team Leader (via teleconference)

Moon Hee V. Choi, PharmD, Designated Federal Officer (via teleconference)

EASTERN RESEARCH GROUP ATTENDEES

Peggh Khorrami, Independent Assessor

APPLICANT ATTENDEES

Sarepta Therapeutics, Inc.

Edward M. Kaye, MD, Chief Medical Officer, Senior Vice President, Clinical Development, and Interim Chief Executive Officer

Shamim Ruff, Vice President, Regulatory Affairs and Quality

Helen Eliopoulos, MD, Senior Director, Strategic Medical Advisor

Diane Frank, PhD, Senior Director, Translational Research

Ping-Yu Liu, PhD, Statistical Consultant (via teleconference)

(b) (4)

1.0 BACKGROUND

NDA 206488 was submitted on June 26, 2015, for Exondys 51 (eteplirsen) Injection.

Proposed indication: Treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping.

Original PDUFA goal date: February 26, 2016.

Extended PDUFA goal date: May 26, 2016.

FDA issued a Background Package on December 23, 2015, in preparation for this meeting. A presentation was submitted by Sarepta via email on January 11, 2016, and is attached below.

2.0 DISCUSSION

1. Introductory Comments

Welcome, Introductions, Ground rules, Objectives of the meeting.

Discussion:

The applicant began the meeting with a presentation that contained their planned agenda, including interpretation of demographic and clinical data from the natural history cohort.

2. Discussion of Substantive Review Issues

- The reliability of biomarker evidence and its potential clinical meaning

Discussion:

The applicant presented Western blot (WB) and immunofluorescence (IF) data. There was discussion about the degree of correlation between the two methods. FDA explained that WB is more quantitative than IF because of the use of a serial dilution in each test, and is considered the primary source of data about relative dystrophin amount. FDA explained that IF is considered as supportive, so that the correlation between the two methods is not the key issue in terms of amounts of protein, especially at very low levels. FDA further explained that IF is considered supportive for the localization of membrane-bound dystrophin.

- Clinical evidence of efficacy and safety

Discussion:

The applicant presented clinical data from more recent time points than reported in the original NDA submission. The applicant reported that most of the subjects in the natural history cohort had lost ambulation, whereas only 2 of 12 eteplirsen treated subjects were currently non-ambulatory. The applicant additionally presented revised data about patient baseline characteristics, including treatment with corticosteroids. The applicant explained that supportive care was similar or more intensive for the natural history patients than for

the eteplirsen treated patients. FDA expressed concern regarding the reliability and comparability of the data.

3. Additional Applicant Data

Discussion:

The applicant indicated that additional analyses could be conducted, but FDA stressed that more important issues were the comparability of study arms and data reliability, and that it appeared unlikely that additional analyses could address such concerns.

4. Information Requests

There are no pending information requests at this time.

Discussion: There was no meeting discussion.

5. Discussion of Upcoming Advisory Committee Meeting

Discussion: There was no meeting discussion.

6. Postmarketing Requirements/Postmarketing Commitments

• Clinical Confirmatory Studies

Discussion:

FDA explained that previous discussions regarding accelerated approval and a non-randomized externally-controlled confirmatory study were based on the applicant's assertion that levels of truncated dystrophin similar to those in Becker muscular dystrophy were produced by eteplirsen, and that based on the current data it was not clear that such a study would represent a viable path forward. FDA noted that during development of eteplirsen, it had consistently urged the applicant to conduct randomized controlled trials.

• CMC

Discussion:

The applicant acknowledged its commitment to revalidate the in-process (b) (4) and investigate the consistent bias in the in-process (b) (4) assay result.

• Nonclinical

Discussion:

The Division noted that carcinogenicity studies in rat and mouse would be required postmarketing if the application were to be approved.

7. Review Plans

Discussion:

The Division will continue to review the efficacy and safety data.

8. Wrap-up and Action Items

This application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.

Action Items:

None

3.0 ATTACHMENT

Sarepta discussion slides dated January 11, 2016.

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/s/

RONALD H FARKAS
02/10/2016



NDA 206488

**LATE CYCLE MEETING
BACKGROUND PACKAGE**

Sarepta Therapeutics, Inc.
Attention: Shamim Ruff, MSc.
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) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Exondys 51 (eteplirsen) Injection, 50 mg per mL

We also refer to the Late-Cycle Meeting (LCM) scheduled for January 11, 2016. Attached is our background package, including our agenda, for this meeting.

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}

Eric Bastings, M.D.
Deputy Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE:
Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: January 11, 2016, 3:00 p.m. – 4:00 p.m. EST
Meeting Location: FDA White Oak Campus, Building 22 Room 1315

Application Number: NDA 206488
Product Name: Exondys 51 (eteplirsen)
Indication: Treatment of Duchenne muscular dystrophy
Sponsor/Applicant Name: Sarepta Therapeutics, Inc.

INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

1. Discipline Review Letters

No Discipline Review letters have been issued to date.

2. Substantive Review Issues

The following substantive review issues have been identified to date:

- Dystrophin
 - Considerable doubt remains about how much dystrophin levels were increased by eteplirsen. The degree of uncertainty about the dystrophin data hinders discussion of its use as surrogate endpoint for eteplirsen. However, to the degree that the

dystrophin data may be interpretable, the amount and distribution of dystrophin in treated patients appears to be within the range typically associated with Duchenne muscular dystrophy, and not Becker muscular dystrophy.

- Clinical endpoints
 - Eteplirsen patients have experienced a sequential loss of ambulatory abilities and increasing muscle weakness, as measured by rise time from floor, NSAA, 6MWT, and other tests. In the context of this considerable variability among patients, the clinical course of eteplirsen patients over more than 3 ½ years of treatment with eteplirsen has been generally similar to expected natural history of patients provided with intensive supportive care.
 - There are important differences between patients enrolled in observational natural history studies and patients enrolled in interventional drug efficacy studies, some of which are quantifiable, and some of which are not. Corticosteroid therapy appears to have been more intensive in eteplirsen patients compared to the natural history patients selected by the applicant, and this, itself, may have been capable of affecting performance. Near the time when patients lose ambulation, decisions are made by patients and caregivers about whether weakness has progressed to the point that it is in the patient's best interest to use a wheelchair to avoid the risk of falls and injuries and to decrease the effort and time required for mobility. Differences in individual care decisions, therefore, seemingly could produce large differences in 6MWT and time to loss of ambulation between eteplirsen patients and natural history controls. NSAA results, potentially representing a more direct measure of strength, suggest that differences in DMD progression between eteplirsen patients and the applicant's natural history controls were too small and variable, in the context of a poorly-controlled trial, to be reliably attributed to drug treatment.

ADVISORY COMMITTEE MEETING

Date of AC meeting: January 22, 2016

Date AC briefing package sent under separate cover by the Division of Advisory Committee and Consultant Management: December 23, 2015

Potential questions and discussion topics for AC Meeting are as follows:

We expect to ask the Advisory Committee to consider the following:

- The reliability of biomarker evidence, and its potential clinical meaning
- Clinical evidence of efficacy and safety
- Design of future efficacy and safety studies, if deemed necessary

We look forward to discussing our plans for the presentations of the data and issues for the upcoming AC meeting. Final questions for the Advisory Committee are expected to be posted two days prior to the meeting at this location:

<http://www.fda.gov/AdvisoryCommittees/Calendar/default.htm>

REMS OR OTHER RISK MANAGEMENT ACTIONS

No issues related to risk management have been identified to date.

LCM AGENDA

1. Introductory Comments – 5 minutes (Ronald Farkas, MD, PhD, CDTL/Fannie Choy, RPM)
Welcome, Introductions, Ground rules, Objectives of the meeting
2. Discussion of Substantive Review Issues – 30 minutes
Each issue will be introduced by FDA and followed by a discussion.
 - The reliability of biomarker evidence and its potential clinical meaning
 - Clinical evidence of efficacy and safety
3. Additional Applicant Data – 5 minutes (Applicant)
4. Information Requests
There are no information requests at this time.
5. Discussion of Upcoming Advisory Committee Meeting – 10 minutes
6. Postmarketing Requirements/Postmarketing Commitments
7. Review Plans – 5 minutes
FDA will continue to analyze efficacy and safety data and to be available for discussion with the applicant about issues that may arise.
8. Wrap-up and Action Items – 5 minutes
Chair will summarize any outstanding action items.

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/s/

ERIC P BASTINGS
12/23/2015